Cardiology in the Young

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Stenting of native right ventricular outflow tract obstructions in symptomatic infants: histological work-up of explanted specimen

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Abstract

Background: Stenting of stenotic right ventricular outflow tract is a palliative measure for severely impaired small babies with Tetralogy of Fallot or similar pathologies. Little is known about the histopathological fate of the stents in the right ventricular outflow tract. *Methods:* Eight samples of surgically removed right ventricular outflow tract stents were histologically analysed according to a predefined protocol. *Results:* The most frequent diagnosis was Tetralogy of Fallot in four patients, pulmonary atresia with ventricular septal defect in two patients, double outlet right ventricle with pulmonary obstruction in one patient, and muscular obstruction of the right ventricular outflow tract in one patient with a syndromic disease with hypertrophic cardiomyopathy. Stents mean implantation duration was 444 days ranging from 105 to 1117 days (median 305.5 days). Histology revealed a variable degree of pseudointima formation consisting of fibromuscular cells surrounded by extracellular matrix. Four of the specimen contained adjacent myocardial tissue fragments, which showed regressive changes. Neither myocardium nor pseudointima tissue or tissue parts locally related to stent struts were infiltrated by inflammatory cells. *Conclusions:* Histological analysis after explantation of early-in-life implanted right ventricular outflow tract stents revealed predominantly pronounced neo-intimal proliferation with a visible endothelial layer, no signs of inflammation, and no prolapse of muscular tissue through the stent struts. Thus, implantation of stents in early life seems to interfere little with the hosts' immune system and might help to open up the right ventricular outflow tract by mechanical forces and regressive changes in adjacent muscular tissue.

In small patients with Tetralogy of Fallot and similar pathologies, the degree of right ventricular outflow tract obstruction determines the immediate and early course of the disease and thus directs early therapy.

Techniques in heart surgery and perfusion medicine developed over the last decades and shifted the median age for corrective surgery for Tetralogy of Fallot from older than a year (1970–1990) towards approximately 4 months (2000–2012).[1] Patients at a younger age at surgery more often require a trans-annular patch implantation, thereby increasing the risk for a less favourable outcome.[2] Thus, alternative palliation strategies might be considered. In a meta-analysis, neonatal surgery for Tetralogy of Fallot was compared to non-neonatal surgery, favouring non-neonatal surgery in terms of mortality and length of stay on the intensive care ward and hospital stay.[3] Thus, an interventional palliation helps avoiding the neonatal period for the corrective surgery. Besides balloon dilatation of the pulmonary valve, stenting of the right ventricular outflow tract is considered one successful strategy of palliating obstructions in case of adverse risks factors for corrective surgery in infants.[4] A recent study favours right ventricular outflow tract stenting over surgical palliation with a Blalock-Taussig shunt to promote pulmonary arterial growth.[5] The histopathological fate of these stents in terms of ingrowth, triggering of inflammatory responses, or intimal proliferation are largely unknown. We describe the first series of explanted right ventricular outflow tract stents and their histological analysis. Thus, this study provides first insights in the previously largely unknown interaction of stents with the right ventricular outflow tract of very young infants.

Material and methods

Between January 2005 and December 2017, eight stented right ventricular outflow tract specimens were analysed in the implant biocompatibility laboratory of the Department of Pediatric Cardiology of the University Hospital Göttingen. All specimens had been surgically excised during surgery with implantation of a valved pulmonary conduit. Patients had been treated interventionally and surgically with written informed consent of the patients or their legal guardians. This study complies with the ethical rules of the institutions. As it is a retrospective analysis of results from routine diagnostics, a formal ethical vote was waived.

Explanted tissue samples were rinsed in normal saline after surgical removal and preserved in formalin. Extended histopathological work-up following a predefined protocol was performed as described previously.[6] According to this protocol, specimen were embedded in a synthetic resin (methyl methacrylate, Technovit 9100, KULZER & Co, Wehrheim, Germany), hardened, and subsequently sectioned in slices of 0.8 mm using a diamond cutter (300CP, Exakt GmbH, Norderstedt, Germany). These slices were ground down to 10–30 µm using a rotational grinder (400CS, Exakt GmbH, Norderstedt). Standard staining was performed with Richardson blue.

Results

Clinical data

Of the eight stents analysed, five were implanted within the first 30 days of life (neonatal period), two were implanted in the third, and one in the fifth month of life. All stents were implanted as a palliative measure due to right ventricular outflow tract obstruction to open up pulmonary blood flow. The most frequent diagnosis was Tetralogy of Fallot in four patients, pulmonary atresia with ventricular septal defect in two patients, double outlet right ventricle with pulmonary obstruction in one patient, and muscular obstruction of the right ventricular outflow tract in one patient with a syndromic disease with hypertrophic cardiomyopathy. Stents mean implantation duration was 444 days ranging from 105 to 1117 days (median 305.5 days). Different stent types were used, diameter of the stent system ranged from 4.5 to 7 mm. In three patients, a Palmaz Blue stent (Cordis, Milpitas, CA), in two patients a Cook Formula stent (Cook, Bloomington, IN), and in one patient a Driver stent (Medtronic, Minneapolis, MI) was implanted whereas in two patients the stent type used was not specified in the database. All identified stent types were bare metal stents. Palmaz Blue stent utilises a L605 cobalt chromium technology, containing cobalt, chromium, tungsten, nickel, and iron. Cook Formula stent is made of 316L stainless steel, containing iron, chromium, and nickel. Driver stent consists of F562 cobalt chromium alloy, containing nickel, cobalt, chromium, and molybdenum. A summary of the data is displayed in Table 1.

Macroscopic evaluation

The specimen had been excised with a variable portion of surrounding tissue (Fig 1). Towards the right ventricular outflow tract lumen, all specimen showed a smooth, thin, and intact whitish surface with all stent fragments covered by tissue. There were no signs of laceration, calcification, superficial thrombus formation, or evidence of stent fractures in any of the specimen.

Histological evaluation

Histology revealed a variable degree of neo-intima formation as a constant finding in all specimen (summary of findings in Table 2). Proliferations encapsuled all stent struts completely and consisted of spindle-shaped fibromuscular cells surrounded by extracellular matrix. Superficially, a one cell layer of endothelial cells was found.

Four of the specimens contained adjacent myocardial tissue fragments which showed regressive changes with marked fibrosis and some fatty degeneration of myocytes (Fig 2a–d; higher magnification in Fig 2b). Neither myocardium nor neo-intima tissue or tissue parts locally related to stent struts were infiltrated by inflammatory cells. One of the specimen showed marked pseudointimal neovascularization (Fig 2f).

Discussion

Little is known about the pathophysiological interactions of stents and tissue of the right ventricular outflow tract in young infants. Although limited by numbers, a pathology registry study is the only possibility to enhance our knowledge of the response of the young native right ventricular outflow tract myocardium to stents. To our knowledge, so far this is the only study to address this issue so far.

What we know about the interaction of vasculature and stents is mostly derived from stents implanted in the coronary arteries by percutaneous transluminal coronary angioplasty (PTCA). But there are some fundamental differences in these scenarios: Patients for PTCA are significantly older, stents are implanted in arteries with lesions, and in many studies newer stent designs with polymer coatings and drug-eluting characteristics are used. The focus of coronary stent development research lies mainly on mid- to long-term patency of the implanted stents and issues of stent design in regard to restenosis, thrombogenicity, healing response, and inflammation. Durable polymer drug-eluting stents have been used to reduce in-stent restenosis rates of bare metal stents due to intima proliferation.[7] However, the first generation drug-eluting stent shows a decreased healing of the arterial wall, leaving stent struts uncovered, which might lead to late stent thrombosis.[8] Second generation drug-eluting stents seem to overcome this limitation by improving arterial wall healing and decreasing inflammation (most probably associated with the durable polymer used) compared to the first generation drug-eluting stent, but interestingly some degree of inflammation has also been found in BMS in this study.[9]

Because other data concerning the nature of interaction of stents with tissues of native right ventricular outflow tracts are missing, these studies serve as a blueprint for analysis – although of limited value.

The patients presented in our study are much younger; the tissue of the right ventricular outflow tract and proximal pulmonary artery is different from atherosclerotic intimal tissue, containing a – mostly dysfunctional and dysplastic – valve, and the intima of the landing zone of the stent is without atherosclerotic or inflammatory lesions. All identifiable implanted stents in our patients were bare metal stents without drug-eluting properties.

We present a collection of eight explanted stents, which were implanted in the right ventricular outflow tract during the neonatal period and early infancy as a palliation for right ventricular outflow tract obstruction. After a variable time period (median time 305.5 days), the stents were explanted and sent for

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Table 1. Summary of sample and patient data.

Patient no.	Diagnosis	Age at implantation [d]	Duration until explantation [d]	Reason for explantation	Stent type	Stent size
1	HCM with RVOT obstruction	107	1117	Outgrown stent	Stainless steel (not specified)	Not known
2	ToF	10	287	Surgical correction	Palmaz blue	7 × 12 mm
3	ToF	10	155	Surgical correction	Palmaz blue	6 × 15 mm
4	PA-VSD	143	439	Surgical correction	Palmaz blue	6 × 15 mm
5	ToF	17	1008	Stent obstruction	Not specified	Not known
6	ToF	4	324	Surgical correction	2× Driver	4.5 × 15 mm; 4.5 × 12 mm
7	PA-VSD	98	117	Surgical correction	Cook Formula 414	5 × 16 mm
8	DORV (ToF-type)	16	105	Surgical correction	Cook Formula 414	5 × 16 mm

HCM=hypertrophic cardiomyopathy; RVOT=right ventricular outflow tract; ToF=Tetralogy of Fallot; PA-VSD=pulmonary atresia with ventricular septal defect; DORV=double outlet right ventricle.

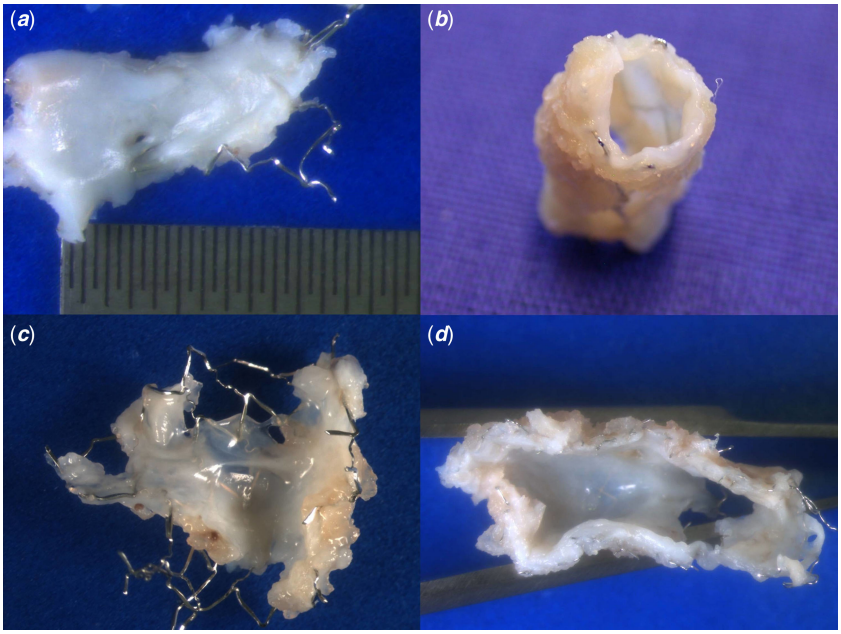

Figure 1. Gross pathology. Representative images of excised specimen (***a*** – patient 2; ***b*** – patient 3; ***c*** – patient 6; ***d*** – patient 8).

histological examination. Macroscopic and histologic analysis showed in all cases proliferation of neo-intimal tissue to a variable but mostly distinct degree. All samples showed endothelialisation of the exposed stent material as far as we can judge, although some of the stents were fractured or damaged during explantation. We did not see signs of relevant inflammation in any sample. In those samples with adjacent parts of myocardial tissue, we did not see prolapse of muscular tissue through the stent struts. In four samples, we found signs for degenerative changes of myocardial tissue in close vicinity to stent struts.

All identifiable stents in our collection are non-drug-eluting stents. It is known that neo-intima formation is reduced by drug-eluting stents by inhibiting vascular smooth muscle cell proliferation, which are responsible for production of extracellular matrix proteins.[7] The samples of our study demonstrate a variable degree of neo-intima proliferation. The only cells on the luminal side of the stent struts were proliferated fibromuscular cells and endothelial cells. One can speculate this proliferation could have been reduced by employment of drug-eluting stents, although its usage in small infants is controversial due to systemic resorption and effect of the immunosuppressive drug. But not only vascular smooth muscle cell proliferation is impaired by drug-eluting stents, also endothelial cell proliferation seems to be impaired. And impaired endothelial cell proliferation might be associated with late stent thrombosis, at least in coronary stents.[8] In contrast, our samples showed no evidence of impaired endothelial cell proliferation.

Strikingly, there are some differences between the previously published series of explanted stents and our sample: Published studies refer to stents implanted in elderly people, mostly coronaries, with a completely different pathophysiological burden of degenerated, calcified, atherosclerotic arterial walls. Significant inflammatory reactions were described histologically which were related to the extent of media damage during implantation and subsequent neo-intima proliferation.[10–13]

Interestingly, in our sample cohort, we found no inflammatory response in any of the implanted stents. We believe that this is due to the fact that in the patients of our study stents were implanted in

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Table 2. Summary of macroscopical and histological findings.

Patient no.	Macroscopic image	Proliferation	Inflammation	Endothelial layer	Surrounding tissue
1	Whitish, shiny surface, no vegetations	Neo-intimal layer of up to 1 mm, vascularisation visible, high density of cells	No significant	Present	No surrounding tissue
2	Whitish, shiny surface, no vegetations	Neo-intimal layer of up to 1 mm, little vascularisation visible, low density of cells	No	Present	Muscular tissue
3	Whitish, shiny surface, no vegetations	Neo-intimal layer non-uniform in thickness (0.2–1 mm)	No	Present	Little muscular tissue
4	Whitish, shiny surface, little surrounding tissue	Neo-intimal layer of up to 2 mm, little vascularisation visible, in parts high density of cells	No	Present	Media and adventitia
5	Whitish, little thin surrounding tissue	Little neo-intimal proliferation, no fibrin visible	No	Present	Little tissue of media and adventitia
6	Whitish, shiny surface	Neo-intimal layer of up to 0.5 mm, partially fibrin visible	No	Present	Muscular tissue
7	Little tissue, whitish, shiny surface	Neo-intimal layer of up to 0.5 mm, no vascularisation visible, low density of cells	No	Present	No surrounding tissue
8	Several fragments, little tissue, whitish, shiny surface	Neo-intimal layer of up to 1 mm, little vascularisation visible, high density of cells	No	Present	Muscular tissue

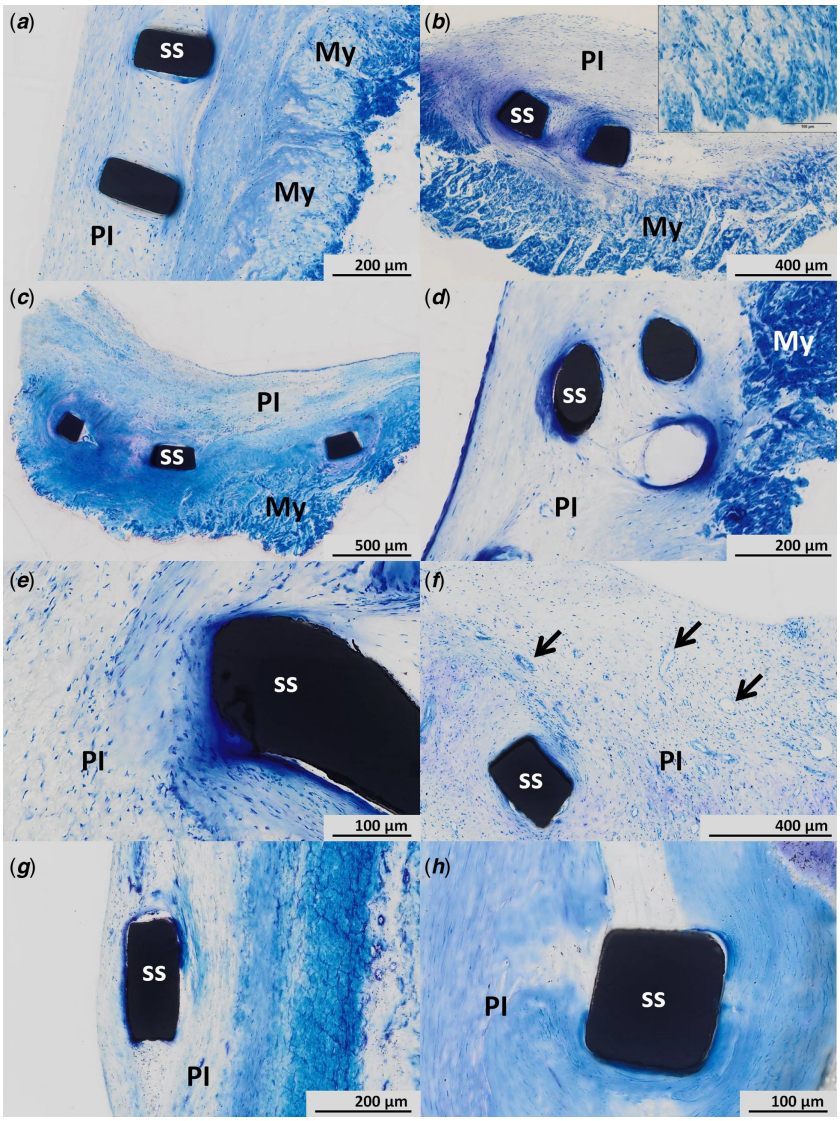

Figure 2. Histology of all specimen. Four of the specimens (***a***–***d***) contained RVOT myocardial tissue fragments (My) with regressive changes in the area adjacent to the pseudointima (PI); (***e***) no cellular inflammation locally related to stent strut (SS); (***f***) pseudointima with neovascularization (arrows); (***g***, ***h***) no cellular inflammation in pseudointima. Richardson staining.

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native right ventricular outflow tracts and proximal main pulmonary arteries and tissue characteristics there differ significantly from atherosclerotic coronary arteries with pre-existing inflammatory changes. As a standard procedure in many centres, aspirin or clopidogrel is given after stent implantation in the right ventricular outflow tract. Whether this treatment is able to suppress or modulate inflammatory reactions in proximity to the implanted stents in our patient group remains unknown. However, in elderly people after coronary stenting these drugs are given and nevertheless inflammatory reactions are seen in this patient group. [10–13]

To our knowledge, our study is the first study that describes the interaction of the stents with the muscular tissue of the right ventricular outflow tract. We show some degree of regressive changes in the muscular tissue directly adjacent to the stent struts as a result of the mechanical force of the stent, but no signs of inflammation.

Conclusions

Histological analysis after explantation of early-in-life implanted right ventricular outflow tract stents revealed predominantly pronounced neo-intimal proliferation with a visible endothelial layer, no signs of inflammation, and no prolapse of muscular tissue through the stent struts.

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Conflicts of interest. None.

Authors' statement. All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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