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Inflammatory response after ExoVasc® personalized external aortic root support (PEARS) procedure in patients with Marfan syndrome or non-Marfan genetic aortopathy

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SOUHRN

Kontext: Cílem studie bylo zjistit závažnost zánětlivé odpovědi po výkonu PEARS (personalized external aortic root support) s vytvořením personalizovaného externího stentu pro aortální kořen ve srovnání se standardní profylaktickou operací aortálního kořene (standard prophylactic aortic root surgery, SPARS).
Materiál a metody: Studie byla monocentrickou, retrospektivní analýzou nemocničních záznamů pacientů, u nichž byla v období 1998–2017 provedena buď PEARS (skupina PEARS), nebo SPARS (skupina SPARS). U všech pacientů se rutinně stanovovaly hodnoty C-reaktivního proteinu (CRP) a počet bílých krvinek (white blood count, WBC) a provádělo se echokardiografické vyšetření. Horečka byla definována jako tělesná teplota ≥ 38 °C. Diagnóza perikarditidy se stanovovala na základě nejméně tří známek z bolesti na hrudi, perikardiálního výpotku, elevace úseku ST, zvýšených hodnot CRP a tělesné teploty.
Výsledky: Do skupin PEARS a SPARS bylo zařazeno 13, resp. 14 pacientů s indikací k profylaktické operaci aortálního kořene. Většina pacientů v obou skupinách měla Marfanův syndrom s kauzální mutací v genu pro fibrilin 1 (FBN1) (62 % vs. 79 %). Vstupní charakteristiky pacientů v obou skupinách byly podobné s výjimkou aortálního kořene, který byl ve skupině SPARS statisticky významně větší než ve skupině PEARS (60 ± 12 mm vs. 48 ± 5 mm; $p = 0{,}003$). Všechny operace byly úspěšné a proběhly bez větších komplikací. Nejvyšší hodnoty CRP a WBC byly statisticky významně vyšší ve skupině PEARS (264,5 ± 84,4 mg/l vs. 184,6 ± 89,6 mg/l; $p = 0{,}034$, resp. 15,2 ± 3,8 10^9/l vs. 11,9 ± 3,3 10^9/l; $p = 0{,}029$). Časná a recidivující horečka vyžadující opětovnou hospitalizaci se vyskytla častěji ve skupině PEARS (77 % vs. 36 %; $p = 0{,}032$, resp. 46 % vs. 7 %; $p = 0{,}020$). Časná a recidivující perikarditida vyžadující hospitalizaci byla rovněž častější ve skupině PEARS (31 % vs. 0 %; $p = 0{,}024$, resp. 31 % vs. 0 %; $p = 0{,}024$).
Závěry: Metoda PEARS je velmi slibná chirurgická metoda; pooperační zánětlivá odpověď se však vyskytuje častěji a ve srovnání s metodou SPARS je závažnější. Tyto výsledky je však samozřejmě nutno dále zkoumat a ověřovat.

ABSTRACT

Background: The study aimed to determine the severity of inflammatory response after the personalized external aortic root support (PEARS) procedure in comparison to after the standard prophylactic aortic root surgery (SPARS).
Materials and methods: The study was a single-centre, retrospective, based on hospital record analysis of patients who underwent the PEARS procedure (PEARS group) or SPARS (SPARS group) during 1998–2017. C-reactive protein (CRP), white blood count (WBC), and echocardiography were routinely obtained. Fever was defined as body temperature ≥38 °C. Diagnosis of pericarditis included a minimum of three signs from chest pain, pericardial effusion, ST elevation, elevated CRP, and body temperature.
Results: PEARS and SPARS groups consisted of 13 and 14 patients, respectively, scheduled for prophylactic aortic root. A majority of patients in both groups had Marfan syndrome with causal mutation in the fibrillin 1 (FBN1) gene (62% vs 79%). Patient baseline characteristics were similar in the two groups, except aortic root was significantly larger in the SPARS group than in the PEARS group (60±12 mm vs 48±5 mm; $p = 0.003$). All surgical procedures were successful and without major complications. The peak values of CRP and WBC were significantly higher in the PEARS group (264.5±84.4 mg/L vs 184.6±89.6 mg/L; $p = 0.034$ and 15.2±3.8 10^9/L vs 11.9±3.3 10^9/L; $p = 0.029$). Early and recurrent fever requiring hospital readmission was significantly

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more frequent in the PEARS group (77% vs 36%; $p = 0.032$ and 46% vs 7%; $p = 0.020$). Early and recurrent pericarditis requiring hospital readmission was also more frequent in the PEARS group (31% vs 0%; $p = 0.024$ and 31% vs 0%; $p = 0.024$).

Conclusions: The PEARS procedure is an extremely promising surgical technique, but the postoperative inflammatory response occurs frequently and more severely in comparison to SPARS. Clearly, these findings warrant further investigation.

Introduction

Prophylactic aortic root surgery is essential for patients with increased risk of aortic dissection. These are in particular patients with aortic root dilatation due to various genetic disorders. In addition to the widely used standard prophylactic aortic root surgery (SPARS), there is a novel technique, the ExoVasc® personalized external aortic root support (PEARS).[1,2] The idea behind PEARS is to utilize a less invasive surgical procedure that involves wrapping macroporous mesh around the aortic root[3] to support the aorta and prevent further aortic dilatation and dissection. PEARS implantation is generally a safe procedure and cardiopulmonary bypass (CPB) is not mandatory.[4,5] The macroporous polyethylene mesh is wrapped around the entire ascending aorta, thereby leaving both coronary artery origins intact.[6] The risk for late development of an aortic pseudoaneurysm is considered to be extremely low, because the aortic root remains without an anastomosis or another vessel wall injury after the procedure. Since 2015, the PEARS procedure has become optional for patients within our tertiary centre having genetic disorders leading to aortic root dilatation. Somewhat surprisingly, the rate of inflammatory response after the PEARS procedure is rather high in our single-centre experience. The aim of the present study was to investigate formally whether an inflammatory response after PEARS implantation is more frequent or severe in comparison with that after SPARS.

Material and methods

Study group

This was a retrospective, single-centre, observational study based on detailed patient chart analysis. All patients included had undergone prophylactic aortic root surgery at the Institute for Clinical and Experimental Medicine tertiary centre in Prague during 1998 to 2017. Informed consent was obtained from all individual participants included in the study. The PEARS procedure had been approved by the local Ethics Committee and by the State Institute for Drug Control.

The study cohort consisted of two groups: a PEARS group and a SPARS group. The PEARS group included all consecutive patients who had undergone the PEARS procedure at our centre exclusively from 2015 to 2017. All patients undergoing PEARS had had aortic root dilatation plus either a causal mutation in the fibrillin 1 (FBN 1) gene or a strong family history of aortic dissection and/or aortic root dilatation in two or more relatives. For the SPARS group, the hospital database was searched and all consecutive patients with a causal mutation in the FBN 1 gene who had undergone a prophylactic aortic root replacement within the period 1998–2017 were included. To obtain a composition of the SPARS group similar to that of the PEARS group, the first three patients with bicuspid aortic valve who had undergone prophylactic aortic root surgery recently in 2017 were also included into the SPARS group.

Perioperative assessment and signs of inflammation

All PEARS procedures were performed by a single, most experienced surgeon. The surgical procedures in the SPARS group were performed by four experienced surgeons. During the perioperative hospitalization, the body temperature and vital signs were checked at least once a day. The highest body temperature each day was included into the analysis. A body temperature ≥38°C was considered as fever. Early fever was that which occurred early after the surgery and prior to hospital discharge while late fever was defined as fever occurring after hospital discharge. The blood tests including white blood count (WBC) and C-reactive protein (CRP) were checked prior to surgery and at least twice after the procedure before hospital discharge. Electrocardiography (ECG) was performed prior to surgery, at least twice daily on the day of surgery, and repeated daily during the first three postoperative days. ST elevation was defined as a temporary >1 mm ST segment elevation in more than two leads on the ECG in comparison to the pre-procedural ECG. Echocardiography was routinely performed in all patients prior to hospital discharge. A diagnosis of acute pericarditis was based on the presence of at least three signs from the following: ST elevation, typical chest pain, increased body temperature or CRP level, and presence of pericardial effusion on echocardiography (Fig. 1). Early pericarditis was that occurring early after the surgery and prior to hospital discharge. Acute pericarditis presentation after the hospital discharge was regarded as late pericarditis.

Patient follow-up

The follow-up consisted of clinical examination, including echocardiography, ECG, and blood analysis by a single cardiologist at 3, 6, and 12 months and then every year after the surgery in the PEARS group. All patients in the SPARS group were scheduled for outpatient check-up 3 and 12 months after the surgery. Each visit also included a clinical examination, echocardiography, ECG, and blood analysis.

In the case of hospital readmission during the first year after the surgery, the ECG, WBC, CRP, body temperature, and echocardiography were routinely checked. Blood cultures, leukocyte scintigraphy, or transesophageal echocardiography were performed whenever clinically relevant.

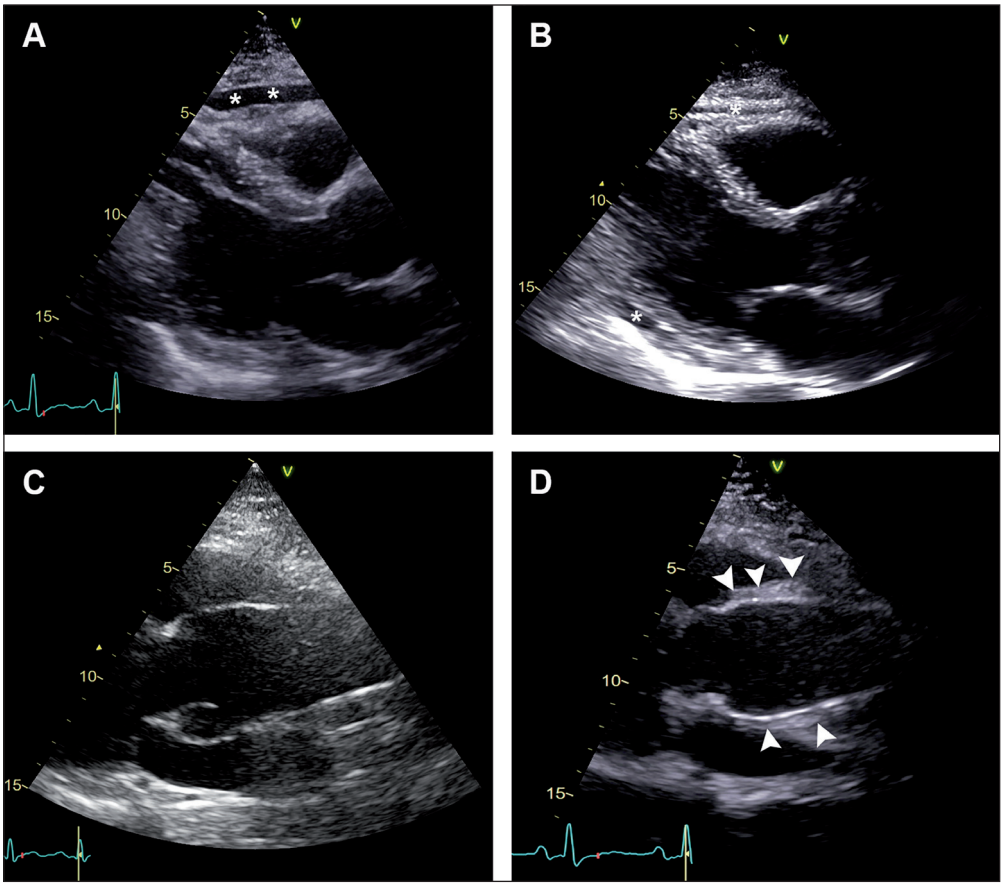

Fig. 1 – Transthoracic echocardiography demonstrating signs of inflammation after PEARS procedure. (A) Late acute pericarditis 227 days after PEARS implantation; asterisks indicate pericardial effusion. (B) Late acute pericarditis 43 days after PEARS implantation; asterisk indicates pericardial effusion. (C) Aortic root in a patient with Marfan syndrome prior to PEARS implantation (thin aortic walls). (D) Thickening of the aortic walls 6 days after PEARS implantation in the same patient as (C), having early and late recurrent fever; arrowheads indicate the inflammatory aortic wall thickening.

Statistical analysis

Continuous variables were expressed as means ± standard deviation. Categorical variables were expressed as percentages. Differences between study groups were assessed by two-tailed *t*-test. *P* values ≤0.05 were regarded as significant. The analysis was performed using Excel 2016.

Results

The PEARS group consisted of 13 patients from the total of 14 patients who had undergone the PEARS procedure. One Romanian patient was excluded from the analysis for lack of complete follow-up. All patients eligible for the SPARS group were included in the analysis, and the SPARS group consisted of 14 patients. The average follow-up in the PEARS group was 456 (94–830) days and that in the SPARS group was 2002 (117–4605) days. Patient baseline characteristics did not differ significantly between the groups except that aortic root diameter was 48±5 mm in the PEARS group versus 60±12 mm in the SPARS group with $p = 0.003$ (Table 1). A majority of patients in both groups (62% vs 79%; $p = 0.352$) had been diagnosed with Marfan syndrome and a causal mutation in the FBN 1 gene (Table 1). With the exception of total procedural time, differences in procedural characteristics were highly significant between the two groups (Table 1). All surgical procedures were technically successful in both groups without major complications.

The average body temperature peaked between the 2nd and 4th postoperative days in both groups and with no significant difference (Table 1). Peak average of CRP was significantly higher in the PEARS group that in the SPARS group (264.5±84.4 mg/L vs 184.6±89.6 mg/L; $p = 0.034$). White blood count was also significantly more elevated in the PEARS than the SPARS group (15.2±3.8 10^9/L vs 11.9±3.3 10^9/L; $p = 0.029$; Table 1). ST elevation occurred significantly more frequently in the PEARS group than in the SPARS group (85% of patients vs 43%; $p = 0.024$; Table 1). Early fever was present significantly more frequently in the PEARS group than the SPARS group (77% vs 36%; $p = 0.032$; Table 1). Late fever occurred in 46% of patients in the PEARS group versus 7% of patients in the SPARS group ($p = 0.020$; Table 1). Readmission for severe symptomatic fever was required in two patients of the PEARS group, and one of these two patients was readmitted twice for symptomatic recurrent fever within the time

Table 1 – Patients baseline characteristics, procedural characteristic, and postprocedural inflammatory characteristics

Characteristics	PEARS group (N = 13)	SPARS group (N = 14)	*p* value
Patient baseline characteristics			
Age (years)	37±8	43±11	0.178
Males	11 (85)	10 (71)	0.430
Marfan syndrome	8 (62)	11 (79)	0.352
Arterial hypertension	5 (39)	5 (36)	0.888
Diabetes mellitus	1 (8)	2 (14)	0.603
Creatinine clearance (MDRD, ml/min)	133±30	126±30	0.678
Systemic inflammatory disease (N)	0 (0)	2 (14)	0.169
Aortic root dimension (mm)	48±5	60±12	0.003
Previous cardiac surgery (N)	0 (0)	2 (14)	0.195
CRP (mg/L) prior to surgery	2.6±1.6	4.8±6.2	0.474
WBC (10^9/L) prior to surgery	7.0 (1.7)	7.1 (1.6)	0.874
Procedural characteristics			
Cardiopulmonary bypass (N)	9 (69)	14 (100)	0.024
Time aortic cross-clamping (min)	4±13	140±44	<0.001
Total procedural length (min)	279±57	294±45	0.472
One-/two-valve surgery (N)	0 (0)	13 (93)	<0.001
Postprocedural inflammatory characteristics			
Peak level of CRP (mg/L)	264.5±84.4	184.6±89.6	0.034
Peak WBC (10^9/L)	15.2±3.8	11.9±3.3	0.029
ST elevation (N)	11 (85)	6 (43)	0.024
Average body temperature (°C)	37.7±0.5	37.6±0.4	0.642
Early fever (N)	10 (77)	5 (36)	0.032
Recurrent fever (N)	6 (46)	1 (7)	0.020
Early pericarditis (N)	4 (31)	0 (0)	0.024
Recurrent pericarditis (N)	4 (31)	0 (0)	0.024
Persistent atrial fibrillation (N)	4 (31)	6 (43)	0.534

span of 6 to 251 days. There was one episode of late fever in the SPARS group which required hospital readmission 49 days after the surgery. An infective origin of fever was ruled out in all patients of the PEARS and SPARS groups after a detailed comprehensive investigation.

Early and recurrent pericarditis was diagnosed solely in patients from the PEARS group. Both early and late pericarditis occurred in 31% of patients in the PEARS group, and thus the difference in the occurrence of pericarditis was highly significant between the two groups ($p = 0.024$; Table 1). Hospital readmission for acute pericarditis was required 6 times in 4 patients of the PEARS group within the time span of 11 to 284 days. One of these patients required hospital readmission for acute pericarditis three times in total.

Discussion

The present study is to our knowledge the first attempting formally to investigate whether an inflammatory response after the PEARS procedure is more frequent and severe in comparison to after SPARS. In the present study, inflammatory response occurred significantly more frequently in patients undergoing the PEARS procedure. Fever and acute pericarditis were the two main clinical presentations of the inflammation after the cardiothoracic surgery. Transient fever was present in both groups, but it developed significantly more frequently in the PEARS group. Acute and late pericarditis occurred only in the PEARS group. It is noteworthy that the relapse of both fever and acute pericarditis occurred over a long period ranging from 6 to 251 days and from 11 to 284 days, respectively, after the PEARS procedure. In comparison, there was only one case of late clinical inflammatory presentation in SPARS. In that case, the fever developed 49 days after the surgery.

The inflammatory response termed postimplantation syndrome (PIS) after various surgical or endovascular procedures involving thoracic or abdominal aorta has been previously reported.[7–9] Most authors define PIS as post-procedural fever coinciding with CRP and WBC el-

evation.[10,11] Although some researchers suggest that PIS is only a transient (early or late) and probably harmless event,[10] there is also evidence of an increased rate of major cardiac events in association with PIS.[11] Arnaoutoglou et al. reported in their prospective study that patients diagnosed with PIS after endovascular aortic aneurysm repair were about 4-1/2 times more likely to suffer an adverse event than were patients without PIS.[11] Moreover, PIS has been reported after surgical or endovascular aortic valve replacement,[7] after the surgical treatment of thoracic or abdominal aortic aneurysm, and after endovascular aortic repair.[8,9,11]

High implantation pressure followed by a development of aortic hematoma after stent-graft implantation perhaps explains the PIS in part, but a biological immune reaction to foreign material might be the most likely explanation.[10] The activation of polymorphonuclear cells, lymphocytes, macrophages, and epithelioid cells in a manner that has been well described plays an important role in incorporating the foreign material into the vessel wall.[12] It can be assumed that the chemical composition and perhaps the porosity of a particular graft might play an important role in PIS.[11] Voûte et al. showed that endovascular grafts made of woven polyester were associated with higher clinical post-procedural inflammation than were endovascular grafts made of expanded polytetrafluoroethylene.[10] The ExoVasc® is made of the polyester polyethylene terephthalate (known commercially as Dacron®), and this material might lead to increased immune reaction after implantation. The porosity of the ExoVasc® is very different from that of the commonly used woven polyester, because ExoVasc® is a knitted macroporous mesh.[3] Van Hoof et al. studied woven and knitted polyethylene terephthalate materials wrapped around the aorta in sheep. They showed the macroporous knitted mesh to be better incorporated into the aortic wall after 1 year than is the low-porosity woven material. Both types of vascular grafts showed significant aortic wall thickening secondary to the expected acute and chronic inflammatory reaction to foreign material and thinning of media.[3]

Another inflammatory event besides PIS occurring with variable incidence after cardiothoracic surgical procedures and that has been well described is postpericardiotomy syndrome (PPS). Lehto et al. reported the incidence of PPS to be 8.9% and median time until diagnosis to be 21 days in patients after isolated coronary artery bypass grafting. The PPS diagnosis in their study was based on presence of fever accompanied by signs of pleuritis and pericarditis.[13]

Clearly, there exists a number of factors leading to inflammation after vascular graft implantation and surgical opening of the pericardium as is necessary during ExoVasc® implantation. We suggest that because the PEARS procedure involves wrapping a large aortic surface with the prosthesis, indeed covering the entire ascending aorta from the aortic annulus to the aortic arch, in combination with the aortic root's expansibility during the cardiac cycle might play an important role in the pronounced and more frequent post-procedural inflammation. The more frequent early and late transient fever after PEARS implantation is probably not of major concern. As documented in the present study within 1-year follow-up, we suggest this to be a harmless event with no clinical consequences. A majority of these fever events after the PEARS procedure are of noninfective cause and might be successfully suppressed using nonsteroidal anti-inflammatory drugs (NSAID), usually on an outpatient basis.

The relatively high incidence of early and recurrent episodes of acute pericarditis after PEARS implantation is more worrying. Late symptomatic constrictive pericarditis might be a threat because its treatment involves high-risk surgical pericardectomy.[14] A total of 4 patients out of 13 in the PEARS group experienced an acute episode of recurrent pericarditis requiring hospital readmission due to the severity of symptoms. Medical treatment based on colchicine and NSAID while following the 2015 guidelines for the diagnosis and management of pericardial diseases was successful in all patients and pericardiocentesis was not required.[14] Repeated admission for acute pericarditis occurred in the case of one of these patients and additional treatment with corticosteroids perorally over a course of 7 months was required until the symptoms completely resolved (Fig. 1). Long-term follow-up in all these patients is warranted to determine their risk of late complications such as constrictive pericarditis.

Consistent with previously published data,[4] the PEARS procedure was successful in all patients and no major adverse events were reported in the present study. The procedure appears to be relatively safe and is less complex in comparison to SPARS. CPB was used in 69% of patients within the PEARS group, and aortic cross-clamping was necessary for one patient of the PEARS group. By contrast, all patients in the SPARS group required CPB and aortic-cross clamping during surgery. Despite the presented data on the inflammatory response after the PEARS procedure, the overall evidence suggests that the procedure itself is very promising.[2,4,5]

Study limitations

The main limitations of the present study consist in its small size and retrospective character. The PEARS technique is still rather novel, however, and an inflammatory response after PEARS is a factor that should be taken into consideration.

Conclusions

Our single-centre experience demonstrates PEARS to be a feasible, generally safe, and less complex procedure with a higher rate of post-procedural inflammatory response. Early and late fever after PEARS is usually noninfective, and outpatient medical treatment might be appropriate. Recurrent acute pericarditis often requires hospitalization and a combination of drugs. Prospective studies on postimplantation syndrome after the PEARS procedure are warranted.

Conflict of interest
None.

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Data availability statement
The patient's data used to support the findings of this study are restricted by the Ethics Committee of the Institute for Clinical and Experimental Medicine and Thomayer Hospital (MEK-640/15; A 15-03-02) in order to protect patient privacy. Anonymized data might be available upon request from the corresponding author for researchers who meet the criteria for access to confidential data.

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