European Journal of Cardio-Thoracic Surgery 45 (2014) 1070–1074
doi:10.1093/ejcts/ezt579 Advance Access publication 10 January 2014

ORIGINAL ARTICLE

Incidence and risk factors for Contegra graft infection following right ventricular outflow tract reconstruction: long-term results

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Received 23 June 2013; received in revised form 18 October 2013; accepted 21 October 2013

Abstract

OBJECTIVES: The aim of this study was to evaluate the risk factors associated with Contegra graft (Medtronic Minneapolis, MN, USA) infection after reconstruction of the right ventricular outflow tract.

METHODS: One hundred and six Contegra grafts were implanted between April 1999 and April 2010 for the Ross procedure ($n = 46$), isolated pulmonary valve replacement ($n = 32$), tetralogy of Fallot ($n = 24$), double-outlet right ventricle ($n = 7$), troncus arteriosus ($n = 4$), switch operation ($n = 1$) and redo of pulmonary valve replacement ($n = 2$). The median age of the patients was 13 years (range 0–54 years). A follow-up was completed in all cases with a median duration of 7.6 years (range 1.7–12.7 years).

RESULTS: There were 3 cases of in-hospital mortality. The survival rate during 7 years was 95.7%. Despite the lifelong endocarditis prophylaxis, Contegra graft infection was diagnosed in 12 (11.3%) patients at a median time of 4.4 years (ranging from 0.4 to 8.7 years). Univariate analysis of preoperative, perioperative and postoperative variables was performed and the following risk factors for time to infection were identified: female gender with a hazard ratio (HR) of 0.19 ($P = 0.042$), systemic-to-pulmonary shunt (HR 6.46, $P < 0.01$), hypothermia (HR 0.79, $P = 0.014$), postoperative renal insufficiency (HR 11.97, $P = 0.015$) and implantation of permanent pacemaker during hospitalization (HR 5.29, $P = 0.075$). In 2 cases, conservative therapy was successful and, in 10 patients, replacement of the infected valve was performed. The Contegra graft was replaced by a homograft in 2 cases and by a new Contegra graft in 8 cases. Cox's proportional hazard model indicated that time to graft infection was significantly associated with tetralogy of Fallot (HR 0.06, $P = 0.01$), systemic-to-pulmonary shunt (HR 64.71, $P < 0.01$) and hypothermia (HR 0.77, $P < 0.01$).

CONCLUSION: Contegra graft infection affected 11.3% of cases in our cohort, and thus may be considered as a frequent entity that can be predicted by both intraoperative and early postoperative factors. After the diagnosis of infection associated with the Contegra graft was confirmed, surgical treatment was the therapy of choice.

Keywords: Pulmonary valve • Ross operation • Xenograft • Endocarditis

INTRODUCTION

Bovine jugular vein conduit (Contegra; Medtronic, Inc., Minneapolis, MN, USA) is routinely used for reconstruction of the right ventricular outflow tract (RVOT) nowadays, as part of the repair of congenital heart defects and/or as a replacement for the pulmonary valve in the Ross procedure. In 1999, the Contegra graft was first proposed as a substitute for the reconstruction of the continuity between RVOT and pulmonary arteries. Since then, due to its encouraging initial clinical results [1–3], this xenograft gained wide popularity and acceptance in cardiac surgical practice.

Early and mid-term clinical results of the Contegra graft are controversial. The initial enthusiasm over mid-term results in early reports [4, 5] was soon replaced by more realistic data on stenosis and/or conduit insufficiency [6, 7]. Although numerous retrospective trials have evaluated clinical outcomes following Contegra graft implantation, no report exists that deals with postoperative incidence and predictive factors for Contegra graft infection, apart from some case reports.

The aim of this retrospective study was to describe the incidence and predictive factors for postoperative Contegra graft infection after RVOT reconstruction in a heterogeneous mix of patients (age range 0–54 years).

MATERIALS AND METHODS

Patient population and data collection

Institutional review board approval and informed patient consent were obtained for this retrospective study. Data for all implanted Contegra grafts for reconstruction of the RVOT between April

1999 and April 2010 were retrospectively collected from University Hospital Lausanne.

Data from our institutional database were collected for variables such as age, sex, weight, type of surgical intervention, type of congenital malformation, congestive cardiomyopathy, history of myocardial ischaemic disease, smoking, hypertension, history of previous intervention, preoperative ejection fraction, New York Heart Association (NYHA) state, RVOT pathology and renal functional impairment. Procedural data were also collected on the use of cardiopulmonary bypass, the degree of hypothermia and concomitant procedures. Postoperative parameters included emergency exploration due to haemodynamic instability, hospital mortality, length of hospital stay, intensive care unit (ICU) stay, intubation time and incidence of major cardiovascular events (e.g. myocardial ischaemic event, stroke, death for cardiac reasons). The haemodynamic status of patients with an implanted Contegra was evaluated by transthoracic echocardiogram upon discharge from hospital.

The follow-up ended on 15 April 2012 and was performed via phone calls to the patients, referred physicians and referred cardiologists.

All patients were started on aspirin for antiplatelet therapy postoperatively for 6 weeks, and received a lifelong antibiotic prophylaxis for the prevention of endocarditis. The median follow-up was 7.6 years with a range between 1.7 and 12.7 years, and was completed in 100% ($n = 106$) of cases.

Conduit endocarditis was defined according to the Duke criteria [8], with consideration of the following factors: new cardiac murmur over the second left intercostal space, evidence of mobile mass and/or destruction of leaflets in the Contegra graft, positive haemoculture and presence of systematic inflammatory response syndrome [9].

Prophylactic antibiotic therapy

According to our institutional protocol, oral prophylaxis was started 24 h before the operation, followed by a single intravenous premedication dose. A second single dose was introduced during the priming of the cardiopulmonary bypass. Postoperative antibiotic therapy was continued intravenously until the drains were removed (usually 48–72 h after the operation). Cefaclor and cefadroxil were used as oral antibiotics, and cefotiam was used intravenously.

Statistics

Categorical variables are summarized with number (percent) and compared across groups using the χ^2 test or the Fisher's exact test. Continuous variables are presented as medians (interquartile range) and compared across groups using a non-parametric version of the Kolmogorov–Smirnov test. Time-to-event end points are summarized using a Kaplan–Meier estimate and compared across groups with a Cox proportional hazard model. The end point of interest in the present study is time-to-Contegra infection. A Cox proportional hazard model was used to model time-to-Contegra infection, with deaths excluded. Selection of statistically significant covariates was carried out into two different ways: (i) using stepwise methods (i.e. likelihood ratio test) and (ii) calculating the *c*-statistic (a generalization of Somer's D), which is a measure of the rank correlation between the time to infection censored response and a series of covariates. All statistical analyses were performed using the R version 2-15-2 statistical package.

RESULTS

One hundred and six patients were included in this study, of which 29.2% were females. The median age was 13 years (range from 0 to 54), and the mean weight was 42.3 kg (ranging between 4.3 and 95.0 kg). In all 106 cases, RVOT reconstruction was performed by implantation of a Contegra graft.

Indications of RVOT reconstruction were as follows: tetralogy of Fallot ($n = 24$), Ross procedure ($n = 46$), troncus arteriosus communis ($n = 4$), isolated pulmonary valve stenosis ($n = 32$), double-outlet right ventricle ($n = 7$) and transposition of the great arteries ($n = 3$). Closure of ventricular septal defect by patch was performed as a concomitant procedure in 4 cases. Twelve of the 32 cases of isolated pulmonary valve replacement were reoperations of tetralogy of Fallot, while 20 cases were isolated pulmonary valve pathologies.

Additionally, prior to Contegra implantation, a systemic-to-pulmonary shunt ($n = 10$) and Blalock–Taussig shunt ($n = 8$) were carried out. The preoperative characteristics of patients are presented in Table 1.

All available Contegra graft sizes (10–22 mm) were used in the patients involved in the study, and the mean size of the implanted graft was 20 mm. The operative technique has been described in detail previously [10]. The mean duration of intervention was 304.0 ± 77.5 min, extracorporeal circulation time was 151.4 ± 51.1 min and aortic cross-clamping time was 71.2 ± 34.8 min. The mean intubation time was 4.8 ± 13.9 days and the mean ICU time was 9.4 ± 23.0 days. Reoperation due to bleeding was performed in 12 cases (11.3%). In the postoperative period, major cardiovascular events were as follows: incidence of myocardial ischaemia in 6 cases (5.7%), cerebrovascular events in 2 cases (1.9%) and renal impairment was registered in 3 cases (2.8%). A permanent pacemaker was implanted in 4 cases (3.8%) due to a high degree of atrioventricular block. In-hospital mortality was registered in 3 cases (2.8%) and was of a cardiac cause.

The follow-up was completed in 100% of cases with a median duration of 7.6 years (ranging 1.7–12.7 years). Mortality during the follow-up occurred in 2 cases (1.9%) and was of a cardiac cause (Table 2).

Table 1: Preoperative variables in 106 cases having reconstruction of RVOT with a Contegra graft

Preoperative variables	
Female gender	31 (29.2%)
Age, mean (years)	17.4 ± 16.0
Age > 18 years	38 (35.8%)
Preoperative coronary artery disease	15 (14.2%)
Active smoker	13 (12.3%)
Preoperative renal failure	3 (2.8%)
Hypercholesteraemia	5 (4.7%)
NYHA class > II	33 (31.1%)
LVEF	64.3 ± 9.6%
Preoperative pathology	
Tetralogy of Fallot	24 (22.6%)
Double-outlet right ventricle	7 (6.6%)
Truncus arteriosus communis	4 (3.8%)
Isolated pulmonary stenosis	10 (9.4%)
Transposition of great vessels	3 (2.8%)
Isolated aortic valve disease	47 (44.3%)

Endocarditis of the Contegra graft was diagnosed in 12 patients (11.3%) and developed at a median time of 4.4 years (range 0.4–8.7 years). In 2 cases, conservative therapy was successful, and in 10 patients, replacement of the infected valve was performed. The Contegra graft was replaced by a homograft in 2 cases and by a new Contegra graft in 8 cases.

Table 2: Perioperative incidence of mortality and morbidity after Contegra graft implantation including follow-up events, during a maximum follow-up period of 12.7 years

Perioperative variables	
Renal impairments	3 (2.8%)
Reoperation because of bleeding	12 (11.3%)
Neurological event	2 (1.9%)
Mediastinitis	1 (0.9%)
Permanent pacemaker implantation	4 (3.8%)
Myocardial ischaemic event	6 (5.7%)
In-hospital mortality	3 (2.8%)
Cardiac cause of death	3 (2.8%)
Follow-up events	
Mortality	2 (1.9%)
Cardiac cause of death	2 (1.9%)
Infection of Contegra graft	12 (11.3%)
Reoperation because of Contegra graft infection	10 (9.4%)
Reoperation because of structural deterioration of Contegra graft	10 (9.4%)
Angioplasty of the distal anastomosis of Contegra graft	6 (5.7%)

According to Kaplan–Meier analysis, the rates of freedom from Contegra graft infection were 98.0% at 1 year, 88.% at 5 years and 82.0% at the end of the follow-up (12.7 years) (Fig. 2).

Univariate analysis suggested that time to infection was significantly associated with female gender (hazard ratio (HR) 0.19, $P = 0.042$), systemic-to-pulmonary shunt (HR 6.46, $P < 0.01$), hypothermia (HR 0.79, $P = 0.014$), postoperative renal insufficiency (HR 11.97, $P = 0.015$) and marginally with implantation of a permanent pacemaker during hospitalization (HR 5.29, $P = 0.075$).

Cox's proportional hazard model analysis indicated that the presence of tetralogy of Fallot significantly decreases the risk of infection by 94% ($P = 0.01$). Risk of infection for participants with systemic to pulmonary shunt is 64.71 times higher than those without ($P < 0.01$). In patients with hypothermia, each increase in temperature by 1°C was found to decrease the risk of infection by 23% ($P < 0.01$; Fig. 1). Finally, the *c*-statistic for the time-to-infection censored variable is estimated at 0.54 (P-value = 37.0%) for 'Fallot', at 0.36 (P-value = 3.5%) for 'central confection' and at 0.68 (P-value = 2.7%) for 'hypothermia'.

Following discharge, all patients underwent a bacterial endocarditis prophylaxis, as suggested by the American Heart Association. In this matter, the first-line antibiotic was Amoxicillin 50 mg/kg orally. In case of penicillin allergy with exanthema, we propose Cefuroxim-Axetil 50 mg/kg orally and in case of Penicillin allergy with urticaria and immediate reaction, we proposed Clindamycin

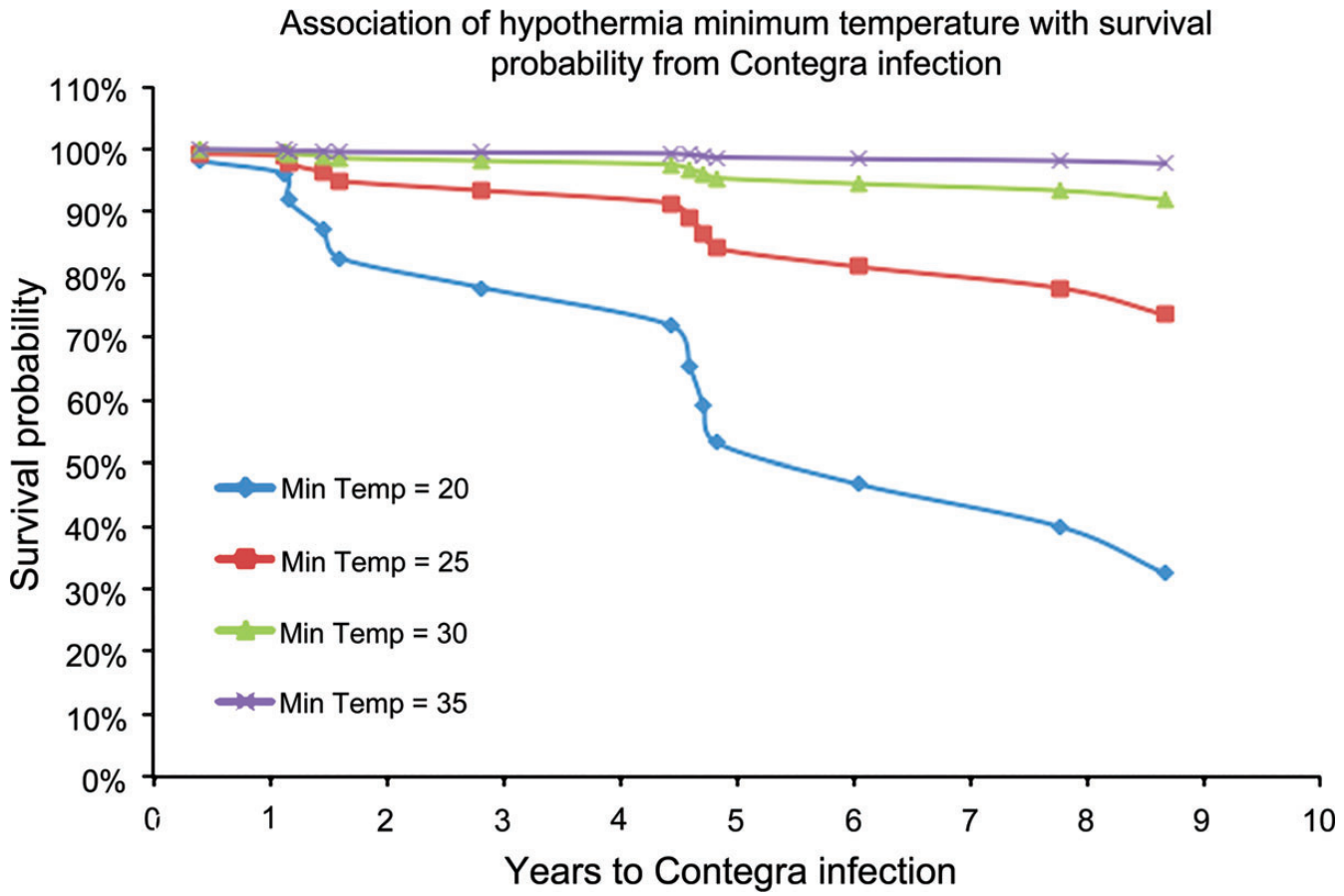

Figure 1: Association between grade of intraoperative hypothermia and time to Contegra graft infection. Each increase in temperature towards the normal core temperature decreases the hazard of infection by 23%.

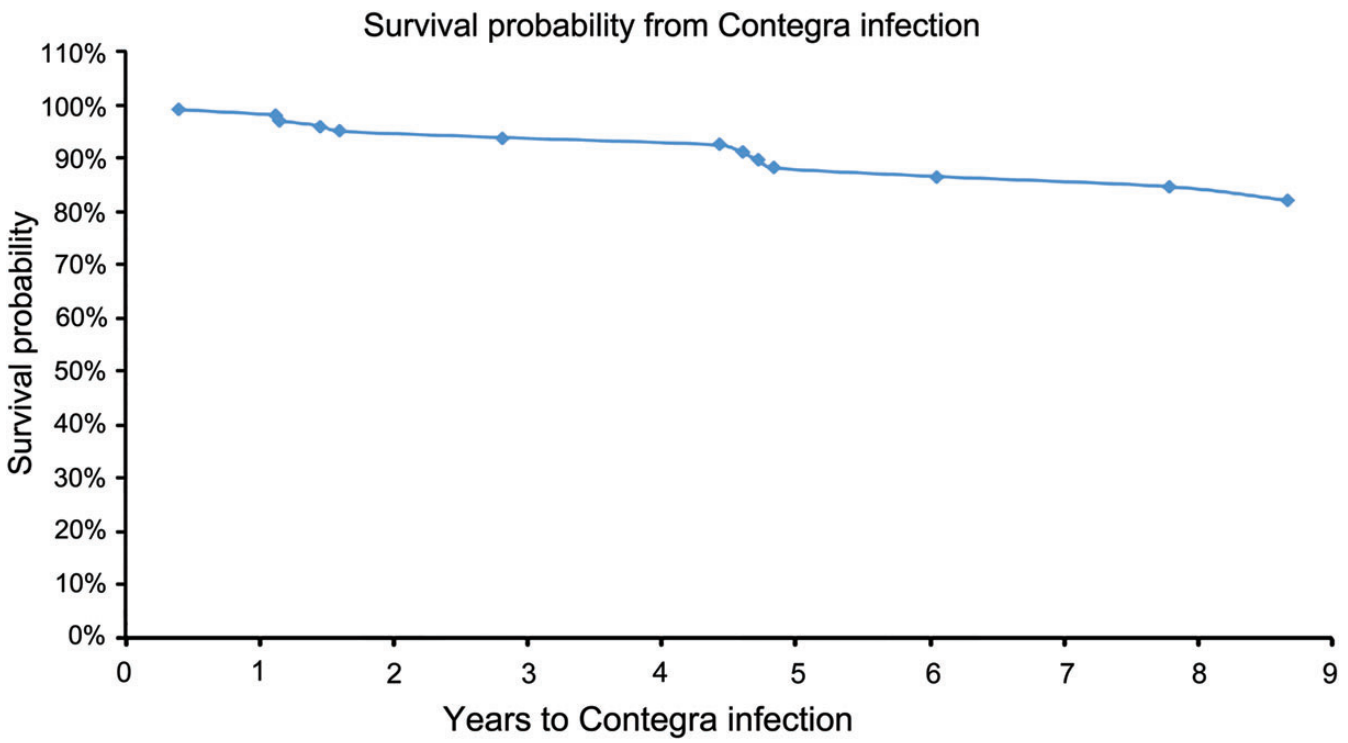

Figure 2: Kaplan–Meier evaluations for the probability of Contegra graft infection during the follow-up of 12.7 years. At the end of the follow-up, the cumulative risk for infection is estimated to be at 18%. Two peaks of infection rate are observed: the first is between the first and the second year and the second is between the fourth and the fifth year of the follow-up.

20 mg/kg orally. In the follow-up, general physicians found no association between the incidence of infection and invasive procedures such as dental intervention, respiratory tract procedures or gastrointestinal invasive diagnostic procedures.

Of the 12 patients with encodarditis, 1 was treated for septicaemia caused by an unknown pathogen 1 month preceding endocarditis and 2 patients prior to infection had dental treatment without prophylaxis. The germ identified in these 2 cases was streptococcus epidermidis. One patient underwent a dental extraction under prophylaxis (the germ isolated was staphylococcus saprophyticus). One subject was hospitalized due to mediastinitis. In addition, one subject was found to have *Streptococcus salivarius*, and another *Streptococcus viridans*, as the pathogen responsible for their endocarditis without any recent history of dental intervention or other infection, as determined by haemoculture. Fungal infection was not identified in any of these cases.

CONCLUSION

Since the introduction of the Contegra graft to daily clinical practice in 1999, it appeared that a reliable substitute for homografts in the reconstruction of the RVOT in complex congenital heart diseases had been found. Owing to its ready availability and wide range of sizes, the Contegra graft was, and still is, of great interest to clinically active cardiac surgeons. Controversy regarding graft durability in long- and mid-term time periods does exist. It seems that the age, size and extra-anatomical position of the graft are independent predictive factors for graft failure. Age and graft size show an inverse relationship and are actually an indication of the overgrowth of the graft [3, 11]. Graft overgrowth is indeed a subject of intensive debate in the recent literature. The fact is that the recent literature on the Contegra graft is extensive and, on first gaze, one would have the impression that every facet of its clinical implication in RVOT reconstruction was evaluated. However, with the exception of a few case reports [12, 13], no reports on Contegra graft infection currently exist. This lack of evidence may be due to the limited clinical signs and haemodynamic effects of the deteriorated valve on right ventricular function.

This report has evaluated the incidence and the predictive factors for Contegra graft infections for the first time. The incidence rate of graft infection was 11.3% (12 patients out of 106), and the risk rate of infection by the end of the first year after surgery was 1.0%. After this period, the risk rate of infection rose by 2.1% per year during the 12.7 years of follow-up.

It is well known that heart valve prostheses represent a strong risk factor for endocarditis in the postoperative period. The overall risk rate of endocarditis in patients who underwent aortic valve replacement ranges from 1 to 5% in the first year after implantation, and is ~1% per year thereafter. Risk factors such as gender, reoperation and mechanical prosthesis were identified. The risk of endocarditis linked to prosthesis emerges between 3 and 12 months after surgery and then a low constant risk rate of ~0.5% per year occurs thereafter [14].

In contrast, in the case of the Contegra graft, the probability of infection in the first year following implantation was 1.0%. Two peaks of infection occurrence were noted, the first of which is between the first and second years, when the probability of infection increases from 2.0 to 5.0%, and the second between the fourth and fifth years, when the probability of infection increases from 6.2 to 11.9% (Fig. 2). The results of the present investigation suggest that perioperative factors do not play a major role in this

pathology, since the incidence of Contegra infection in the first year is relatively low. However, gender, grade of hypothermia, performance of a central shunt and implantation of a permanent pacemaker during hospitalization were identified as independent predictive factors for Contegra graft infection. Surprisingly, factors such as ICU stay, intubation time and reintervention for bleeding were not identified as risk factors for Contegra graft infections. These results may be explained due to the relatively small cohort included in the study. The female gender as a predictive factor for prosthesis endocarditis is in contrast to recent results from other studies, where the female gender has been identified as a protective element for endocarditis. The development of native as well as prosthetic valve endocarditis was found to be two times higher in males compared with females [15, 16].

The influence of permanent pacemaker implantation and central shunt as predictive factors for infection is not surprising. The central shunt as a predictive factor is related to the theory of high velocity flow and turbulence in mechanical erosion of the endothelium [17, 18]. The same phenomenon of mechanical damage to the endothelium may be supposed in cases of pacemaker implantations. However, the influence of perioperative hypothermia on infection is less clear. It can be hypothesized that hypothermia in combination with cardiopulmonary bypass provokes endothelial apoptosis as well as altered haemodynamics of the pulmonary artery [19]. Endothelial damage may contribute to apposition of thrombi to the vessel wall; thrombi that later serve as an anchoring substrate for infection. Considering damage to the endothelium as a trigger factor for the development of endocarditis, it could be expected that the incidence of infection would peak in the early postoperative period, as this is the case in aortic valve prosthesis implantation [14]. In contrast, our results showed two peaks; the first was registered between the first and second postoperative years and the second between the fourth and fifth postoperative years (Fig. 2). The reason for this late appearance of infection is not clear, and it is likely that the cause is multifactorial. The initial endothelial damage that is either due to mechanical factors (e.g. pacemaker implantation), ischaemia (e.g. hypothermia) or turbulence (e.g. central shunt) contributes to the apposition of initial thrombi to the vessel wall. These thrombi may serve as an anchoring substrate for bacterial colonization. It should be noted that the low-flow, low-pressure conditions do not contribute to the wash-out of the thrombi apposition, as would be the case in the left-sided circulation. Consequently, it is probable that thrombi generated in the perioperative period, and fibrous appositions, would stay attached to the vessel wall for longer. Later, these thrombi may be strongly prone to becoming a host structure due to transient bacteraemia and may, therefore, be a cause for prosthesis infection.

This theory is suggested since a common factor identified in this study was mechanical, haemodynamical or chemical damage to the endothelium. To our knowledge, this is the first study to investigate Contegra graft infection over a long time period. With an incidence of 11.3%, Contegra graft infection is a serious complication that in the majority of cases required surgical intervention. Predictive factors were identified, but the exact mechanism of the Contegra endocarditis is still unclear. It is obvious that, for such a frequent complication, it is essential to explore the pathological mechanism in detail. In particular, the cause of the late appearance is not clear. Only further clinical and experimental research will provide a deeper insight to help prevent this complication.

Conflict of interest: none declared.

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