European Contegra Multicentre Study: 7-Year Results after 165 Valved Bovine Jugular Vein Graft Implantations

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Key words
- heart valve surgery
- right ventricular outflow tract
- bovine valved conduit
- long-term follow-up
- homograft

Abstract

Objective: The valved bovine conduit "Contegra" for RVOT reconstruction became available for clinical use within a 100% source data monitored and echo core lab controlled prospective European Multicentre Study, carried out from 1999 to 2006. We present the results of this study.

Methods: A total of 165 Contegras were implanted in 8 centres. The mean patient age was 3.9 years (2 days – 18 years, median 2.0). Total follow-up was 687 patient years. Diagnoses included: tetralogy of Fallot (64 patients, 39%), truncus arteriosus (50, 30%), double outlet right ventricle (16, 10%), aortic valve disease/Ross procedure (11, 7%), pulmonary valve atresia (10, 6%), transposition of the great arteries (10, 6%), 4 other malformations (2%). Previous procedures were: 82 patients (50%) – none; 37 (22%) – valved conduit implantation; 14 (8%) aortopulmonary shunt; 6 (4%) catheter intervention. Follow-up appointments which included standardised echocardiography investigations were scheduled at 1, 3, 6, and 12 months, then annually. We evaluated freedom from death, explantation, intervention, stenosis, insufficiency, and degeneration. Results were stratified by age, diagnosis group and conduit size.

Results: The 5-year freedom-from rates were: explantation – 90% (for patients aged 1 to 10 years) and 68% (for younger patients); endocarditis – over 92%; catheter intervention – 74% (patients with congenital malformations); stenosis – 75% and more (any group); insufficiency – 50% (12 and 14 mm diameter conduits); any event – 13% (patients under 1 year), 58% (1 to 10 years), 82% (> 10 years). Trace or mild insufficiency was a frequent, but not progressive finding. Mild calcification was detected in only 8 examinations.

Conclusions: The performance of the Contegra conduit compares well with that of homografts when used to reconstruct paediatric right ventricular outflow tracts.

Introduction

Homografts have been used for decades to replace pulmonary arteries [1]. They are often considered the gold standard [2] for the reconstruction of the right ventricular outflow tract (RVOT), but their limited availability, especially in small sizes [3], their surgical handling properties and their imperfect durability [4,5] has encouraged the search for alternatives. A glutaraldehyde-fixed bovine jugular vein with a naturally grown integrated trileaflet valve, the Contegra conduit, became available for implantation within a prospective European clinical multicentre trial that started in April 1999. A total of 165 non-adult recipients of a Contegra in the pulmonary position, operated on in 8 centres in 7 European countries, were enrolled. The accrual period lasted until January 2004; patients were monitored until August 2006. The conclusive findings obtained with this first, extensive, echo core lab controlled Contegra study include 1071 echos and a total of 687 observation years (mean: 4.2 years).

In the evaluation of this material, special emphasis was placed on various endpoints for a series of common subgroups in order to allow for comparisons with previously published results obtained with other kinds of conduits. Another focus was on insufficiency as a clinical endpoint and the course of observed insufficiency during the follow-up time.

received October 27, 2008

Bibliography
DOI 10.1055/s-0029-1185513
Thorac Cardiov Surg 2009; 57: 257–269 © Georg Thieme Verlag KG Stuttgart · New York · ISSN 0171-6425

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Table 1 Patient and outcome summary by patient age at implantation.

Age group		0–1 year n = 57 (34.5%)	1–10 years n = 86 (52.1%)	10–18 years n = 22 (13.3%)
Sex	males	n = 25 (43.9%)	m = 45 (52.3%)	m = 8 (36.4%)
	females	n = 32 (56.1%)	f = 41 (47.7%)	f = 14 (63.6%)
Age at implantation [years]	median	0.14 years	2.74 years	13.7 years
	average	0.26 ± 0.27	3.7 ± 2.5	13.8 ± 5.7
	range	0 to 0.9	1.0 to 9.8	10.4 to 18.5
Main diagnoses	TOF	16 (28.1%)	32 (37.2%)	16 (72.7%)
	TAC	29 (50.9%)	19 (22.1%)	2 (9.1%)
	TGA	0 (0%)	10 (11.6%)	0
	PV atresia	2 (3.5%)	6 (7.0%)	2 (9.1%)
	others	2 (3.5%)	2 (2.3%)	0
	DORV	5 (8.8%)	11 (12.8%)	0
	PA stenosis	0 (0%)	0	0
	Ross	3 (5.3%)	6 (7.0%)	2 (9.1%)
Previous operations/interventions	homograft	1 (1.8%)	12 (14.0%)	4 (18.2%)
	porcine conduits	3 (5.3%)	16 (18.6%)	1 (4.5%)
	primary operations	46 (80.7%)	31 (36.0%)	5 (22.7%)
	extracardiac repair	1 (1.8%)	11 (12.8%)	2 (9.1%)
	intracardiac repairs	4 (7.0%)	12 (14.0%)	10 (45.5%)
	intervention	1 (1.8%)	4 (4.7%)	0
Contegra diameter [mm: no. of grafts (%)]	12	46 (80.1%)	6 (7.0%)	0
	14	8 (14.0%)	23 (26.7%)	0
	16	1 (1.8%)	24 (27.9%)	0
	18	0	17 (19.8%)	3 (13.6%)
	20	0	8 (9.3%)	7 (31.8%)
	22	2 (3.5%)	8 (9.3%)	12 (54.5%)
Follow-up [years]	mean; median	3.4 ± 2.5; 3.9	4.4 ± 2.2; 5.5	5.1 ± 1.8; 5.5
	range; sum	0 to 7.0; 193.6	0 to 7.1; 379.4	0.7 to 7.0; 113.7
Survivors	n (%)	43 (75.4%)	79 (91.9%)	20 (90.9%)
Explanted	n (%)	15 (26.3%)	10 (11.6%)	2 (9.1%)
Main reason for explantation	dilatation	1 (1.8%)	0	0
	endocarditis	2 (3.5%)	1 (1.2%)	1 (4.5%)
	outgrowth	1 (1.8%)	0	0
	PPA stenosis	6 (10.5%)	4 (4.7%)	1 (4.5%)
	technical	1 (1.8%)	4 (4.7%)	0
	thrombus	1 (1.8%)	1 (1.2%)	0
	valve degeneration	3 (5.3%)	0	0

TOF = tetralogy of Fallot; TAC = truncus arteriosus communis; TGA = transposition of the great arteries; PA = pulmonary artery; DORV = double outlet right ventricle; PPA stenosis: stenosis of peripheral pulmonary arteries

Patients and Methods

The 165 patients were included after approval by the local ethics committees and individual written informed consent of the parents and the patients, if appropriate.

The 8 centres treated between 6 and 60 patients. The patients' mean age was 3.9 years (2 days – 18 years, median 2.0 years); 13.9% were neonates, 34.5% under 1 year of age, and 86.7% under 10 years. 77 (46.7%) were females, 88 (53.3%) males.

Patients had the following malformations: tetralogy of Fallot (64 patients, 39%, mean age 5.6 years), truncus arteriosus communis (50, 30%, mean age 2.1 years), double outlet right ventricle (16, 10%, mean age 3.1 years), aortic valve dysfunction (11, 7%, mean age 4.2 years; among them 5 patients with complex aortic valve diseases, 4 with mixed aortic valve lesions and 2 with predominant stenoses) treated by Ross procedure, pulmonary valve atresia (10, 6%, mean age 3.9 years), transposition of the great arteries (10, 6%, mean age 3.7 years), 4 other congenital malformations (2%, mean age 0.9 years). For 82 patients, the conduit implantation was the primary procedure; in 37 (22%) patients, previously implanted valved conduits were replaced (20 xenografts and 17 homografts); 20 (12.1%) had previous aortopulmonary shunts, 6 (4%) had previous catheter interventions.

The size of the implanted Contegras was 12, 14, 16, 18, 20, 22 mm in 52, 31, 26, 20, 15, 21 cases, respectively, so that half of the patients received the smallest sizes of 12 and 14 mm. **Tables 1** to **3** show the details for the analysed subgroups.

Follow-up investigations (including standardised echo examinations) were scheduled at discharge, at 1, 3, 6, 12 months after discharge, then annually.

The echo registration tapes underwent a central evaluation (N. Weissman, Echo Core Lab, Cardiovascular Research Institute, Washington, DC, USA). The intervals that determine freedom from dysfunction result from the core lab's findings. Explanted conduits were sent to a central pathology institute (A. Farb, Armed Forces Institute of Pathology, Washington DC, USA) for histopathological examination. Blood samples taken at every examination were part of the initial protocol; the specimens were sent for examination to a central core laboratory.

Table 2 Patient and outcome summary by kind of operation.

Implantation	No Ross procedure n = 154 (93.3%)		Ross procedure n = 11 (6.7%)	
Sex	75 males	(48.7%)	3 males	(27.3%)
	79 females	(51.3%)	8 females	(72.7%)
Patient age at implantation [years]	median 1.9	average 3.8 ± 4.7	median 2.3	average 4.2 ± 4.0
	range 2 days to 18.5 years		range 0.3 to 12.2	
	under 1 year	54	under 1 year	1
	under 10 years	134	under 10 years	9
Main diagnoses	TOF	64 (41.6%)	11 aortic valve pathology (100%)	
	TAC	50 (32.5%)		
	DORV	16 (10.4%)		
	TGA	10 (6.5%)		
	PA atresia	10 (6.5%)		
	others	4 (2.6%)		
Previous operations	homografts	17 (11.0%)	11 primary operations (100%)	
	xenografts	20 (13.0%)		
	extracardiac repairs	14 (9.1%)		
	intracardiac repairs	26 (16.9%)		
	interventions	6 (3.9%)		
	primary operations	71 (46.1%)		
Contegra diameter [mm: no. of grafts (%)]	12	51 (33.1%)	12	1 (9.1%)
	14	30 (19.5%)	14	1 (9.1%)
	16	22 (14.3%)	16	3 (27.3%)
	18	17 (11.0%)	18	3 (27.3%)
	20	15 (9.7%)	20	0
	22	19 (12.3%)	22	3 (27.3%)
Follow-up [years]	mean; median	4.2 ± 2.4; 5.5	mean; median	3.5 ± 2.2; 4.0
	range; sum	0–7.1; 648.3	range; sum	0–6.0; 38.5
Survivors	n (%)	134 (87.0%)	n (%)	8 (72.7%)
Explanted	n (%)	27 (17.5%)	n (%)	0
Reason for explantation	dilatation	1 (0.6%)		
	endocarditis	4 (2.6%)		
	outgrowth	1 (0.6%)		
	PPA stenosis	11 (7.1%)		
	technical	5 (3.2%)		
	thrombus	2 (1.3%)		
	valve degeneration	3 (1.9%)		

Implantation technique

Prior to tailoring and implantation, the Contegras were rinsed according to the manufacturer's recommendations (swirled gently for 10 minutes in 1 litre of saline solution, repeated 3 times with fresh saline solution each time) in order to remove the glutaraldehyde in which the device was stored before implantation. The tubular segments of the vein were then tailored to fit proximally onto the ventricle (forming a hood onto the right ventricular outflow tract incisions), and distally onto the pulmonary artery or its branches. This technique has been illustrated previously [6]; the benefits of such technical modifications have been analysed extensively [7]. By far the most proximal anastomoses were extra-anatomic, requiring a special incision of the right ventricular outflow tract. In contrast, the proximal conduit anastomoses in procedures such as the Ross operation where the pulmonary valve was placed in a more physiologic position were considered anatomical anastomoses. Augmentation plasties of both pulmonary artery branches were repeatedly performed with the vein section distal from the valve. Virtually all sutures were continuous, and the use of pledgets was registered only in one case.

Eleven Contegras were implanted within a Ross procedure, 44 were classified as orthotopic implantations, 110 as non-orthotopic. Proximal trimming was oblique in 141 patients (85.5%), transverse in 20 (12.1%) and longitudinal in 4 patients (2.4%). Distal trimming was transverse in 115 patients (69.7%), oblique in 47 (28.5%) and longitudinal in 1 (1.8%). Measurement of the length of the tubular conduit segment on either side of the valve after tailoring was part of the protocol. The shortest tubular segment on either side of the valve was 10 mm or longer in 102 (61.8%) patients. Considering the absence of a vessel wall proximal from the valve in homografts, at least in all of these patients additional material would have been necessary for analogue implantation techniques. The average length of the shortest tubular segment in these 61.8% of patients was 31 mm, far beyond the reach of native homografts.

Concomitant procedures

In 154 patients (93.3%), other procedures were performed in addition to the conduit implantation. Ventricular septal defects were repaired in 95 patients (57.6%), atrial septal defects were closed in 48 patients (26.7%). Several patients required reconstruction of the pulmonary arteries (PA) in various segments: the PA trunk in 3 patients, the bifurcation in 7, the left PA in 23, the right PA in 19. Twenty aortopulmonary shunts were closed. In 11 patients, a patent ductus arteriosus was closed. The aortic valve, ascending aorta or the aortic arch were repaired in 11 patients.

Table 3 Patient and outcome summary by Contegra size group.

Size group (diameter at implantation)		12 or 14 mm n = 83 (50.3%)	16 or 18 mm n = 45 (27.3%)	20 or 22 mm n = 37 (22.4%)
Sex	males	n = 40 (48.2%)	m = 25 (55.6%)	m = 13 (35.1%)
	females	n = 43 (51.8%)	f = 20 (44.4%)	f = 24 (64.9%)
Age at implantation [years]	median	0.45 years	3.2 years	10.4 years
	average	0.83 ± 1.1	4.2 ± 2.9	10.2 ± 4.8
	range	0 to 6.5	0.9 to 14.7	0.1 to 18.5
	under 1 year	5 (18.5%)	1 (0.8%)	0
	under 10 years	22 (95.7%)	13 (10.9%)	3 (2.5%)
Main diagnoses	TOF	29 (34.9%)	14 (31.1%)	16 (72.7%)
	TAC	34 (41.0%)	8 (17.8%)	2 (9.1%)
	TGA	1 (1.2%)	8 (17.8%)	0
	PV atresia	5 (6.0%)	4 (8.9%)	2 (9.1%)
	others	3 (3.6%)	1 (2.2%)	0
	DORV	9 (10.8%)	4 (8.9%)	3 (8.1)
	PA stenosis	0	0	0
	Ross	2 (2.4%)	6 (13.3%)	2 (9.1%)
Previous operations/interventions	homografts	3 (3.6%)	5 (11.1%)	9 (24.3%)
	porcine conduits	10 (12.0%)	7 (15.6%)	3 (8.1%)
	primary operations	55 (66.3%)	16 (35.6%)	11 (29.7%)
	extracardiac repairs	5 (6.0%)	6 (13.3%)	3 (8.1%)
	intracardiac repairs	7 (8.4%)	8 (17.8%)	10 (45.5%)
	Interventions	3 (3.6%)	3 (6.7%)	0
Contegra diameter [mm: no. of grafts (%)]		12: 52 (62.7%)	16: 25 (55.6%)	20: 15 (40.5%)
		14: 31 (37.3%)	18: 20 (44.4%)	22: 22 (59.5%)
Follow-up [years]	mean; median	3.7 ± 2.5; 4.1	4.6 ± 2.1; 5.5	4.6 ± 2.1; 5.6
	range; sum	0–7.0; 307.9	0–7.1; 207.1	0–7.0; 171.8
Survivors	n (%)	67 (80.7%)	42 (93.3%)	33 (89.2%)
Explanted	n (%)	21 (25.3%)	3 (6.7%)	3 (8.1%)
Main reason for explantation	dilatation	1 (1.2%)	0	0
	endocarditis	3 (3.6%)	0	1 (2.7%)
	outgrowth	1 (1.2%)	0	0
	PPA stenosis	8 (9.5%)	2 (4.4%)	1 (2.7%)
	technical	4 (4.8%)	0	1 (2.7%)
	thrombus	1 (1.2%)	1 (2.2%)	0
	valve degeneration	3 (3.6%)	0	0

Statistical evaluation

Data was 100% source document verified, collected by the sponsor and subsequently entered into a central Microsoft Access database; SPSS 15.0 (SPSS Inc., Chicago, IL, USA) was used for evaluation. The sponsor did not influence the evaluation. Kaplan-Meier curves on freedom from various events are given with standard errors; mean values are shown with 95% confidence intervals. Cox regression models were formed to identify risk factors for the various endpoints; for details, see the Results section.

Endpoint definitions

Survival

Death for any reason.

Explantation

Any reason for explantation is included in the relevant evaluation.

Stenosis

Often it was not possible to differentiate exactly between stenoses in the peripheral anastomoses area and native pulmonary artery branch stenoses. So we included gradients over any region between the right ventricle and the pulmonary artery branches in our analyses. The time between conduit implantation and the first appearance of a velocity corresponding to a peak gradient of 50 mmHg or more was considered, independent of the region and kind of measurement: either transvalvular pulse wave Doppler velocity or continuous wave Doppler velocity, and including proximal and peripheral pulmonary artery anastomoses as well as anastomoses of either of the pulmonary artery branches. For patients whose conduits were explanted for stenosis, but who had a gradient lower than 50 mmHg at their last regular visit (n = 9), the event "gradient of at least 50 mmHg" was assumed to have happened in the middle of the interval between last visit and explantation.

Insufficiency

Based on the level of diastolic flow reversal and the diameter of the regurgitation jet in relation to the annular width, regurgitation was scored as absent, mild, moderate or severe. All patients with insufficiency grades classified as "moderate", regardless of the aetiology, were considered to have reached the endpoint "insufficiency". Two Contegras which were explanted for reasons of insufficiency had been classified as less than moderately insufficient at the last visit; as with analogous stenotic conduits, we considered the "moderate" insufficiency to have begun exactly between last visit and explantation. In order to describe the development of all the observed insufficiency grades (in the Results section), we assigned the value zero to absent insufficiency, 1 to mild, 2 to moderate and 3 to severe insufficiency.

Stenosis and insufficiency

At least moderate insufficiency or gradient of or above 50 mmHg, whichever was observed first, were the endpoints for this evaluation.

Endocarditis

Onset of endocarditis was based on clinical evidence, as reported by the investigators.

Intervention

All interventions in the right ventricular outflow tract and any pulmonary artery (branch), regardless of the reason, were included in this category. The indication for an intervention was not homogeneous over time and institution. None of the Contegra recipients in this study had received a transcatheter implantable pulmonary valve [8] before termination of the study.

All RVOT-related adverse events

This endpoint includes all of the above-mentioned adverse events. For each patient, the first of any adverse events terminated the event-free time.

Results

Follow-up completeness

A total of 10 patients from 2 small volume centres were lost to follow-up due to lack of an ability to carry out the required follow-up visits; thus, the completeness of patient-follow-up is 94%. According to the protocol, 1204 echos should have been performed (considering all scheduled intervals). 133 of them are missing, resulting in an echo examination completeness of 89%. The last expected study echo of 85% of the patients was available for the evaluation. At study termination, the survival status and freedom from explantation were known for all patients except the 10 patients referred to above

Survival (Fig. 1)

Causes of death. 23 patients did not survive until the end of the study, corresponding to a survival rate of 86.5 (± 2.7)% after 5 years. 12 patients died from (unspecified) heart failure or low cardiac output, 3 from right heart failure (one of them after injury of the right coronary artery). The causes of death of the other patients were aortic valve incompetence, a pulmonary hypertensive crisis, pneumonia, aneurysm at the proximal conduit anastomosis, sepsis, pulmonary bleeding, cerebral oedema and sudden death. 18 of the 23 patients died in the first postoperative month, the other 5 within the first year.

- *Expected versus observed mortality:* According to the RACHS-1 risk classification [9], the hospital death of 19 patients was to be expected for the study population.
- *Conduit-related deaths:* 2 deaths were considered conduit-related: one was a patient with heart failure, whose moderate conduit insufficiency contributed to exhausting the already damaged ventricle; the other patient had an aneurysm at the proximal conduit anastomosis.
- *Univariate risk factors:* Age under 1 year was a univariate risk factor for death ($p = 0.017$): 10 of 57 (17.5%) in this youngest patient group died within the first month, 14 (24.6%) within the first year after implantation.

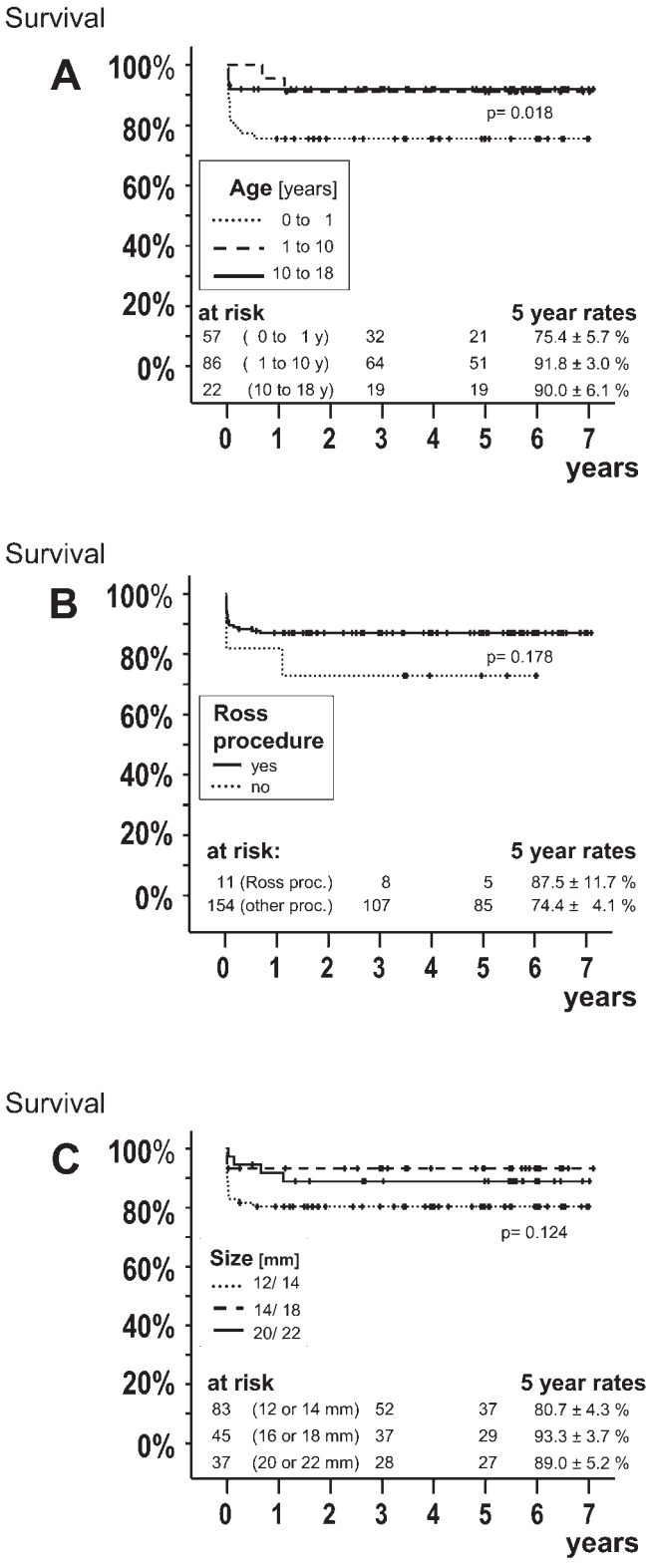


Fig. 1 A to **C** Survival after conduit implantation, by age (**A**), procedure (**B**) and conduit size (**C**).

Endocarditis

There were 5 cases of endocarditis in patients from 2 centres noted throughout the entire follow-up. The involved Contegras were explanted at 2, 2, 17, 26 and 48 months after implantation, respectively. Fig. 2 shows the interval between onset of endo-

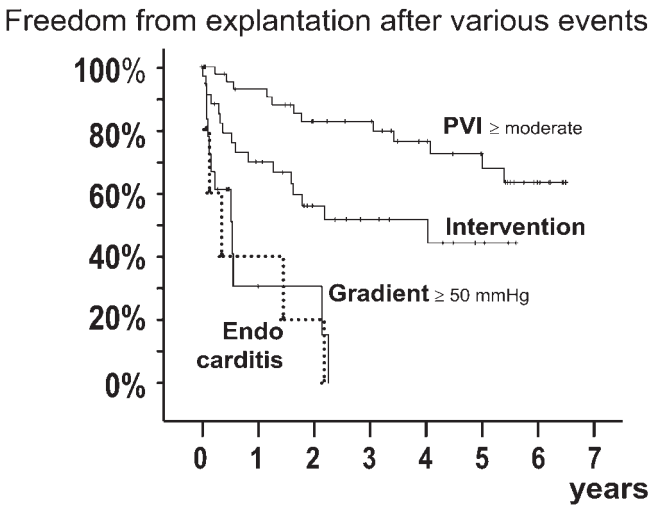


Fig. 2 Interval between various events and conduit explantation.

carditis and explantation. Freedom from endocarditis at 7 years was 92.4 ± 3.7% in recipients of 12- and 14-mm conduits, 100% in 18- and 20-mm conduit recipients, 96.3% in patients with a 20- or 22-mm Contegra. In addition to the aforementioned 5 cases, two cases of aortic valve endocarditis without involvement of the Contegra were noted.

Insufficiency (Fig. 3)

- *Using insufficiency as an endpoint for a Kaplan-Meier analysis:* Using the endpoint "insufficiency" in a Kaplan-Meier (survival) curve is controversially discussed among investigators, because some of the Contegra recipients show a decrease in insufficiency over time. One single measurement of moderate insufficiency is a less terminal event than death. We performed the evaluation so as to remain compatible with other reports, but we do consider other illustrations to be clinically more relevant.
- *Alternative illustrations of insufficiency observed over time:* One common way to show the insufficiency course is by stacked bars, as in **Fig. 3D**. Displaying the development by forming mean values and confidence limits from the semiquantitative grading values is another way which reflects the clinical reality better than a survival curve. **Fig. 3E** shows that patients with initially elevated insufficiency grades tend towards normalisation in the later course. The overall summary per examination interval (**Fig. 3F**) demonstrates a rather constant grade of insufficiency over time: a nearly flat trend can be observed for both groups of conduits – those which were later explanted and those which were still functioning when the study was terminated.

  Another approach to get an overview of the development of insufficiency over time is to assign the above-mentioned numbers to the relevant insufficiency grades and to look at the annual individual differences at each examination compared to the result of one year ago. The average value for this annual change – including all performed examinations with available insufficiency determinations – was − 0.01 insufficiency points, indicating an almost constant and not a growing insufficiency.
- *Clinical consequences of insufficiency observations:* Postoperative insufficiency measurements showing the grade "moderate" or more were noted on at least one occasion in 45 patients. **Fig. 2** suggests this "endpoint" is the weakest of all with regard to the urgency of conduit exchanges after the first appearance: 62% of all conduits remained in place for more than 6 years after the first detection of a moderate insufficiency. Seven patients had a severe insufficiency found in 10 examinations. The device of one of these patients was explanted 2 years after the first severe insufficiency echo finding. In 5 of the remaining 6 patients, the insufficiency grade returned to milder grades up to 6 years later.

Stenosis (Fig. 4)

Twenty-one patients had a total of 22 echo examinations in which peak gradients of 50 mmHg or more were observed in any region of the conduit or the peripheral pulmonary arteries.

- *Location of observed stenoses:* The protocol included a pulse wave Doppler measurement of the transvalvular gradient (with a more exact spatial resolution) and, additionally, a continuous wave Doppler measurement (with a less distinct spatial resolution) of the maximal gradient near the valve. Since the Contegra high profile valve and the peripheral pulmonary artery branches were often in a close relationship, we could interpret a continuous-wave measured gradient of above 50 mmHg in combination with a pulse-wave measured gradient of less than 40 mmHg as a predominantly extravalvular gradient. This was the case in all but one of the examinations; the only time when a transvalvular Doppler gradient of more than 50 mmHg was found was in a patient who had a thrombus within the Contegra.
- *Average course:* The development of transvalvular stenoses (as described above) is not a frequent or typical issue for Contegras: the course of the average transvalvular peak gradients is shown in **Fig. 4D**.
- *Clinical consequences of stenosis observation:* The freedom from Contegra explantation after the first detection of a gradient ≥ 50 mmHg is shown in **Fig. 2**: at 2.5 years, all patients in whom such a gradient was detected had their conduits exchanged. If gradients do develop, they are mainly due to intimal hyperproliferation of the native vessel at the distal conduit anastomosis.

Catheter-based interventions (Fig. 5)

Fifty-eight catheter-based interventions were performed in 28 patients during the follow-up. 14 patients had 1 intervention, 10 had 2. Two patients each had 3 and 4 interventions. 29 interventions (50% of all interventions) were carried out for supravalvular stenoses within the peripheral anastomosis of the Contegra after a mean implantation period of 1.8 ± 1.4 years. Twenty-six interventions (45%) were due to stenoses of the pulmonary artery branches distal from the anastomoses with the Contegra; they had virtually no relationship to the conduit, but were included in the evaluation to maintain comparability with the literature and to avoid ambiguity. These interventions for peripheral pulmonary artery stenoses took place at a mean interval of 2.4 ± 1.7 years after implantation. Three cases of interventions on the proximal conduit anastomosis account for 5% of all interventions; they were performed 4.0 ± 1.9 years after implantation. 5 years after the first intervention, 56% of the Contegras that had interventions were explanted (**Fig. 2**).

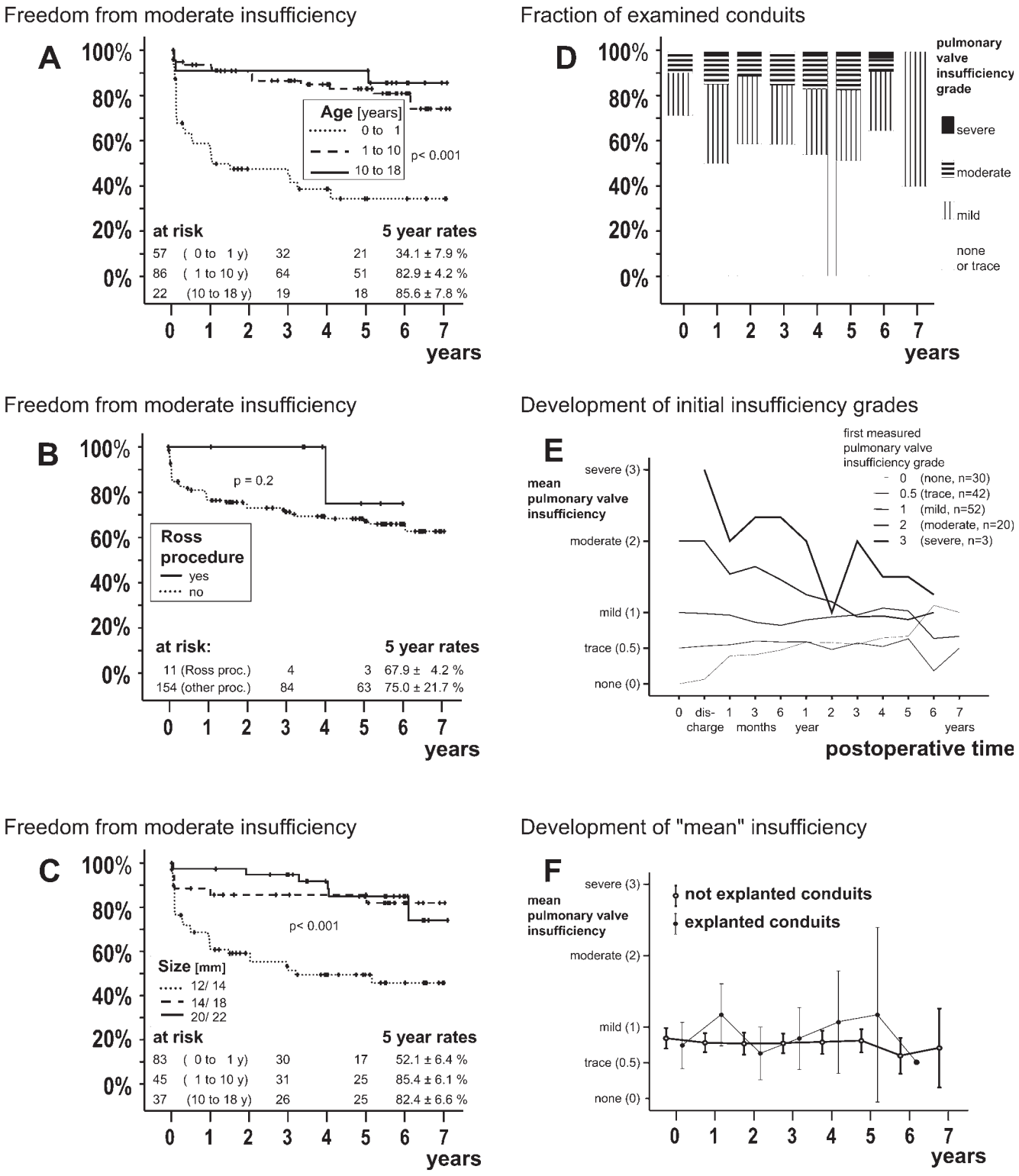


Fig. 3 A to **F** Insufficiency. **A** Freedom from the first detection of at least moderate insufficiency, by age (**A**), procedure (**B**) and conduit size (**C**). **D** Fraction of insufficiency grades at the annual examinations. **E** Development of initial insufficiency grades. **F** Development of the average valve insufficiency grade, according to the devices that were later explanted and those which were not explanted.

Dilatation

One of the Contegras was explanted for dilatation after 2.6 years. A general trend towards dilatation cannot be deduced from ▶ **Fig. 6**.

Calcification

In 7 patients, mild calcifications were noted in 9 (0.8%) of the 1086 performed echo examinations. 70.6% of the echos showed no calcification, the rest were classified as “unable to assess”. No calcification grades higher than “mild” were observed throughout the whole study period.

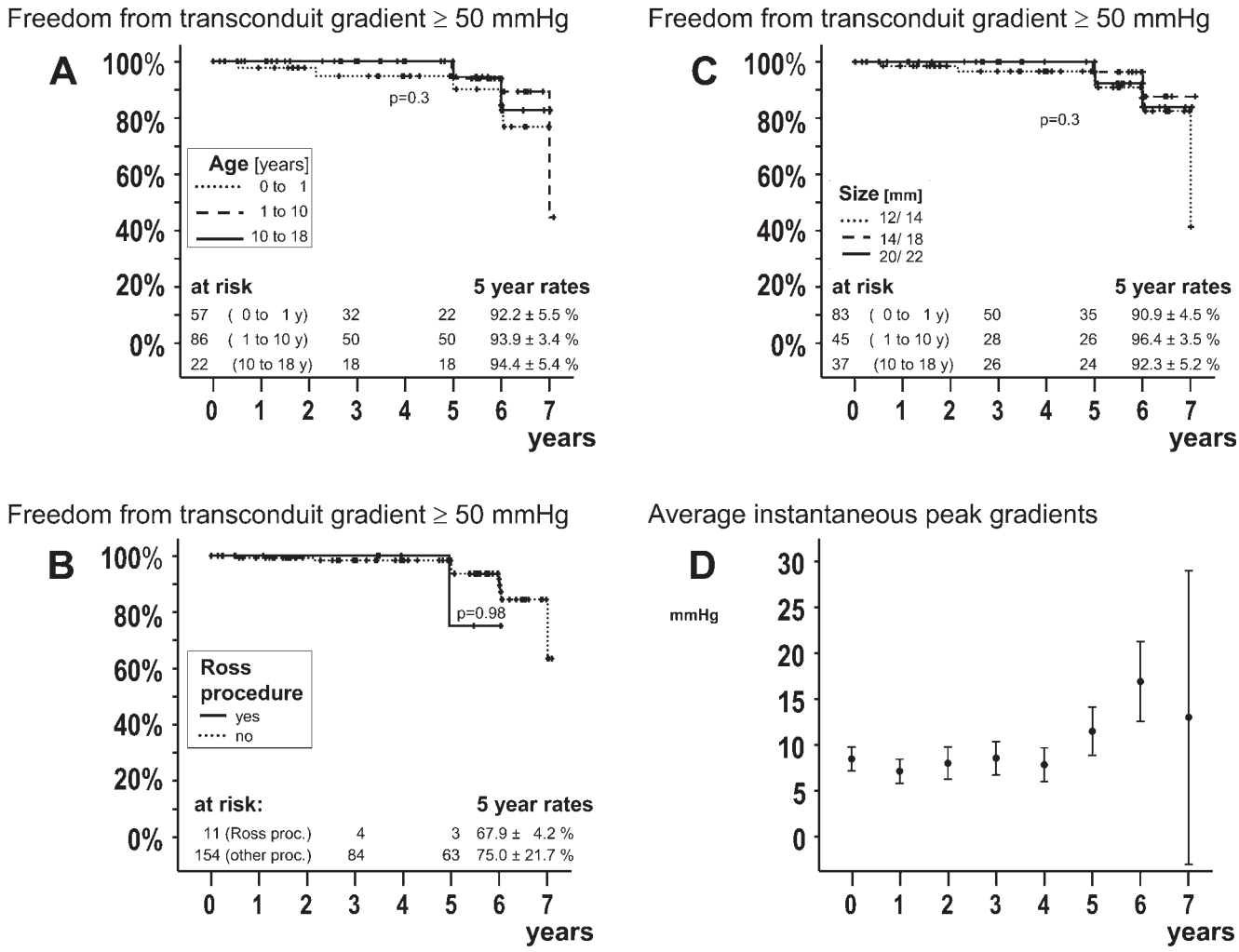


Fig. 4 A to **D** Stenosis (defined as the first measurement of a gradient of 50 mmHg or more). **A** Freedom from stenosis, by age (**A**), procedure (**B**) and conduit size (**C**). **D** Transvalvular peak gradient development.

In one patient, the calcification was observed after endocarditis, and the conduit was exchanged after 4 years. Another calcification was seen in a patient who had received his Contegra at 3 months; it was explanted after 5.5 years. One patient with observed calcifications (at 0.5 years) has had plasties of both PA branches with pericardial patches as concomitant procedures. The remaining 4 patients have had their conduits for more than 5 years; 2 of them showed no more signs of calcification in subsequent examinations.

All RVOT-related events

Fig. 7 characterises the problematic patient as a patient under 1 year of age (**A**) with a congenital malformation (**B**) that has conduit diameter less than 15 mm (**C**). The clinical impact of the applied definitions is limited, especially the insufficiency statement accounts for most of the failure-defined events, although the majority of the patients continued to keep their conduits for more than 6 years after the initial "failure" statement. 75 patients had some kind of failure by the end of the observation interval, while 90 patients (55%) had no complications related to their reconstructed RVOT.

Explantation (Fig. 8)

At the end of the observation phase, 27 conduits were explanted, corresponding to a 74.0 ± 0.5% freedom from explantation at 7 years. Stenoses of the peripheral pulmonary arteries were the reason for the explantation of 10 Contegras (37.0% of all explanted ones) after 2.6 ± 1.6 years. Technical reasons (accidental valve cusp stenting, conduit distortion, muscular RVOT stenosis, aneurysm of the right ventricular outflow tract, access facilitation to a stenotic pulmonary artery branch) accounted for other 5 explants (18.5%) after 5.11 ± 0.9 years. 5 Contegras (18.5%) were explanted for endocarditis after 4.1 ± 1.7 years, 3 (11.1%) were explanted for valvular degeneration after 4.2 ± 2.8 years, 2 (7.4%) for thrombus formation after 0.6 ± 0.8 years, and 1 for dilatation at 2.6 years; 1 Contegra which was still working well was explanted for outgrowth at 5 years after implantation.

Risk factor analysis

We formed a Cox regression model using the stepwise logistic method, with a p value of 0.1 or less as an inclusion threshold; factors with p values of 0.05 or less were considered statistically significant. We evaluated the illustrated factors (Ross operation vs. congenital malformation correction, age group, Contegra diameter group) as well as patient gender and site implantation

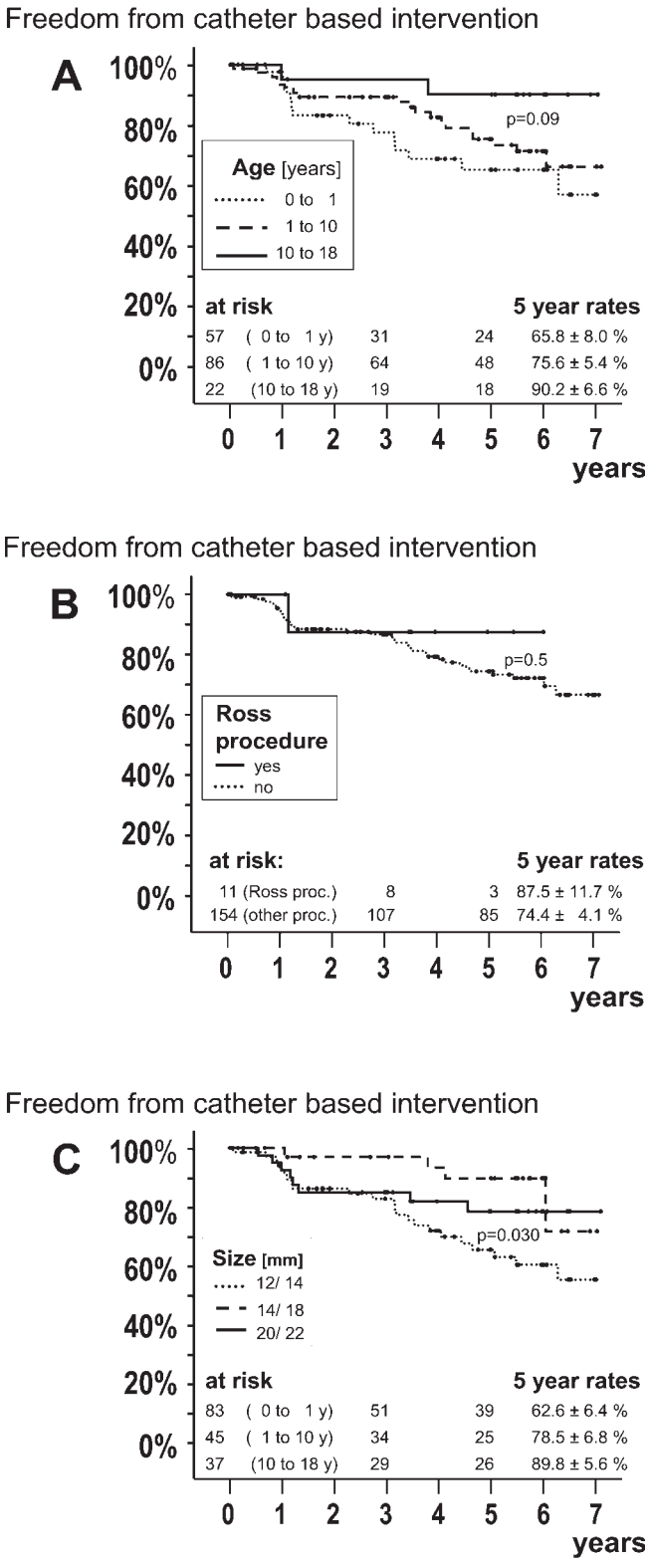


Fig. 5 A to **C** Freedom from catheter based intervention, by age (**A**), procedure (**B**) and conduit size (**C**).

volume group. In contrast to the two sites with > 30 implantations, the sites with fewer than 20 implantations were classified as low implantation volume centres. All factors described as significant in this paragraph were confirmed by forwards and backwards analysis.

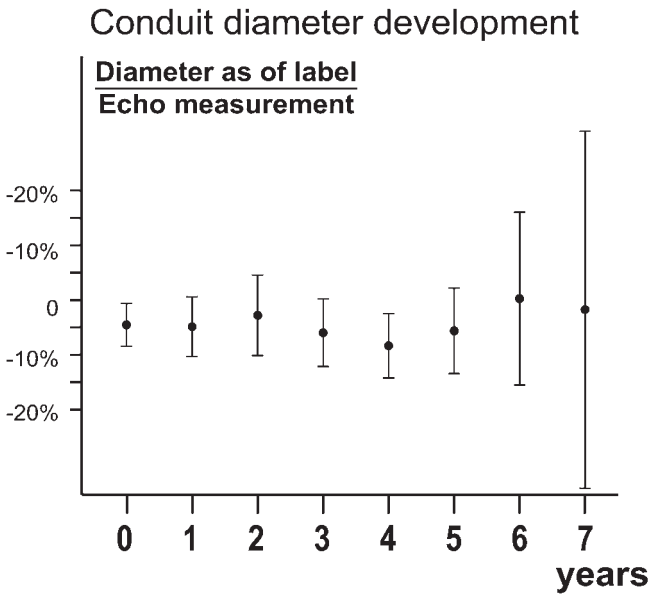
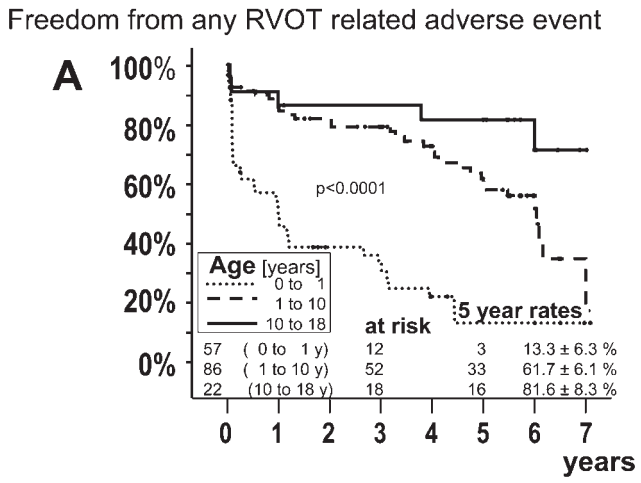


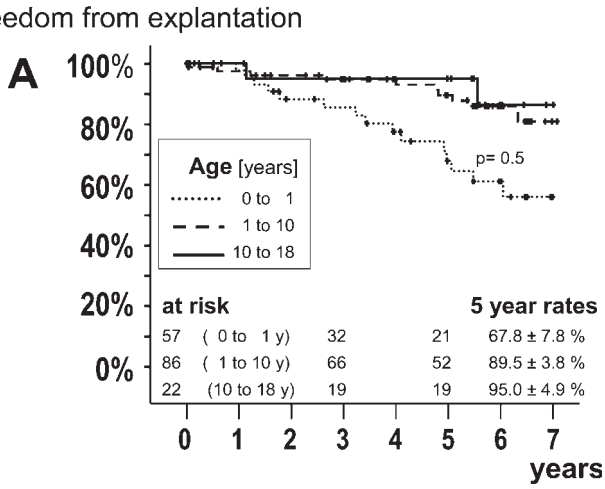
Fig. 6 Conduit diameter development, based on conduit diameter at implantation.

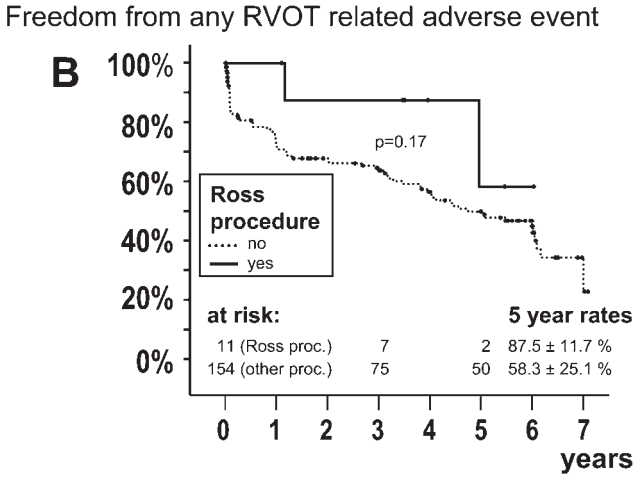
Diameters below 15 mm ($p = 0.006$) and diameters between 16 and 18 mm ($p = 0.025$, OR = 4) were risk factors for earlier explantation. Age under 1 year ($p = 0.007$) and age from 1 to 10 years ($p = 0.037$, OR = 6.0) were risk factors for insufficiency. For stenosis, none of the entered factors was significant. Small volume sites were more prone to require catheter-based interventions: freedom from the first intervention was significantly shorter at small inclusion volume sites ($p = 0.003$, OR = 2.9) and in patients with conduits < 15 mm ($p = 0.007$). For the first appearance of any of all described adverse events, again age under 1 year ($p = 0.005$) and age from 1 to 10 years ($p = 0.06$, OR = 6.1) were risk factors.

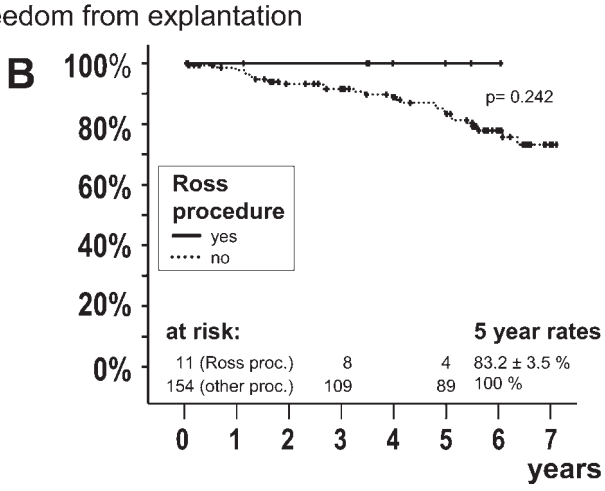
Discussion

The need for an available [10] and durable [11, 12] alternative to homografts drove the investigators to use the bovine jugular vein. The company VenPro (Irvine, CA, USA) suggested use of a bovine valved conduit in 1999 and began to provide it for implantation under the European Multicentre study protocol. So this study summarises the longest experience with this device. Later on, VenPro was purchased by Medtronic, and the device was sold under its current name. The sum of results obtained by the pioneering investigators of this study confirms the decision to implant the Contegra, although one of the investigators has returned to implanting homografts after his first experience with the bovine jugular vein graft. Stating an "equivalence to homografts" in a statistically strict sense requires a proper definition of equivalence margins and (possibly) a prospective randomised trial; it cannot be a result of this first observational study that was designed to achieve approval for regular use of the device. The limited availability of homografts (and the lack of very small and very large Contegras) are some of the obstacles that have hindered such a trial until today.









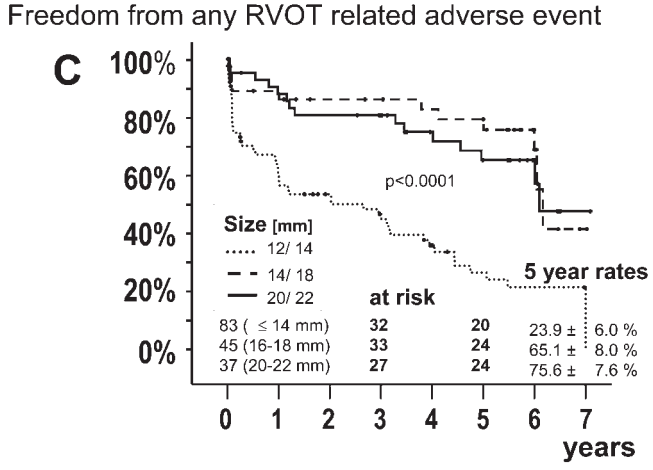


Fig. 7 A to **C** Freedom from any RVOT-related adverse event, by age (**A**), procedure (**B**) and conduit size (**C**).

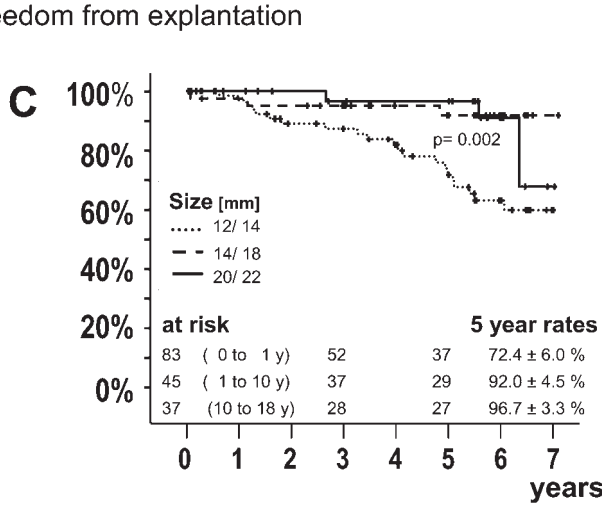


Fig. 8 A to **C** Freedom from explantation, by age (**A**), procedure (**B**) and conduit size (**C**).

Limitations

No randomisation with an alternative device such as the homograft was performed. The fact that 2 small volume centres with a total of 10 included patients were not able to perform the scheduled follow-up visits reduces the amount of data available for evaluation, but represents no structural distortion. The abundant, core lab reviewed echo data is an advantage of this study, but magnetic resonance imaging might have resulted in even more reliable information on regurgitation quantities and ventricle volumes. Last, but not least, this patient population in-

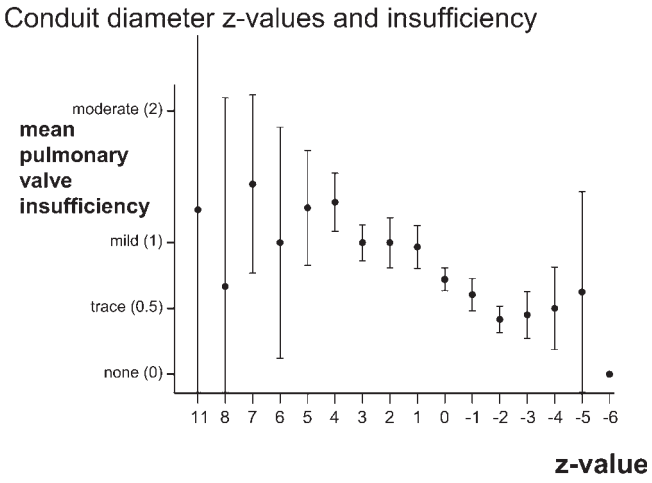


Fig. 9 Z-values and conduit valve insufficiency.

cludes the learning curves of at least 8 surgeons who all had to learn how to prepare and handle the new device. Although all of the participating surgeons were experienced, a single centre study with the same number of patients might have shown different results.

The early **mortality** (17.5%) observed in the youngest patient group (less than 1 year) corresponds to observations of other groups [13, 14] Comparing freedom from **degeneration** with reports on homograft performance in neonates [15], children with congenital malformations and young patients who underwent the Ross procedure [16] suggests the equivalence of the bovine device. One potential reason for reduced freedom from stenosis might be insufficient rinsing of the Contegras, as remnants of the toxic glutaraldehyde storage solution might accelerate peeling formation and stenosis, especially of the narrow distal anastomoses. One of the coinvestigators abandoned the use of Contegras in favour of homografts due to the distal stenoses he observed [17].

Reports on Contegra **dilatations** [18–21] and **peel formation,** mainly at the distal anastomoses [17], show the Contegra is not perfect. Although dilatation has also been described in homografts [22], the number of reports about such events in Contegra recipients suggests that this complication happens less frequently in homografts. On the other hand, many observations of an uneventful course even in patients with elevated pulmonary resistance might indicate that the Contegra is not *per se* prone to dilate. Dilatation is a rare complication of Contegras, causes reoperations, but no emergencies, and a potentially more frequent occurrence of dilatation might be outweighed by the advantages of availability, more convenient surgical properties, less **calcification** and better durability.

Endocarditis, too, may have been reported slightly more frequently in the study population than is described for homografts [23, 24] or other xenografts [25]. It is unclear whether this is due to publication bias, inadequate antibiotic prophylaxis, the fact that the novel device requires extensive rinsing before implantation, or indeed an increased propensity towards infections after Contegra implantation. A comparative randomised study would help to clarify the role of chance in this small number of observations.

The most striking issue regarding the Kaplan-Meier freedom from event curves including **insufficiency** as an endpoint is the high percentage of infants who were not "free from" moderate insufficiency. As already mentioned, the concept of defining a unique observation of moderate insufficiency as an endpoint in this population is questionable, since often the subsequent examinations in the same patient showed reduced insufficiency grades. The observer-related scatter in the assignment of a certain insufficiency observation to the applied grading system was minimised in this study by the central core lab, where only one person interpreted all results. Nonetheless, results cannot be more reliable than the methods used to find them. The Kaplan-Meier curve in **Fig. 3A** suggests that about half of the patients had at least a moderate insufficiency at 7 years. In reality, the fraction of patients with moderate or severe insufficiency exceeds 20% at no time in the observation period and does not tend to increase (**Fig. 3D**). This is the case for patients whose conduits were explanted at study termination and as well for patients who still have their conduits (**Fig. 3F**). This divergence between impression and fact is what makes Kaplan-Meier curves seem inappropriate to illustrate conduit durability.

The long leaflets of the high-profile valved Contegra might contribute to this effect: if the blood volume in the tubular Contegra segment within the valve apparatus is regurged during diastole, this closing volume remains constant over time, because the Contegra does not grow. But the right ventricle grows. So the closing volume of the valve accounts for a decreasing fraction of the entire stroke volume if the child (and its stroke volume) grows. If the valve itself does not degenerate, the regurgitant fraction should be expected to decrease with the z-value. And this is in fact what we observed (**Fig. 9**). **Fig. 2** and the relevant paragraphs in **Tables 1** to **3** show that insufficiency was not a typical reason for explantation.

Insufficiency quantification by transthoracic echo is not very reliable, and the scatter of findings is relevant. Studies with a lower observation frequency have a longer average latency interval between the occurrence of insufficiency and its entry in the database, resulting in virtually better freedom from insufficiency. The lack of clinical relevance when considering the first moderate insufficiency observation a "terminal event" is underlined by **Fig. 2**: 5 years later, 66% of these conduits were still in place.

A publication on insufficiency after comparable homograft implantations in children [26] reported 63% mild and 3% severe regurgitations in the immediate postoperative period. 29% of the patients described in this study developed higher degrees of insufficiency in later examinations. Fiore and coworkers [27] reported a median insufficiency grade of homograft valves in the pulmonary position above 1, using the same semiquantitative classification. **Fig. 3D** and **E** show numbers which compare well with this; moreover, no general tendency towards an increase in insufficiency over time was observed (**Fig. 3F**). In contrast to homografts there are no reports describing missing Contegra cusps after a few years of implantation.

Interventions

One traditional endpoint, freedom from explantation, is obscured by the opportunity for percutaneous therapies. Opinions on the appropriateness and the time for the dilatation of stenoses are controversial. The elastic neointima, which is frequently seen in patients with stenosis, is less susceptible to dilatations than calcified or fused commissures. The indications for carrying out such interventions with the new device had to be found during the course of the study – some centres were reluctant, some were enthusiastic to dilate or to stent the new device. The benefit of

such interventions [28] is not evident for every single patient, so different attitudes are justified. It is debatable to compare the results of these heterogeneous and not well defined approaches to the results of other groups.

Freedom from **explantation** is comparable to results reported in other publications cited above on homografts and other Contegra reports. Degeneration occurs also in Contegras, and peeling at the distal anastomosis, possibly following insufficient rinsing of the glutaraldehyde storage solution, appears more often than is desirable. The peel-preventive role of antiplatelet medication remains to be determined. On the other hand, severe calcifications, as frequently observed after homograft implantations, are not a frequent problem after bovine jugular vein implantations. Facilities for intervention and the propensities, alternatives and thresholds for explantation are subject to changes over time and vary between teams, resulting in great difficulties in telling which conduit is more suitable for RVOT reconstruction. Even for subgroups, such as patients with elevated pulmonary resistance or redo conduit implantations, recommendations are controversial. Meta-analyses are ideally conducted by the inclusion of several randomised controlled trials, but if they do not exist, comparisons are difficult. Briefly reviewing the current literature, the opponents and proponents of homografts and Contegras appear to be nearly balanced. However, statistically more refined comparisons [29,30] tend to favour the bovine jugular vein.

Consequences

Some surgeons (among them one of the coinvestigators of the presented study group) prefer to use homografts after their initial experience with the Contegra [17].

Several recent North American reports [29–31] concluded their comparative observations by finding an advantage in using the Contegra compared to homografts. The role of the blood group compatibility of homografts [32] and the question whether homografts of aortic or pulmonary origin are preferable might be answered better based on large registries than by evaluations of single centres or small groups; the same is true for monocusps [33].

The lack of a growth potential might terminate the use of Contegras in the future. But until then, most of the investigators of this European Contegra multicentre trial consider Contegras to be a valid option for children requiring a valved conduit in the right ventricular outflow tract.

Financial support

The study was sponsored first by VenPro, then by Medtronic (CoreLab, central pathology and blood draw lab, monitoring, central data collection, investigator compensation to cover the efforts required to perform, document and verify the examinations and their results). The sponsors did not influence the evaluation. None of the authors has or has had a financial relationship with or a financial interest in the sponsors or manufacturers.

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References

1 *Ross DN.* Homograft replacement of the aortic valve. Lancet 1962; 2 (7254): 487
2 *Askovich B, Hawkins JA, Sower CT et al.* Right ventricle-to-pulmonary artery conduit longevity: is it related to allograft size? Ann Thorac Surg 2007; 84: 907–911
3 *McMullan DM, Oppido G, Alphonso N, Cochrane AD, d'Acoz Y, Brizard CP.* Evaluation of downsized homograft conduits for right ventricle-to-pulmonary artery reconstruction. J Thorac Cardiovasc Surg 2006; 132: 66–71
4 *Brown JW, Ruzmetov M, Rodefeld MD, Vijay P, Turrentine MW.* Right ventricular outflow tract reconstruction with an allograft conduit in non-Ross patients: risk factors for allograft dysfunction and failure. Ann Thorac Surg 2005; 80: 655–663
5 *Stark J, Bull C, Stajevic M, Jothi M, Elliott M, de Leval M.* Fate of subpulmonary homograft conduits: determinants of late homograft failure. J Thorac Cardiovasc Surg 1998; 115: 506–516
6 *Boethig D, Thies WR, Hecker H, Breymann T.* Mid term course after pediatric right ventricular outflow tract reconstruction: a comparison of homografts, porcine xenografts and Contegras. Eur J Cardiothorac Surg 2005; 27: 58–66
7 *Corno AF, Mickaily-Huber ES.* Comparative computational fluid dynamic study of two distal Contegra conduit anastomoses. Interact Cardiovasc Thorac Surg 2008; 7: 1–5
8 *Bonhoeffer P, Boudjemline Y, Saliba Z et al.* Percutaneous replacement of pulmonary valve in a right-ventricle to pulmonary-artery prosthetic conduit with valve dysfunction. Lancet 2000; 356: 1403–1405
9 *Jenkins KJ, Gauvreau K, Newburger JW, Spray TL, Moller JH, Iezzoni LI.* Consensus-based method for risk adjustment for surgery for congenital heart disease. J Thorac Cardiovasc Surg 2002; 123: 110–118
10 *Goffin YA, Van Hoeck B, Jashari R, Soots G, Kalmar P.* Banking of cryopreserved heart valves in Europe: assessment of a 10-year operation in the European Homograft Bank (EHB). J Heart Valve Dis 2000; 9: 207–214
11 *Homann M, Haehnel JC, Mendler N et al.* Reconstruction of the RVOT with valved biological conduits: 25 years experience with allografts and xenografts. Eur J Cardiothorac Surg 2000; 17: 624–630
12 *Boethig D, Goerler H, Westhoff-Bleck M, Ono M, Daiber A, Haverich A, Breymann T.* Evaluation of 188 consecutive homografts implanted in pulmonary position after 20 years. Eur J Cardiothorac Surg 2007; 32: 133–142
13 *Levine AJ, Miller PA, Stumper OS et al.* Early results of right ventricular-pulmonary artery conduits in patients under 1 year of age. Eur J Cardiothorac Surg 2001; 19: 122–126
14 *Rodefeld MD, Ruzmetov M, Turrentine MW, Brown JW.* Reoperative right ventricular outflow tract conduit reconstruction: risk analyses at follow up. J Heart Valve Dis 2008; 17: 119–126
15 *Sinzobahamvya N, Wetter J, Blaschczok HC, Cho MY, Brecher AM, Urban AE.* The fate of small-diameter homografts in the pulmonary position. Ann Thorac Surg 2001; 72: 2070–2076
16 *Karamlou T, Ungerleider RM, Alsoufi B et al.* Oversizing pulmonary homograft conduits does not significantly decrease allograft failure in children. Eur J Cardiothorac Surg 2005; 27: 548–553

17 *Meyns B, Van Garsse L, Boshoff D et al.* The Contegra conduit in the right ventricular outflow tract induces supravalvular stenosis. J Thorac Cardiovasc Surg 2004; 128: 834–840
18 *Tiete AR, Sachweh JS, Roemer U, Kozlik-Feldmann R, Reichart B, Daebritz SH.* Right ventricular outflow tract reconstruction with the Contegra bovine jugular vein conduit: a word of caution. Ann Thorac Surg 2004; 77: 2151–2156
19 *Delmo-Walter EM, Alexi-Meskishvili V, Abdul-Khaliq H, Meyer R, Hetzer R.* Aneurysmal dilatation of the Contegra bovine jugular vein conduit after reconstruction of the right ventricular outflow tract. Ann Thorac Surg 2007; 83: 682–684
20 *Göber V, Berdat P, Pavlovic M, Pfammatter JP, Carrel TP.* Adverse midterm outcome following RVOT reconstruction using the Contegra valved bovine jugular vein. Ann Thorac Surg 2005; 79: 625–631
21 *Boudjemline Y, Bonnet D, Agnoletti G, Vouhé P.* Aneurysm of the right ventricular outflow following bovine valved venous conduit insertion. Eur J Cardiothorac Surg 2003; 23: 122–124
22 *Troost E, Meyns B, Daenen W et al.* Homograft survival after tetralogy of Fallot repair: determinants of accelerated homograft degeneration. Eur Heart J 2007; 28: 2503–2509
23 *Meyns B, Jashari R, Gewillig M et al.* Factors influencing the survival of cryopreserved homografts. The second homograft performs as well as the first. Eur J Cardiothorac Surg 2005; 28: 211–216
24 *Hopkins RA, Reyes 2nd A, Imperato DA, Carpenter GA, Myers JL, Murphy KA.* Ventricular outflow tract reconstructions with cryopreserved cardiac valve homografts. A single surgeon's 10-year experience. Ann Surg 1996; 223: 544–553
25 *Kanter KR, Fyfe DA, Mahle WT, Forbess JM, Kirshbom PM.* Results with the freestyle porcine aortic root for right ventricular outflow tract reconstruction in children. Ann Thorac Surg 2003; 76: 1889–1894
26 *Meliones JN, Snider AR, Bove EL et al.* Doppler evaluation of homograft valved conduits in children. Am J Cardiol 1989; 64: 354–358
27 *Fiore AC, Rodefeld M, Turrentine M.* Pulmonary valve replacement: a comparison of three biological valves. Ann Thorac Surg 2008; 85: 1712–1728
28 *Powell AJ, Lock JE, Keane JF, Perry SB.* Prolongation of RV-PA conduit life span by percutaneous stent implantation. Intermediate-term results. Circulation 1995; 92: 3282–3288
29 *Hickey EJ, McCrindle BW, Blackstone EH et al.* Jugular venous valved conduit (Contegra®) matches allograft performance in infant truncus arteriosus repair. Eur J Cardiothorac Surg 2008; 33: 890–898
30 *Karamlou T, Blackstone EH, Hawkins JA et al.* Can pulmonary conduit dysfunction and failure be reduced in infants and children less than age 2 years at initial implantation? J Thorac Cardiovasc Surg 2006; 132: 829–838
31 *Morales DL, Braud BE, Gunter KS et al.* Encouraging results for the Contegra conduit in the problematic right ventricle-to-pulmonary artery connection. J Thorac Cardiovasc Surg 2006; 132: 665–671
32 *Sierra J, Christenson JT, Lahlaidi NH, Beghetti M, Kalangos A.* Right ventricular outflow tract reconstruction: what conduit to use? Homograft or Contegra? Ann Thorac Surg 2007; 84: 606–610
33 *Turrentine MW, McCarthy RP, Vijay P et al.* Polytetrafluoroethylene monocusp valve technique for right ventricular outflow tract reconstruction. Ann Thorac Surg 2002; 74: 2202–2205