

Review

Current Status of the Contegra Conduit for Pediatric Right Ventricular Outflow Tract Reconstruction

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Reconstruction of the right ventricular outflow tract (RVOT) is needed in a wide variety of congenital heart diseases at the time of primary repair, or later for replacement of existing valves or conduits. Ideally, the conduit or valve needed for such reconstruction should be formed of autologous tissue that grows, resists infection, lasts for the life span of the patient, and is readily available in all sizes. Such a conduit is not available, though several alternatives have been used, none of which is without potential drawbacks. One alternative - the *Contegra* bovine jugular vein conduit (Medtronic, Inc., Minneapolis, MN, USA) - was introduced in 1999 and has gained

Although surgical management of congenital heart diseases involving the right ventricular outflow tract (RVOT) has evolved extensively over the past two decades (1-6), reconstruction of the tract remains problematic. Different techniques, including the implantation of bioprostheses fixed in woven Dacron tubes as supportive housing, glutaraldehyde-fixed porcine or bovine pericardial valves, glutaraldehyde-fixed porcine aortic or pulmonary roots, non-valved conduits, homografts or valvuloplasties are used to reconstruct continuity between the right ventricle and the pulmonary arteries (7-11). It is generally accepted that valved conduits should be used as the first choice (12,13), with homografts being considered the 'gold standard' (14,15). However, owing to a shortage of small homografts, together with early degeneration and calcification - particularly in very young patients (16) - the search for suitable alternatives continues.

In mid-1999, following a successful series of studies conducted in animals (17-22), a new conduit using a bovine jugular vein that contains a natural valve with a sinus was introduced for human use (23). The

widespread application, with increasing enthusiasm for its use. The *Contegra* conduit consists of a bovine jugular vein with an incorporated trileaflet valve. The conduit tissue is extremely pliable and offers optimal conditions for surgical handling. Moreover, the proximal tubular segment allows construction of the proximal anastomosis to the right ventricle, without the use of additional material. Increasingly, experience with the *Contegra* conduit is being published; hence, a literature search was conducted to evaluate available evidence on current use of the device in pediatric RVOT reconstruction.

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Contegra conduit (Medtronic, Inc., Minneapolis, MN, USA) is a zero-pressure glutaraldehyde-preserved heterologous bovine jugular vein which has a trileaflet venous valve (23). The venous wall, in the form of a conduit, is soft and ideal for suturing, and usually necessitates neither artifice nor interposition of other materials to make the anastomoses with the right ventricle and the pulmonary artery. Moreover, the off-the-shelf availability of the conduit, in a range of diameters (from 12 to 22 mm), makes its use possible in neonates (23). The *Contegra* conduit is also available in a supported model, in which two external cloth-covered polypropylene rings support either side of the valve. All of these advantages have encouraged cardiac surgeons to use this new biological valved conduit with increasing enthusiasm over the past five years for pediatric RVOT reconstruction. Thus, a literature search was conducted to evaluate available evidence on the functional and hemodynamic performance of this conduit, in order to assess its safety and efficacy.

Search methodology

The English language scientific literature was reviewed primarily by searching MEDLINE from 1966 to October 2004 using PubMed interface (24). Key words used in the search included *Contegra*, *Venpro*,

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bovine jugular vein, xenograft, bovine valved xenografts, pulmonary valved conduits, pediatric cardiac surgery, congenital cardiac surgery, congenital heart surgery, congenital heart disease, right ventricle outflow tract reconstruction, and pediatric RVOT reconstruction. The 'related articles' function was used to broaden the search, and all abstracts, studies and citations scanned were reviewed. The reference lists of articles found through these searches were also reviewed for relevant articles. In addition, links on web sites containing published articles were searched for relevant information. The present authors chose studies relevant to the topic. The search was made in stages so as to achieve a search strategy with a high sensitivity (meaning that it has the highest likelihood of retrieving all relevant papers). Similar search terms were combined using the Boolean operator 'OR' to find all abstracts that contained information about a particular search term. These individual terms were then combined using the Boolean operator 'AND' to find papers that contained information on all the search terms. This is a well-recognized method for performing sensitive searches, and has been described in detail in the British Medical Journal (25).

The papers found by the search strategy were then appraised using a structured format, with critical appraisal checklists. These are widely available in several formats, and aid in assessing the paper for methodological and analytical soundness and help to uncover any significant methodological flaws (26). In addition, after appraisal, the paper was categorized in terms of the type of study and the level of evidence presented (27). The levels of evidence are presented in Table I, and enable readers to evaluate available evidence on the topic.

Contegra-related mortality

Early and intermediate clinical results from use of the Contegra conduit to reconstruct the pediatric RVOT are encouraging. To date, only one Contegra-related death has been reported (28). This was secondary to complete thrombosis of the conduit valve and resulted in cardiac and hepatic failure and multiple pulmonary emboli. Although all other published studies have suggested no Contegra-related mortality, the follow up for these studies is not yet long enough and cannot be extrapolated to predict longer-term results for the conduit.

Contegra-related adverse events

Although most published series of Contegra use suggest that the graft itself is never the reason for any adverse event, anecdotal reports of early complica-

tions in the form of non-fatal and fatal thrombosis, aneurysmal dilation, confluence stenosis and endocarditis requiring reoperation have been described after its use for congenital cardiac defect repairs (29).

Thrombosis

Tiete et al. (30) reported the largest incidence of Contegra-related adverse events. In their series of 29 patients, four conduit-related adverse effects were observed. In two small patients with relatively large conduits, thrombus formation was detected early post-operatively, and this necessitated anticoagulant therapy. According to Tiete et al. (30), the thrombus formation was most likely due to a mismatch in valve sizes causing a relatively low blood flow and an incomplete valve leaflet motion. A similar event was reported in one of 15 patients by Chatzis et al. (31), and in two of 28 patients by Boudjemline et al. (28). Recently, Schoof et al. (32) also reported thrombosis of Contegra conduits (two non-valved, one valved) implanted as extracardiac conduits for Fontan circulation completion. These authors attributed the increased thrombogenicity to a lack of endothelial resurfacing and an inflammatory response to the glutaraldehyde, as well as to the large cytotoxic surface area of the conduit. Although the flow characteristics of a Fontan conduit are different from those of an RVOT conduit, this observation of conduit thrombosis in a slow, non-pulsatile blood flow may compare partly with the data reported by Tiete et al. (30) in their observation of thrombus formation in oversized RVOT conduits with a pulsatile, but relatively slow, blood flow and incomplete valve function.

Tiete et al. (30) also reported one reoperation for severe regurgitation of a 12-mm Contegra conduit in their series. The valve dysfunction was caused by fibrous peel, not by leaflet destruction, which most likely had been caused primarily by thrombus formation. Although this patient had factor V Leiden mutation with an increased susceptibility to thrombosis, Kadner et al. (33) have recently reported a similar event in two patients who did not have any increased genetic predisposition to thrombosis. Both patients suffered conduit failure from the formation of an intimal membrane that led to severe RVOT stenosis at eight and 12 months after implantation, respectively. Microscopic analysis of the explanted conduits demonstrated a moderate generalized inflammatory reaction of the grafts, with disruption of the native extracellular matrix and architecture. Similar observations have been reported for explanted homografts, and further long-term evaluation and follow up are clearly needed to determine the significance of these findings (34).

Due to the potential risk of thrombosis, it is vital that

an anti-aggregant therapy (e.g. aspirin) be prescribed to all recipients of the Contegra conduit for at least 6-12 months after implantation. This is based upon the hypothesis that endothelialization of the implant should be complete after 6-12 months, and that thrombus formation is unlikely to occur (28).

Aneurysm formation

Tiete et al. (30) also reported one incident of pseudoaneurysm formation under systemic right ventricular pressure a few months after implantation. In the opinion of these authors, this might have been due to a decreased resistance of the conduit wall to high pressure, in combination with a perivascular unspecific inflammatory reaction. Boudjemline et al. (35) also reported severe dilatation of a Contegra conduit in a five-year-old boy, with a similar clinical picture, leading to its premature replacement. Unlike Tiete et al. (30), these authors had used a supported conduit, and although rings located at each end of the valve were efficient to prevent dilatation of the valve, thus preserving its function, the bovine vein below the inferior ring was unprotected and an aneurysmal dilatation of that region was observed.

Endocarditis

Endocarditis of the Contegra conduit has also been reported in both animal (22) and human (36,37) studies. Carrel et al. (36) observed endocarditis of the conduit at 11 months after implantation, secondary to septicemia of urogenital origin. Endocarditis resulted in the formation of an abscess cavity, which led to supravulvar pulmonary stenosis necessitating explantation of the conduit and replacement with a pulmonary homograft. Corno et al. (37) also encountered endocarditis (*Enterococcus faecalis*) of the conduit valve at 30 months after implantation of an 18-mm conduit. However, this patient was successfully managed with medical treatment.

Hemolysis

Although hemolysis due to prosthetic cardiac valves is well documented in the literature (38), it is quite rare in normally functioning biological valves (39). Boethig and Breyman (39), in their recently published clinical Phase I study of the Contegra bovine valved conduit, determined levels of hemoglobin, plasma-free hemoglobin, haptoglobin and reticulocytes before implant, before hospital discharge, and at one, three, six and then every six months after implantation, and concluded that Contegra valves do not cause hemolysis owing to a relatively streamline flow. According to these authors, hemolysis of clinical significance would only be noticed if there was valve degeneration or stenosis distal to the conduit in the branch pulmonary

arteries. Similar results have been shown by Carrel et al. (36).

Confluence stenosis

Confluence stenosis has been the single most important reason for reoperation and reintervention (40,41). In the largest series published to date, Breyman et al. (41) performed seven bifurcation plasty operations among a total of 108 conduits implanted over a four-year period. Carrel et al. (36) also undertook patch augmentation of the distal suture line in one of their patients who developed a significant stenosis at the level of the distal anastomosis. In the series of Tiete et al. (30), two patients had interventional balloon dilation for the same reason, while one patient was scheduled for conduit replacement following failed balloon dilation.

Twisting

Twisting and compression of the conduit is another problem reported by Corno et al. (37). In their study, three patients among 67 (4.5%) required unscheduled treatment. Two of these patients had stent implantation, and one patient had surgical replacement. In two of these patients this was because of conduit twisting due to technical problems at the time of implantation, and in one patient it was because of extrinsic compression between the conduit valve and the distal anastomosis. The authors correlated the observed twist of the conduit with the learning curve in the use of this type of conduit, which is much more soft and pliable than the conventional homograft and therefore less forgiving with regard to potential twisting.

Inflammatory-immunological reaction

An inflammatory-immunological reaction with the Contegra valved conduit has also been reported recently (42,43). Bottio et al. (42) conducted a post-mortem examination (including histology of the bovine jugular vein) in two of their patients who died postoperatively. The first death occurred perioperatively after a Ross procedure, while the second occurred at home, two months after a reconstruction for truncus arteriosus. As expected, the Contegra conduit wall and venous Valsalva valvular leaflets, implanted during the Ross procedure, were well preserved. Nevertheless, in this case immunohistochemistry showed periadventitial inflammation. The second Contegra conduit, which was in place for two months, also showed periadventitial inflammation which was confirmed by immunohistochemistry against leukocytes. Along with low-grade inflammation in the endothelial layer, calcium deposits were present in the leaflets at valve level. Boudjemline et al. (28), in their series of 28 patients, had to reoperate on three patients

Table I: Levels of evidence.

Level I: Strong evidence from at least one published systematic review of multiple well-designed randomized controlled trials.
Level II: Strong evidence from at least one published properly designed randomized controlled trial of appropriate size and in an appropriate clinical setting.
Level III: Evidence from published, well-designed trials without randomization, single group pre-post, cohort, time series, or matched case-control studies.
Level IV: Evidence from well-designed, non-experimental studies from more than one center or research group.
Level V: Opinion of respected authorities, based on clinical evidence, descriptive studies or reports of expert consensus committees.

with a 12-mm valve due to early failure of the conduit. These patients were noted to have a pathological intimal proliferation which was located predominantly at the pulmonary anastomosis on the inside layer of the conduit resulting in obstruction. The authors raised the possibility of an immunological rejection.

To date, only one study has been published that determined an immune response in recipients of a Contegra valve (44). Wojtalik et al. (44), in a prospective case-control study, revealed that there was cellular as well as humoral immunity activation in children with complex congenital defects who had received a Contegra conduit.

Several reasons have been proposed for the potential immunogenicity and antigenicity of the Contegra xenograft, including: (i) a large surface of contact with the host tissues (in comparison to other biological prosthetic valves); (ii) the presence of cellular remnants (whole endothelial layer) within the implant; (iii) non-homogeneous graft fixation by glutaraldehyde, as demonstrated by studies with fluorescent probes (45); (iv) endothelial lesions made during conduit suture; and (v) residual glutaraldehyde release from the implant. Shear stress related to hemodynamic local condition might amplify this immunological reaction (43). The presence of circulating, preformed xenoantibodies, unspecific complement activation (even by fixed tissues) (46) and an absence of molecular biocompatibility of the endothelium and extracellular matrix can further enhance the immune response to the xenograft (44). The onset of immune response against the Contegra conduit and its intensity is an important issue that merits further investigation owing to its impact on long-term graft survival.

Hemodynamic performance

The hemodynamic performance of the Contegra appears to be quite favorable (37). Early and mid-term

echocardiographic analyses have shown good results, with most studies suggesting absent or trivial valve regurgitation in the majority of patients, and low transvalvular pressure gradients with no tendency to increase over time. In the series of 67 patients reported by Corno et al. (37), echocardiography at a mean follow up of 26.4 months (range: 1 to 56 months; >4 years in 11 patients; >3 years in 24 patients) showed valve regurgitation to be absent in 30 patients (45%), trivial in 21 (31%), and mild in 16 (24%), without recorded changes during the follow up. The transconduit pressure gradient recorded at discharge remained stable during the follow up period, with a mean peak pressure gradient of 17 ± 11 mmHg and a mean gradient of 8 ± 6 mmHg. The Contegra conduit internal diameters measured with electrocardiographically gated multislice computed tomography scanning were $110 \pm 20\%$ of the known diameter of the implanted conduit at the level of the proximal anastomosis, $112 \pm 18\%$ at the level of the valve, and $110 \pm 14\%$ at the level of the distal anastomosis. No significant differences were found among the internal diameters measured for each single patient at the three different levels, with a mean value of $112 \pm 11\%$ of the expected internal diameter (range: 105 to 126%).

In the largest series published to date, with a mean follow up of 2.1 years (total follow up 227.7 patient-years), Breymann et al. (41) evaluated 848 standardized echocardiograms recorded from 104 patients (108 conduits). These authors detected no relevant average gradient development at the level of the valves. Trace and mild-grade valvular insufficiency was common, and showed no tendency to increase. Furthermore, no significant conduit dilation or leaflet calcification was detected. Similar results have been reported by several other published series (28-30,31,36,40,47,48).

Comparison with homografts and other xenografts

As the Contegra conduit has been introduced as a potential alternative to homografts - which are regarded as the 'gold standard' - it is extremely important to compare the performance of the two techniques. Interestingly, whilst no prospective randomized controlled trial has been undertaken to compare the functional and hemodynamic performance of the Contegra against homografts to date, two such retrospective studies have been reported (40,47). Bove et al. (40) retrospectively compared early clinical and echocardiographic results of RVOT reconstruction between 41 children (mean age 1.9 years) who received a Contegra conduit, and 36 children (mean age 2.7 years) who received a size-reduced pulmonary homograft. The study results showed competent valve function in the majority of patients in both groups: 27 (75%) of the homograft patients versus 23 (59%) of the Contegra

patients ($p = 0.13$). Trivial to mild valve leakage was found in nine patients with a bicuspid homograft, and quantified as grade I regurgitation in eight patients and grade II in one patient. Fifteen children with a Contegra conduit had a grade I valve insufficiency, while two had a grade II leakage; this difference was not significant however. The peak gradient across the RVOT conduit was comparable in both groups, although a larger number of homograft patients had a small gradient at the distal junction with the pulmonary arteries than did Contegra patients (12 versus six). None of the patients had a gradient at the valvar level. The clinical outcome was also comparable.

Breyman et al. (47), in another retrospective study, compared their cohort of patients with a Contegra conduit ($n = 71$) with those who had undergone RVOT reconstruction with a homograft ($n = 52$) or with a Tissuemed® porcine xenograft ($n = 30$). The three patient cohorts were operated on chronologically one after the other, starting with the homograft cohort; the groups were essentially similar with regard to diseases, age, and NYHA functional status. The results of this study showed that, over a 27-month follow up period, Contegra conduit function was at least as good as it was for homografts, and was by far superior to that of porcine xenografts.

Caution and concerns

At present, no data are available to assess the long-term outcome of the Contegra conduit. The available evidence contributes to a building sense of excitement that the Contegra may be an ideal substitute for homografts, although issues such as thrombus formation inside the conduit, aneurysmal dilation and pseudoaneurysm formation and host immunological reaction are all very important issues which merit further research and mandatory close echocardiographic follow up. Another cause for concern is the occurrence of early failure in only the 12-mm conduits (28). In addition, uncontrolled dilation of the conduit is a major concern in terms of valvar competence, and questions its use for RVOT reconstruction in conditions with high right-sided pressures.

Use of the Contegra valved conduit has gained interest recently because of its intrinsic qualities and encouraging early and mid-term hemodynamics and clinical outcomes (Table II). However, the occurrence of early failure because of exaggerated intimal proliferation or thrombotic processes within the conduit and aneurysmal dilation emphasize the need for: (i) the prescription of an anti-aggregant therapy (e.g. aspirin) after implantation; (ii) careful rinsing of the conduit before its insertion in order to remove any glutaralde-

Table II: Outcomes of Contegra conduit.

Reference	Study type (Level of evidence)	No. of patients	Duration of follow up	Death ^a	Mean gradient (mmHg)	Severe regurgitation	Thrombosis	Aneurysm	Calcification	Reintervention ^{a,b}
Corno et al. 2004 [37] ^f	Case series (Level 4)	67	26.4 months	Nil	17 ± 11	Nil	Nil	Nil	1 ^c	3
Breyman et al. 2004 [41] ^f	Case series (Level 4)	108	2.1 years	Nil	8 ± 5	Nil	Nil	Nil	1 ^d	4
Tiete et al. 2004 [30]	Case series (Level 4)	29	10.2 ± 6.4 months	Nil	NA	Nil	3	1	Nil	3
Purohit et al. 2004 [29]	Case series (Level 4)	20	13.8 ± 9.1 months	Nil	13.2 ± 4.5	Nil	Nil	Nil	Nil	Nil
Chatzis et al. 2003 [31]	Case series (Level 4)	15	18.5 ± 6.9 months	Nil	7.7 ± 4.9	Nil	1	Nil	Nil	1
Boudjemline et al. 2003 [28]	Case series (Level 4)	31	3 months	1	NA	3	5 ^e	Nil	Nil	3
Carrel et al. 2002 [36]	Case series (Level 4)	22	18 months	Nil	8.5 ± 6.3	Nil	Nil	Nil	1	2

^a, Conduit-related; ^b, includes reoperation; ^c, minimal parietal calcification detected echocardiographically; ^d, calcification detected histologically in an explanted conduit; ^e, three of five patients had a fibrointimal membrane or peel inside the conduit; ^f, earlier series from these centers with shorter follow up have also been published.

hyde; (iii) controlling adequacy of the distal anastomosis on the pulmonary artery bifurcation, particularly in small patients; and (iv) avoiding the implantation of small conduits in conditions with very high right-sided pressures. Finally, a multicenter, randomized, controlled trial with long-term follow up comparing the Contegra against homografts and other available alternative conduits is required to establish conclusively the credentials of this xenograft as a *perfect* alternative for homografts for pediatric RVOT reconstruction.

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