Journal of
Cardiology & Cardiovascular Therapy
ISSN: 2474-7580

Juniper Publishers
key to the Researchers

Review Article
Volume 17 Issue 4 - March 2022
DOI: 10.19080/JOCCT.2022.17.555967

J Cardiol & Cardiovasc Ther

Clinical Results of Decellularized Pulmonary Allografts for Right Ventricular Outflow Tract reconstruction during Ross Procedure. Where are we today?

Öner A[1], Smit FE[2], Alozie A[3] and Dohmen PM[2,3]

[1]*Department of Cardiology, Heart Center Rostock, University of Rostock, Rostock, Germany*

[2]*Department of Cardiothoracic Surgery, Faculty of Health Science, University of the Free State, Bloemfontein, South Africa*

[3]*Department of Cardiac Surgery, Heart Center Rostock, University of Rostock, Rostock, Germany*

Submission: February 25, 2022; **Published:** March 10, 2022

***Corresponding author:** Pascal M Dohmen, Department of Cardiac Surgery, Heart Center Rostock, University of Rostock, Schillingallee 35, D-18057 Rostock, Germany

Abstract

Sir Donald N. Ross established a new era to treat aortic valve disease by introducing the Ross procedure in 1967. The original technique was complex by implanting the pulmonary valve subcoronary into the aortic root with excellent long-term results. The limited part of this specific approach however, was meanly the right ventricular outflow tract (RVOT) reconstruction. Today, the golden standard is the use of a cryopreserved pulmonary allograft, however disadvantageous such as availability and immunogenic response can eventually lead to structural valve deterioration. Tissue engineering could help to create a valve with an excellent durability including remodelling, regeneration and growth potential for RVOT reconstruction. This article reflex a recent literature overview on clinical available solutions of correcting the RVOT by the use of decellularized pulmonary allografts.

Keywords: Ross procedure; Decellularized allografts; Cryopreserved allografts; Tissue engineering

Background

In the western world, it's estimated that over 30 million people suffer from valvular heart disease (VHD) [1]. Life expectancy of severe aortic valve stenosis is less than 10 years in 90% of adult patients, unless interventional or surgical treatment is performed [2]. In case of untreated aortic valve stenosis and heart failure is induced, mortality will be as high as 50% within one year [2]. In younger patients, 33% of congenital heart diseases are related to abnormalities of the aortic or pulmonary valves [2].

The preferred method to treat patients suffering from VHD are valve sparing techniques, however sufficient tissue material must be available to obtain a functional valve. In approximately 300,000 patients per annum aortic valve replacement is performed [2]. In older patients several excellent options are available either surgery or interventional treatment.

In younger patients, however no optimal solution is yet available. The "golden standard" for valve replacement is the use of an allograft, which are today cryopreserved [3]. Disadvantage of these cryopreserved allografts, however, is the immunological response, which might lead to structural valve deterioration [4]. Furthermore, the absence of viability and growth potential, which is needed for young recipients undergoing heart valve replacement, leads to several additional surgeries or interventions.

The Ross procedure was introduced in 1967 by Sir Donald Ross [5] with several advantages for aortic valve replacement due to growth potential, avoiding anti-coagulation therapy, low thromboembolic complications, low endocarditis rate and excellent hemodynamic behavior. The limitation of the procedure, however, is right ventricular outflow tract (RVOT) reconstruction by an available heart valve prosthesis.

Tissue engineering could overcome these limitations by creating a heart valve with remodeling, regeneration and growth potential. Many possibilities have been investigated in animal

models up till now, with promising and less promising results [6]. The number of clinical studies, however, are still limited, in reconstructing the RVOT during Ross and non-Ross procedures.

This manuscript reviews the results of clinical course by two principle pathways namely the *in vitro* autologous seeded decellularized scaffolds and the *in vivo* autologous seeded decellularized scaffolds compared with standard cryopreserved allografts to reconstruct the right outflow tract during the Ross procedure.

1.1. *In vitro* autologous cell seeded of decellularized pulmonary allografts

The first tissue engineered heart valve worldwide was implanted in 2000 [7]. Therefore, a vein was prepared to harvested autologous endothelial cell which cultured and expanded *in vitro.* Simultaneously, a cryopreserved pulmonary allograft was decellularized, coated and seeded in a special developed bioreactor in a GMP laboratory. After sterility was proven, the tissue engineered heart valve was used to reconstruct the RVOT during the Ross procedure. In a later study, ten years follow-up including 11 patients, the results were showing excellent results [8].

At the latest follow-up at 15 years, further promising data were found. Nine patients were alive. Two patients died, during late follow-up. One because of suicide and one of unknown cause. All other patients were in NYHA class I and no elevation of tissue engineering valve stenosis nor regurgitation.

Another concept was constipated by Cebotari et al. [9] published initial results on tissue engineered heart valves in which autologous progenitor cells were harvested and seeded on an alternative decellularized scaffold. The follow-up was 40 months, showing respectable pressure gradients and only mild to moderate regurgitation in all patients. Five years follow-up of these patients confirmed the early results [10].

In vitro seeding of decellularized heart valves is time consuming and extreme demanding. Therefore, alternatives have been evaluated and introduced in clinical application after extensive experimental studies performed on the use of *none in vitro* autologous cell seeded tissue engineered heart valves.

1.2. *In vivo* autologous cell seeded decellularized pulmonary allografts

Initial clinical studies were performed with cryopreserved allografts which were afterwards decellularized by different specific methods.

Bechtel et al. [11] investigated in a small retrospective study the effect of decellularization on cryopreserved allografts by using the SynerGraft-treatment. The study compared 22 patients receiving a SynerGraft pulmonary allograft with a conventional cryopreserved pulmonary allograft. During a 12 months follow-up echocardiographic examination showed no differences between mean pressure gradient (average: 9.1±4.2 mmHg versus 9.6±4.3 mmHg; P =0.64), nor a difference of the effective orifice area (0.93±0.80 cm^2/m^2 versus 0.93±0.42 cm^2/m^2; P =0.96). The median follow-up time for both groups, however, were significant different with a median follow-up time of 10 months (range not available) versus 32 months (range not available); P <0.001).

Additionally, the age of both patient-groups were significantly different, respectively 37.4 ± 10.2 years and 45.7 ± 12.3 years (P =0.01). Since the control group were patients acquired from a large Ross-procedure database, it would be desirable having the baseline characteristics matched to avoid a bias in the study population.

Sarikouch et al. [12] inserted fresh decellularized pulmonary allografts from January 2005 on, after previous studies showed spontaneous host recellularization after implantation. Excluding 38 implants of a prospective trial on decellularized fresh pulmonary allografts from October 2014 onwards, a total of 93 patients were matched to 93 cryopreserved pulmonary allografts as a historical group. In this study freedom of explantation was significant lower in fresh decellularized pulmonary allografts compared with cryopreserved pulmonary allografts respectively 89.95 ± 3.60% (n=52) versus 100% (n=29) at midterm follow-up (P = 0.011). At 10 years of follow-up, only one patient in the fresh decellularized pulmonary allograft group and 30 patients in the conventional pulmonary allografts suffered from pulmonary graft failure. In the conventional pulmonary allograft group 13/93 were Ross patients versus 11/93 of the fresh decellularized pulmonary allograft group, however no subgroup analyses were presented in this study.

Etnel et al. [13] investigated in a propensity-matched study between May 1995 and February 2017 to complete an eight years follow-up comparing fresh decellularized versus standard cryopreserved pulmonary allografts during Ross procedure. After matching the baseline characteristics in both groups, no differences were seen for allograft dysfunction nor allograft re-intervention respectively decellularized allografts =86.7% versus standard cryopreserved allografts = 87.3%; P =0.183 and decellularized allografts =99.2% versus standard cryopreserved allografts = 97.6%; P =0.642 were comparable at eight years follow-up. Right ventricular outflow tact proximal anastomosis patch augmentation was significant more often performed in decellularized allografts group 20.8% versus standard cryopreserved allografts group 7.7% (P =0.005). In this study-population regurgitation rates for allograft dysfunction was addressed at ≥ Grade 3 of pulmonary valve regurgitation.

Bibevski S et al. [14] showed in a retrospective study including 163 SynerGraft allografts and 124 standard cryopreserved allografts implantations for right ventricular outflow tract reconstruction. The actuarial survival was similar in both groups

How to cite this article: Öner A, Smit F, Alozie A, Dohmen P. Clinical Results of Decellularized Pulmonary Allografts for Right Ventricular Outflow Tract reconstruction during Ross Procedure. Where are we today?. J Cardiol & Cardiovasc Ther. 2022; 17(4): 555967. DOI: 10.19080/JOCCT.2022.17.555967

at 10 years of follow-up SynerGraft allografts 91% and 89% at the standard cryopreserved allografts cohort (*P*=0.84). The ratio Ross/non-Ross patients were similar in both cohorts respectively 68/95 versus 44/80 (*P* =0.28). Conduit dysfunction was significantly worse at 10 years in the standard cryopreserved allografts group (42%) as compared with SynerGraft allografts 17% (*P* <0.001). Freedom from conduit re-intervention was significant reduced in the SynerGraft allografts group 16/163 (10%) compared with 32/119 (27%) in the standard cryopreserved allografts group (*P* =0.001). The authors reported significant higher peak pressure gradient for standard cryopreserved allografts (27.4 ± 18.7 mm Hg) compared with SynerGraft allograft respectively (20.7 ± 15.7 mm Hg; *P* =0.003). The demographics of this study, however show mean age of the patients in SynerGraft allografts group were significant older versus the standard cryopreserved allografts allografts (207.6 ± 197.8 versus 151.5 ± 171.5 months; *P* =0.01), which also influences the implanted valve size of the both groups respectively 22.1 ± 5.8 mm versus 19.5 ± 6.0 mm (*P* <0.001).

Discussion

The Ross procedure was introduced to surgical treat congenital aortic valve disease. This surgical treatment improved the outcome of aortic valve disease, especially in younger patients, avoiding anticoagulation therapy and long-term freedom of redo surgery or intervention [4,5,7,8]. Additionally, the autologous pulmonary valve is viable and therefore an optimal valve prosthesis to avoid endocarditis. Furthermore, this valve has growth potential and therefore allows the left ventricle having a normal development in young patients. The reconstruction of the right ventricular outflow tract is standard performed by a cryopreserved allograft, with all limitations as presented in the previous studies [8,9,12,13]. Tissue engineering heart valves could overcome these limitations during the Ross procedure. Previous studies were performed with *in vitro* autologous seeded decellularized scaffolds. The reason for this was to overcome thrombogenicity of the collagen scaffold [15]. Two independent studies showed excellent results also during long-term follow-up, however manufacturing and transporting of these tissue engineering heart valve is demanding and complicated.

Several experimental studies were performed to investigate the needed or *in vitro* cell seeding of decellularized valve scaffolds to avoided thrombogenictiy or early endocarditis due to the absence of the endothelium. Long-term follow-up in large animal models have shown that this can be performed safely [16]. Furthermore, Dohmen et al. [16] was able to show not only remodeling and regeneration potential but also growth potential of these tissue engineered heart valves.

The studies presented in this mini-review support the remodeling and regeneration potential of decellularized pulmonary allografts in patients. This was regardless of the decellularization technique used. Long-term data are needed to support these findings in which the advantages of decellularized allograft over cryopreserved allografts are showed.

The next step will be to introduce decellularized allograft implanted into the aortic position. Da Costa et al. [17] presented favorable results at 19 months follow-up of 38 patients included. Stable structural integrity was shown up to three years of follow-up with one reoperation after decellularized aortic allograft for aortic root replacement.

Helder et al. [18] investigated 42 patients receiving an aortic root replacement with a SynerGraft aortic allograft. Reoperation rate was 37% of the survivors, due to endocarditis 26% (11/41), aortic valve regurgitation 18%, including 12% with associated aortic aneurysm, and 29% aortic valve stenosis. At 10 years follow up 51% (95% CI, 34% - 76%) of the Synergraft aortic allograft group versus 80% (95% CI, 60%- 100%) for the standard cryopreserved allograft (p=0.06).

Decellularization procedure used both studies were different, which could have influence on the outcome. Although these clinical results are very promising, decellularization of pulmonary or eventually aortic allograft is limited by donor availability. Therefore, Smit et al. [19] investigated tissue integrity of prolonged post-mortem cold ischemic harvesting time to reduce allograft shortage.

Conclusion

In conclusion, the Ross procedure is an excellent tool, using the autologous pulmonary valve to replace a diseased aortic valve, with a allografts to reconstruct the right ventricular outflow tract. It seems that decellularized pulmonary allografts have better outcome as standard cryopreserved pulmonary allografts. Progression has been made, however it is still a long way to go.

Conflict of Interest

The authors declare no conflict of interest.

References

1. Dohmen PM (2012) Clinical results of implanted tissue engineered heart valves. HSR Proc Intensive Care Cardiovasc Anesth 4(4): 225-231.
2. Haude M (2017) Management of valvular heart disease: ESC/EACTS guidelines 2017. Herz 42(8): 715-720.
3. Bester D, Botes L, van den Heever JJ, Kotze H, Dohmen P, et al. (2018) Cadaver donation: structural integrity of pulmonary homografts harvested 48 h post mortem in the juvenile ovine model. Cell Tissue Bank 19(4): 743-754.
4. da Costa FD, Dohmen PM, Duarte D, von Glenn C, Lopes SV, et al. (2005) Immunological and echocardiographic evaluation of decellularized versus cryopreserved allografts during the Ross operation. Eur J Cardiothorac Surg 27(4): 572-578.
5. Ross DN (1967) Replacement of the aortic and mitral valves with a pulmonary autograft. Lancet 2(7523): 956-958.

How to cite this article: Öner A, Smit F, Alozie A, Dohmen P. Clinical Results of Decellularized Pulmonary Allografts for Right Ventricular Outflow Tract reconstruction during Ross Procedure. Where are we today?. J Cardiol & Cardiovasc Ther. 2022; 17(4): 555967. DOI: 10.19080/JOCCT.2022.17.555967

6. Dohmen PM (2012) Tissue engineered aortic valve. HSR Proc Intensive Care Cardiovasc Anesth 4(2): 89-93.
7. Dohmen PM, Lembcke A, Hotz H, Kivelitz D, Konertz WF (2002) Ross operation with a tissue-engineered heart valve. Ann Thorac Surg 74(5): 1438-1442.
8. Dohmen PM, Lembcke A, Holinski S, Pruss A, Konertz W (2011) Ten years of clinical results with a tissue-engineered pulmonary valve. Ann Thorac Surg 92(4): 1308-1314.
9. Cebotari S, Lichtenberg A, Tudorache I, Hilfiker A, Mertsching H, et al. (2006) Clinical application of tissue engineered human heart valves using autologous progenitor cells. Circulation 114(1 Suppl): I132-I137.
10. Cebotari S, Tudorache I, Ciubotaru A, Boethig D, Sarikouch S, et al. (2011) Use of fresh decellularized allografts for pulmonary valve replacement may reduce the reoperation rate in children and young adults: early report. Circulation 124(11 Suppl): S115-S123.
11. Bechtel M, Gellissen J, Erasmi AW, Petersen M, Hiob A, et al. (2005) Mid-term findings on echocardiography and computed tomography after RVOT-reconstruction: comparison of decellularized (SynerGraft) and conventional allografts. Eur J Cardiothorac Surg 27(3): 410-415.
12. Sarikouch S, Horke A, Tudorache I, Beerbaum Ph, Westhoff-Bleck M, et al. (2016) Decellularized fresh homografts for pulmonary valve replacement: a decade of clinical experience. Eur J Cardiothorac Surg 50(2): 281-290.
13. Etnel JRG, Suss PH, Schnorr GM, Veloso M, Colatusso DF, et al. (2018) Fresh decellularized versus standard cryopreserved allografts for right ventricular outflow tract reconstruction during the Ross procedure: a propensity-matched study. Eur J Cardiothorac Surg 54(3): 434-440.
14. Bibevski S, Ruzmetov M, Fortuna RS, Turrentine MW, Brown JW, et al. (2017) Performance of SynerGraft decellularoized pulmonary allografts compared with standard cryopreserved allografts: Results from multi-institutional data. Ann Thorac Surg 103(3): 869-874.
15. Meiring M, Khemisi M, Laker L, Dohmen PM, Smit FE (2017) Tissue engineered small vessel conduits – the antitrombotic effect of re-endothelialization of decellularized baboon arteries: A preliminary experimental study. Med Sci Monit Basic Res 23: 344-351.
16. Dohmen PM, Ozaki S, Nitsch R, Yperman J, Flameng W, et al. (2003) A Tissue engineered heart valve implanted in ajuvenile sheep model. Med Sci Monit 9(4): BR97-BR104.
17. Da Costa FDA, Costa ACBA, Prestes R, Domanski AC, Balbi EM, et al. (2010) The early and midterm function of decellularized aortic valve allografts. Ann Thorac Surg 90(6): 1854-1860.
18. Helder MRK, Kouchoukos NT, Zehr K, Dearani JA, Maleszewski JJ, et al. (2016) Late durability of decellularized allografts for aortic valve replaceemnt: A word of caution. J Thorac Cardiovasc Surg 152: 1197-1199.
19. Smit FE, Bester D, van den Heever JJ, Schlegel F, Botes L, et al. (2015) Does prolonged post-mortem cold ischemic harvesting time influence cryopreserved pulmonary homograft tissue integrity? Cell Tissue Bank 16(4): 531-544.

DOI: 10.19080/JOCCT.2022.17.555967

How to cite this article: Öner A, Smit F, Alozie A, Dohmen P. Clinical Results of Decellularized Pulmonary Allografts for Right Ventricular Outflow Tract reconstruction during Ross Procedure. Where are we today?. J Cardiol & Cardiovasc Ther. 2022; 17(4): 555967. DOI: 10.19080/JOCCT.2022.17.555967