Myocardial Protection Strategy Utilizing Retrograde Cardioplegia

for Neonatal Arterial Switch Operations

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Acknowledgements

Abstract

Introduction: Myocardial protection strategies are a central component of neonatal arterial switch operations. Traditionally antegrade cardioplegia through the aortic root has been the method of delivery, but use of retrograde cardioplegia via the coronary sinus has become the standard of practice by many in the field. Methods: After obtaining IRB approval and informed consent, a retrospective chart review was done to assess outcomes between 48 patients receiving antegrade (n= 5) and retrograde (n= 43) cardioplegia during neonatal switch operations. Preoperative demographics and postoperative outcomes were compared between the two groups. Results: Patients from the retrograde cardioplegia group demonstrated a trend towards shorter postoperative ventilation days (6.67 +/- 8.57 vs. 10.2 +/- 10.1) and hospital length of stay (18.3 +/- 15.3 vs. 24.8 +/- 11.8) which were not statistically significant. Patients receiving retrograde cardioplegia demonstrated a trend towards an increased incidence of postoperative arrhythmias which was not statistically significant. The retrograde group also demonstrated an increased cardiopulmonary bypass (CPB) time (95.6 +/- 36.59 vs. 146.74 +/- 44.26) and a trend towards an increased aortic cross clamp (ACC) time (74.4 +/- 24.42 vs. 101.30 +/- 29.56) which was not statistically significant. All patients survived to discharge in both groups. With results trending towards shorter hospital length of stays, postoperative ventilation days and zero mortality in patients receiving retrograde cardioplegia, it can be utilized as a safe and efficacious strategy for myocardial protection during neonatal switch operations.

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Introduction

Transposition of the Great Arteries (TGA) is a neonatal congenital heart defect that in its most common form (dextro-TGA) results in ventriculoarterial discordance of the pulmonary artery and aorta in relation to the ventricles such that parallel circulatory systems would exist without a concomitant intracardiac shunt. This condition is thought to be the result of failure of spiraling of the aorticopulmonary septum, or the migratory neural crest cells of the body that generate the division between the pulmonary and systemic outflow tracts of the heart (via the right and left ventricles)[4]. As a consequence, oxygenated blood is continuously pumped back to the lungs instead of the rest of the body while deoxygenated blood returning from the systemic circulation is unable to be replenished by the lungs. The result is a condition which is fatal if not accompanied by an intracardiac shunt.

While the exact etiology is unknown, there have been associated risk factors such as gestational diabetes mellitus, maternal exposure to rodenticides and herbicides, and maternal use of antiepileptic drugs. The condition represents 5-7% of all congenital heart diseases, with an overall incidence of 20-30/100,000. There seems to be a male predominance with a ratio of 1.5-3.2:1. In 50% of cases a complex transposition is present with ventricular septal defects, left ventricular outflow tract obstruction, aortic arch anomalies, or an anomalous venous systemic return. In the other half of cases the ventriculoarterial disconcordance is an isolated finding.[2]

In a patient with simple TGA, the mixing of blood between pulmonary and systemic circulations is reliant upon a patent ductus arteriosus (PDA) and patent foramen ovale (PFO). The PDA functions to increase pulmonary circulation of deoxygenated blood while the PFO functions to increase shunting of oxygenated blood from the pulmonary to systemic circulation. Those with an intact ventricular septum tend to present with severe cyanosis within the first few hours of life, while a large VSD allows for increased mixing and may result in delay or absence of cyanosis. Supportive measures in those with simple D-TGA include administration of prostaglandin E to increase the ductal systemic-to-pulmonary shunting as well as balloon atrial septostomy to enlarge the atrial opening. While balloon atrial septostomy was historically

performed on all patients with TGA, the advent of the arterial switch operation and trend towards earlier surgical correction has led to a more selective approach.[9]

Without surgery, the condition carries a poor prognosis. Those with an intact ventricular septum often do not survive beyond the first year of life while those with a large VSD and/or PDA suffer from severe pulmonary congestion.[10] Historically, atrial switch operations known as the Mustard and Senning procedures were performed. Both entailed the construction of conduits directing the pulmonary veins through the tricuspid valve to the right ventricle by means of an atrial flap, as well as rerouting the systemic circulation returning from both vena cavae through the mitral valve to the left ventricle via the intraatrial septum. With significant complications including right ventricular failure, atrial arrhythmias, systemic and pulmonary leaks or obstructions and unexpected late sudden deaths, the Mustard and Senning procedures fell out of favor as newer techniques were developed.[11]

With advances in cardioplegia and other surgical techniques, the arterial switch operation gained favor and is now routinely employed in the definitive treatment of TGA. Initially performed by Jatene and colleagues in 1976, the procedure involves the transection and reanastamosis of the great arteries to their appropriate chambers as well as the transposition of the coronary arteries to the neo-aortic root. Performing arterial switch operations on a simple D-TGA necessitates a left ventricle immediately capable of functioning at adequate systemic pressures. From birth, the amount of pressure that the left ventricle is required to produce to overcome pulmonary resistance rapidly decreases. By the end of the first week, the pressure produced is less than half of the right ventricular pressure. It is therefore optimal to operate as early as possible in order to prevent myocardial deconditioning as a result of lower pressures. Patients with a large VSD maintain adequate left ventricular pressures and are therefore candidates for delayed operations if needed.[9]

In order to perform the operation, the heart of the neonate must be temporarily stopped. Cardioplegia, or stopping of the heart, was traditionally done in an antegrade fashion. By this method the cardioplegic solution used for induction and maintenance of diastolic arrest is injected into the aortic root. An aortic cross clamp (ACC) is placed and the solution flows into

the coronary ostia. Once the aorta is opened as occurs during the ASO, repeated doses cannot be easily given. Some surgeons utilized very small catheters to instill repeated doses of cardioplegia directly into the coronary ostia, while others tried to operate quickly as the myocardial protection of the initial cardioplegia continued to diminish.[14] A rare but well known complication of direct ostial antegrade cardioplegia is iatrogenic injury such as intimal dissection or future ostial stenosis upon cannulation of the coronary arteries.[3, 8]

The method routinely employed at St. Joseph's Hospital and Medical Center and Phoenix Children's Hospital to administer repeated doses of cardioplegia is by retrograde infusion into the coronary sinus. This technique, initially described for adult cardiac surgery and commonly used in adult patients, has been less readily adapted by some surgeons in congenital heart surgery. The advantages of retrograde cardioplegia include the ability for repeat doses while the aorta is open and the potential to continue operating during intermittent dose administration.[13] It also avoids the potential risk of direct cannulation of the coronary ostia.

Both approaches necessitate the maintenance of circulation for the duration of the cardiac repair. Previous studies have indicated a shorter ACC time and CPB time amongst patients who underwent retrograde cardioplegia as compared to those receiving antegrade cardioplegia.[8] The goal of this study was to employ a retrospective chart review comparing procedural characteristics and short-term postoperative outcomes in patients who received antegrade vs. retrograde cardioplegia during arterial switch operations.

Materials and Methods

A retrospective chart review of 48 patients who underwent neonatal arterial switch operations at our institution from 2005-2008 was performed. All patients were given an initial loading dose of 4:1 cardioplegic solution through the aortic root. Forty-three patients were given subsequent doses through retrograde coronary sinus perfusion (RCSP) every 20 minutes, while 5 patients received all doses in an antegrade fashion. All patients underwent delayed sternal closure as was standard of care at the time. The study was approved by the institutional review board of St. Joseph's Hospital and Medical Center.

Preoperative demographics (gender, age, admission weight, and presence of VSD), intraoperative characteristics (CPB time, ACC time, and total volume of cardioplegia) and postoperative outcomes (hospital length of stay, postoperative arrhythmias, postoperative ventilation days, and survival to discharge) were compared between the two groups at our institution. Categorical variables were analyzed using Fisher's exact test while continuous variables were analyzed using two sample independent t-testing. A p-value <0.5 was set as the standard for assessment of statistical significance.

Results

When comparing characteristics between the antegrade and retrograde groups, an increased CPB time was noted among the retrograde group. Patients receiving retrograde cardioplegia also displayed a trend towards an increased ACC time which was not statistically significant. (Table 1)

When comparing outcomes between the retrograde and antegrade groups, all patients survived to discharge or transfer. While no statistically significant difference in outcomes was found in comparing the two groups, the patients receiving retrograde displayed a trend towards shorter durations of postoperative ventilation and hospital length of stay. (Figure 1) Patients receiving retrograde cardioplegia displayed a trend towards an increased incidence in postoperative arrhythmias, although this was not statistically significant. (Table 2)

Table 1: Antegrade and Retrograde Patient Characteristics

Variable	Antegrade	Retrograde	P value
# Observed	n = 5	n = 43	
Age (days)	63.2 +/- 107.46	16.63 +/- 44.58	NS
Gender (M/F)	M = 3, F = 2	M = 21, F = 22	
Admission Wt (kg)	3.64 +/- 1.90	3.48 +/- 1.01	NS
Cardiopulmonary Bypass Time (min)	95.6 +/- 36.59	146.74 +/- 44.26	$\leq .05$
Aortic Cross Clamp Time (min)	74.4 +/- 24.42	101.30 +/- 29.56	NS
Total Volume Cardioplegia (mL/kg)	25.58 +/- 14.49	23.47 +/- 13.42	NS
Ventricular Septal Defect	Y = 2 N = 3	Y = 20 N = 23	NS

*All data expressed as mean +/- standard deviation where applicable; NS = not significant (p>.05).

Figure 1: Postoperative Outcomes Between Retrograde and Antegrade Groups
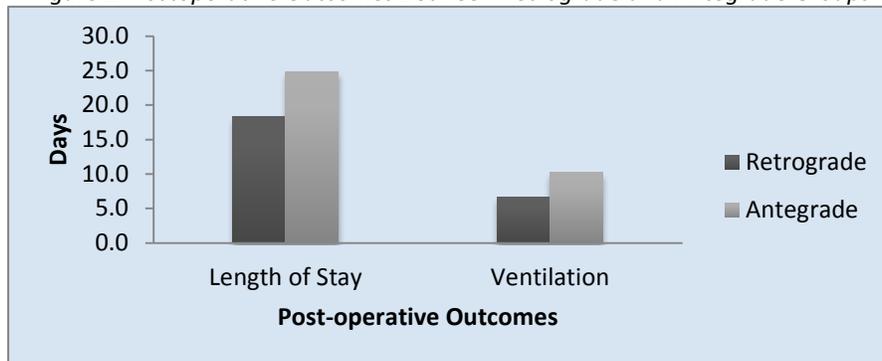
Table 2: Retrograde vs. Antegrade Outcome Comparisons

	Retrograde	Antegrade	P value
# Observed	n = 43	n = 5	
Postoperative ventilation (days)	6.67 +/- 8.57	10.2 +/- 10.1	NS
Postoperative arrhythmias (Y/N)	Y = 12, N = 31	Y = 0, N = 5	NS
Survival at discharge (Y/N)	Y = 43 N = 0	Y = 5 N = 0	NS
Postoperative length of admit (days)	18.3 +/- 15.3	24.8 +/- 11.8	NS

Discussion

As primary outcome measures, patients receiving retrograde cardioplegia displayed a trend toward shorter durations of postoperative ventilation and/or hospital length of stay, a finding that was consistent with previous studies.[6, 8] While hemodynamic indices were not directly measured in this study, a study by Yonenaga and associates found no difference in elevations of cardiac enzymes or inotropic support requirements while another study by Maddali and associates displayed a trend towards increasing inotropic demands in patients receiving antegrade cardioplegia .[6, 8] With some historical concern for the adequacy of retrograde cardioplegia in right ventricular perfusion, these postoperative outcome measures suggest no clinically significant detrimental effects.[1,5,6,8]

A trend towards an increased incidence of postoperative arrhythmias in our retrograde patients was noted. One possible explanation for this finding is the proximity of the AV node and his bundle to the coronary sinus and potential for irritation during cannulation. This finding conflicts with a previous study showing a trend towards a higher incidence of postoperative arrhythmias in patients receiving antegrade cardioplegia.[6]

While it has been postulated that retrograde cannulation obviates the need to pause for intermittent antegrade delivery and thereby decreases ACC and CPB time, this was not reciprocated in our study.[8] Patients receiving retrograde cardioplegia demonstrated an increased CPB time and a trend towards an increased ACC time, which could indirectly reflect the complexity of disease or technical difficulties encountered intraoperatively.

Limitations

       Acknowledged limitations of this study include the design as a retrospective chart review. In addition, the small sample size of antegrade patients cannot be ignored.

Future Directions

      Future directions include a prospective study involving a larger group of antegrade patients. While the incidence of postoperative arrhythmias between our antegrade and retrograde groups was not statistically significant, the observed trend certainly warrants further investigation. In addition, while retrograde cardioplegia has been shown to underperfuse the right ventricle in various populations, there is a paucity of literature on the resultant long-term outcomes of using retrograde cardioplegia as the sole method of myocardial protection.[1, 5]

Conclusions

In addition to previous studies suggesting potentially shorter operation times and the avoidance of continued coronary ostial manipulation, the results of this study suggest possibly shorter durations of postoperative ventilation and hospital length of stay in patients receiving retrograde cardioplegia.[6, 8] While the limitations of this study cannot be ignored, it nonetheless represents the largest group of patients receiving retrograde cardioplegia collected and studied by the same team of surgeons. The encouraging postoperative measures noted and 100% survival-to-discharge/transfer in those receiving retrograde cardioplegia supports its use as an equivalent- if not preferable- means of myocardial protection during neonatal arterial switch operations.

References

1. Allen, B.S., Winkelmann, J.W., Hanafy, H., Hartz, R.S., Bolling, K.S., Ham, J., & Feinstein, S. Retrograde Cardioplegia Does Not Adequately Perfuse the Right Ventricle. The Journal of Thoracic and Cardiovascular Surgery 1995; 109:1116–1126

2. Castela, E. & Martins, P. Transposition of the Great Arteries. Orphanet Journal of Rare Diseases 2008; 3:27

3. Fishman, N., Youker, J.E., & Roe, B. Mechanical Injury to the Coronary Arteries During Operative Cannulation. American Heart Journal 1968; 75(1):26-33

4. Hijazi, Z. M., Sommer, R. J., & Rhodes, J. F. Pathophysiology of Congenital Heart Disease in the Adult; Part III: Complex Congenital Heart Disease. Circulation 2008; 117: 1340-1350

5. Kaukoranta, P., Lepojärvi, M., Kiviluoma, K., Ylitalo, K., & Peuhkurinen, K. Myocardial Protection During Antegrade Versus Retrograde Cardioplegia. The Annals of Thoracic Surgery 1998; 66(3):755-761

6. Maddali, M., Valliattu, J., Fahr, J., Al Delamie, T., & Zacharias, S. Myocardial Protection During Neonatal Cardiac Surgery. The Journal of Tropical Pediatrics 2006; 52(1): 59-62

7. Midell, A. I., DeBoer, A., & Bermudez, G. Postperfusion Coronary Ostial Stenosis: Incidence and Significance. The Journal of Thoracic and Cardiovascular Surgery 1976; 72(1):80-5

8. Yonenaga, K., Yasui, H., Kado, H., Nakamura, Y., Shiokawa, Y., Yamamoto, T., & Miyamoto, K. Myocardial Protection by Retrograde Cardioplegia in Arterial Switch Operation. The Annals of Thoracic Surgery 1990; 50: 238-42

9. Fulton, D. & Fyler, D. D-Transposition of the Great Arteries. Nadas' Pediatric Cardiology 2006; 2: 647-658

10. Liebman, J., Cullum, L., & Belloc, N.B. Natural history of transposition of the great arteries. Anatomy and birth and death characteristics. Circulation 1969; 40:237

11. Dodge-Khatami, A., Kadner, A., Berger, F., Turina, M.I., & Pretre, R. In the Footsteps of Senning: Lessons Learned From Atrial Repair of Transposition of the Great Arteries. The Annals of Thoracic Surgery 2005; 79(4):1433-1444

12. Ott, D. The Arterial Switch Operation for Transposition and Complex Heart Defects. Texas Heart Journal 1992; 19(3):232-238

13. Oriaku G, Xiang B, Dai G, et al. Effects of retrograde cardioplegia on myocardial perfusion and energy metabolism in immature porcine myocardium. The Journal of Thoracic Cardiovascular Surgery 2000; 119:1102–9.

14. DeLeon, S., Idriss, F., Ilbawi, M., Duffy, C.E., Benson, D.W., & Backer, C. Comparison of Single versus Multidose Blood Cardioplegia in Arterial Switch Procedures. The Annals of Thoracic Surgery 1988; 45: 548-553