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Late complications associated with the Fontan circulation

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THE RECENT SIGNIFICANT REDUCTION IN operative mortality associated with surgical completion of the Fontan circulation is clearly multi-factorial. Better understanding of the fundamental physiological and anatomical issues have led to refinements in operative technique, early neutralization of potential risk factors, widespread use of a staged approach, and selective application of the concept of fenestration or incomplete partitioning. While further reduction of operative mortality is important, and may be anticipated in the future, major emphasis now must be placed on optimizing functional outcome, and understanding and managing the late complications associated with the unique physiology produced by the Fontan circulation.

Can there be a "perfect" Fontan procedure?

In 1990, Fontan, together with Kirklin, Blackstone, and associates[1] applied meticulous statistical methods to a heterogenous group of patients undergoing an initially complete non-staged and non-fenestrated Fontan operation. The hazard function for death had three phases. The early phase was of about 1-year duration, with rapidly declining risk of death. There followed a relatively flat period of very low constant risk of death, and then a third, gradually rising, late phase of hazard, which became evident about 8 years after the surgical operation. Fontan et al.[1] reasoned that many deaths occurring after creation of the Fontan circulation may have been due to circumstances that, based upon lessons learned, could be avoided. To address the question of whether the persisting and rising hazard function for death existing for years after creation of the Fontan circulation could be a result of these now avoidable circumstances, they undertook an analysis of survival under circumstances that they considered ideal. Into the multi-variable equation for risk factors derived from the analysis of their group of patients, they entered optimal values, considered to be "within the realm of realism", for each of their identified risk factors. Under these ideal circumstances, survival after 15 years was predicted to be 73%, and the gradually rising late phase of hazard was still present. The only risk factor identified for this late phase of hazard was older age at operation. Is it then the case that the late phase of hazard for premature death is an inevitable accompaniment of creation of the Fontan circulation? The answer is unknown. Many of the issues and events that complicate the course of survivors with the Fontan circulation are only now beginning to be understood.

Functional state

Studies of patients having the Fontan circulation have found that resting cardiac indexes were often not different from those of healthy controls, but a minority of patients with the Fontan circulation were able to achieve cardiac indexes at exercise similar to controls. The predominant mechanism for achieving high cardiac output during exercise is increased heart rate, with low-normal resting ejection fraction and smaller increments in ejection fraction with exercise than in normals. One recent study[2] demonstrated an inverse relationship between peak uptake of oxygen and age at creation of the Fontan circulation, particularly, in patients with a dominant morphologically right ventricle. Mahle et al.,[3] at the Children's Hospital of Philadelphia, undertook an evaluation of the impact of

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early ventricular unloading on exercise performance in pre-adolescents with functionally univentricular hearts converted to the Fontan physiology. Evaluating the results of exercise stress testing in 46 patients, they concluded that volume unloading at younger age was associated with significantly increased aerobic capacity. Patients who had surgical reduction of ventricular volume work by either hemi-Fontan or Fontan procedures earlier than 2 years of age were compared to a group who had successful Fontan operations, but in whom the volume-loaded state of the dominant ventricle had persisted for more than 2 years. They observed better peak exercise capacity in the group in which the unloading had been achieved at an early age.

Neurologic state

As operative survival has improved, emphasis has been placed on assessment of neurodevelopmental outcomes. Uzark et al.,[4] in San Diego, tested 32 patients with the Fontan circulation and found, on average, normal developmental indexes. Goldberg and colleagues,[5] at the University of Michigan, studied a group of 51 similar patients. They undertook developmental testing, evaluated behaviour, and imaged the central nervous system. Most of the survivors achieved intelligence scores within or above the normal range. They performed significantly better in areas of verbal intelligence than in non-verbal areas. The diagnosis of hypoplasia of the left heart, and a history of perioperative seizures, proved to be independent risk factors for lower developmental scores. Nearly half of the patients who underwent imaging of the central nervous system, using either magnetic resonance or computerized tomography, were demonstrated to have acquired abnormalities, but there was no evidence that significant developmental abnormalities were related to evidence of central nervous systemic ischaemia. An evaluation of 133 patients who had been converted to the Fontan circulation at Children's Hospital Boston in the 1970s and 1980s[6] revealed that most individual patients had cognitive outcomes and academic function within the normal range, but the performance of the cohort was lower than that of the general population. Importantly, in a review of 645 patients who had undergone Fontan procedures at the same institution, duPlessis and associates[7] found a 2.6% incidence of stroke. The risk period for stroke extended from the first postoperative day to 32 months after the Fontan procedure.

Thromboembolic complications

Thromboembolic events account for significant morbidity and mortality in the setting of the Fontan circulation. Retrospective studies have reported the incidence of such events to range from 3% to 20%.[8,9] Their time course ranges from 24 hours after surgery to as late as 16 years. Efforts have been made to characterize abnormalities of coagulation that are associated with the Fontan circulation[10,11] but they are hampered in part by lack of age-specific controls. There is general agreement that ligation of the pulmonary trunk, leaving a blind cul-de-sac distal to the pulmonary valve, is a worrisome substrate for the occurrence of thromboembolism. Almost every other assertion with regard to thromboembolic events after creation of the Fontan circulation is the subject of debate. And, to date, there is a lack of evidence from randomized controlled trials to support the use of any specific strategy for anti-coagulative therapy. In the absence of any compelling evidence to support the routine use of Warfarin, it is our practice to give aspirin, at a dose of 81 milligrams daily, to all our patients with the Fontan circulation. We commence treatment on the first postoperative day, and continue indefinitely. This strategy, combined with the operative techniques that we utilize, has resulted in freedom from clinically apparent thromboembolic complications in a large group of young patients.[12]

Obstruction of the systemic ventricular outflow tract

Subaortic obstruction is a frequent accompaniment of the functionally single ventricle. It generally occurs when the aorta arises from an incomplete right ventricle that is connected to the dominant ventricle by the ventricular septal defect. This defect may be restrictive to flow at birth, or may become obstructive after surgical procedures that reduce the volume work of the dominant ventricle. This phenomenon impacts on the management of patients at many stages. In neonates, significant obstruction is often associated with hypoplasia of the aortic arch. With parallel pulmonary and systemic circulations, and particularly when the arterial duct is patent, it is difficult to quantitate subaortic obstruction. In the setting of discordant ventriculo-arterial connections, the potential for development of obstruction in the systemic outflow tract must be presumed, even if it is not readily apparent. Thus, it must be considered in planning initial palliation. For some time, it has been recognized that banding of the pulmonary trunk is associated with a tendency for progression of subaortic obstruction.[13] This technically simple means of palliation, therefore, must be considered carefully when there is an anatomic substrate for obstruction of systemic ventricular outflow. Appropriate alternatives are the performance of a Norwood Procedure, or a palliative arterial switch as the initial operation. Placement of

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conduits from the ventricular apex to the aorta, or direct relief of subaortic obstruction by enlargement of the ventricular septal defect, are less desirable strategies. If systemic obstruction is not addressed definitively at the time of initial palliation, it may progress, with important consequences, at any stage during the sequence of reconstructive procedures, or may develop after completion of the Fontan circulation.[14] This fact, together with the known deleterious effects of systemic ventricular outflow obstruction, and the associated secondary myocardial changes on the function of the dominant ventricle, suggests that an optimal strategy for dealing with subaortic obstruction in the setting of the functionally univentricular heart is simply to prevent it. Thus, if present in the neonate, subaortic stenosis is best managed by amalgamation of the proximal part of the pulmonary trunk with the ascending aorta, and relief of any obstruction within the arch.[15,16] Alternatively, the same goal can be achieved by a palliative arterial switch operation combined with repair of the aortic arch.[17,18] In patients in whom subaortic obstruction was not important, or not apparent at initial presentation, but where there remains the potential for its development, such as those with discordant ventriculo-arterial connections and a complete muscular subaortic infundibulum, it is advisable to address the issue by anastomosing the pulmonary trunk to the aorta by means of the Damus–Kaye–Stansel procedure at the time of the hemi-Fontan or bidirectional Glenn anastomosis. If these guidelines are followed, only rarely will a direct ventricular approach be required to relieve subaortic stenosis, and the adverse impact of myocardial hypertrophy on the outcome of creation of the Fontan circulation should be effectively neutralized by its prevention.

Arrhythmias

Both tachyarrhythmias and bradyarrhythmias complicate the course and management of patients converted to the Fontan circulation. They are thought to be consequences either of injury to the sinus node or its blood supply, extensive atrial incisions and sutures lines, or chronic exposure of the atrial myocardium to elevated pressure, with subsequent dilation. In some instances, they are directly related to the underlying anatomic substrate, as in hearts with discordant atrioventricular connections or isomerism of the atrial appendages with left-handed ventricular topology, when there are intrinsic abnormalities of the atrioventricular conduction system, or to haemodynamic factors such as atrioventricular valvar regurgitation. Analysis of risk factors for the development of tachyarrhythmias in patients with the Fontan circulation support these hypotheses. A study of nearly 500 patients who underwent modified Fontan operations at the Mayo Clinic between 1985 and 1993[19] revealed multiple risk factors for supraventricular tachyarrhythmias, including atrioventricular valvar regurgitation, abnormal atrioventricular valves, preoperative supraventricular tachyarrhythmias, and age at operation. The procedure used to create the Fontan circulation was not strongly predictive, though the frequency of supraventricular tachyarrhythmias was slightly lower in patients with an atriopulmonary connection using a lateral tunnel than in those with a total cavopulmonary connection. In a study from the Children's Hospital Boston,[20] involving 334 early survivors with the Fontan circulation created between 1973 and 1991, atrial flutter was identified in one-sixth of the cohort at a mean of 5.3 plus or minus 4.7 years, and with a range from 0 to 19.7 years. The flutter developed sooner, and was more likely to occur, in patients who were older at the time of creation of the Fontan circulation. The presence of sinus nodal dysfunction was associated with a higher incidence of atrial flutter. While there was a lower prevalence of atrial flutter in patients with a total cavopulmonary connection, the follow-up for that group was shorter. Analysis of a smaller series of similar patients by Paul et al.[21] in Hannover, Germany, also revealed a lower risk of supraventricular tachyarrhythmias in those with a total cavopulmonary as compared to an atriopulmonary connection.

Efforts to minimize the risk of arrhythmias in those with the Fontan circulation are based upon technical modifications that minimize injury to the sinus node and its blood supply, minimize atrial incisions and sutures line, particularly in the region of the terminal groove, and guard against or reduce atrioventricular valvar regurgitation. It is not yet clear whether creation of the total cavopulmonary connection using a lateral atrial tunnel is superior to the atriopulmonary connection with regard to the risk of arrhythmias, though increasing evidence suggests that this is the case. Proponents of the extracardiac conduit for creation of the total cavopulmonary connection suggested the potential advantage of avoiding incisions and suture lines in the region of the sinus node and its blood supply, and predicted a lower frequency of postoperative arrhythmias. At least one study comparing the incidence of early sinus nodal dysfunction between groups of patients who had either a lateral tunnel or an extracardiac conduit used to create the Fontan circulation has shown no discernable difference in the incidence of early postoperative sinus node dysfunction.[22] Options for management of recurrent or persistent postoperative arrhythmias following creation of the Fontan circuit include pharmacological anti-arrhythmic therapy, permanent pacing to address sinus nodal dysfunction and potentially minimize

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the likelihood of tachyarrhythmias, and in selected instances, conversion from an atriopulmonary to a total cavopulmonary connection using either a lateral tunnel or an extracardiac conduit.[23] The most aggressive and most productive approaches have combined conversion to the total cavopulmonary connection, atrial reduction, performance of a modified Maze-type procedure, and permanent pacing.[24,25]

Protein-losing enteropathy

This syndrome, thus far incompletely understood, is characterized by excessive loss of proteins from the serum into the intestinal lumen. Manifestations include oedema, immunodeficiency from hypogammaglobulinemia, malabsorption of fat, loss of lymphocyte from the intestine, hypercoagulopathy from loss of clotting factors, and electrolytic disorders, including hypocalcemia and hypomagnesemia. The syndrome is known to occur with certain primary gastrointestinal disorders, abnormalities of lymphatic drainage from the gut, and certain cardiovascular disorders, such a constrictive pericarditis. Its incidence in those with the Fontan circulation has been estimated to be as high as 13.4%,[26] though the prevalence in an international multi-centric study was only 3.7%.[27] The time to onset after creation of the Fontan circuit is variable. Survival after its development is poor, with half the dying within 5 years of diagnosis, and four-fifths within 10 years. The pathophysiology is not clear. While those with the Fontan circuit share the common feature of elevated central venous pressure with other cardiac patients know to be at risk for the syndrome, such as those with constrictive pericarditis, tricuspid regurgitation, and obstruction of the inferior caval vein, the syndrome has been known to occur in patients with generally very satisfactory haemodynamics in the Fontan circuit, with low venous pressures. It is not, therefore, an invariable accompaniment of those in whom the Fontan circulation is failing with markedly elevated venous pressure. It has been hypothesized that the enteropathy is related to low cardiac output and low states of flow after creation of the Fontan circuit, which may result in increased mesenteric vascular resistance and lead to altered intestinal mucosal function. A relationship has been proposed between protein-losing enteropathy and altered flow through the portal venous system after creation of the Fontan circuit.[28] While protein-losing enteropathy is associated with a high rate of mortality, certain interventions appear to have merit in selected cases. All patients with the syndrome should undergo full haemodynamic evaluation, including catheterization. Adverse anatomic and haemodynamic factors, including obstruction within the venous pathways, atrioventricular valvar regurgitation, and obstruction in the systemic ventricular outflow tract, must be addressed. Beyond this, fenestration by surgical means[29] or catheter techniques[30] has been reported to result in resolution in some patients, albeit at the expense of arterial desaturation. When the syndrome has occurred in patients with significant sinus nodal dysfunction, pacing has sometimes been associated with improvement.[31] Medical therapy with corticosteroids or heparin has been utilized with some success. Ultimately, in patients with protein-losing enteropathy refractory to all of these measures, transplantation may represent the only therapeutic alternative.

Conclusion

For the vast majority of patients with a functionally univentricular heart, creation of the Fontan circulation represents, at the present time, the best form of surgical reconstruction. The evolution over three decades from the initial "corrective" operations proposed for tricuspid atresia, to the current forms of surgical management, has been associated with progressive decline in the risk of operative mortality. Though the body of knowledge concerning patients with functionally single ventricles, and strategies for management culminating in creation of the Fontan circulation, has become vast, many questions remain unanswered. Perhaps most important of these is the issue of whether or not the late phase risk of premature death after a presumed "ideal" surgical procedure as identified a decade ago by Fontan et al.[1] is, in fact, inevitable. Clearly the concept of what constitutes an "ideal" operation, under ideal conditions, has evolved and must be continually updated and redefined.

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