Aspirin as a Novel Anti-Inflammatory Modality in the Fontan Patients

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Background:

Over the past 40 years, one of the most important advances in the field of congenital heart disease has been the development of a long-term palliation strategy for individuals with single ventricle. Pioneers such as Fontan [1], Kreutzer[2]], de Leval [3], Bove [4], as well as many others, have contributed to creating an effective surgical palliation for individuals with single ventricle physiology by using a unique surgical reconstruction strategy of directing systemic venous blood flow to the pulmonary circulation in the absence of the pulsatile force of the sub-pulmonary ventricle. As a result of this surgical strategy, newborns with single ventricle congenital heart disease that were felt to have a near uniformly lethal type of heart disease 45 years ago, now have over a 70% chance of surviving 15-25 years after surgery. [5-8]

However, as these individuals have grown into adolescence and adulthood, it is now clear that there are significant long-term limitations with this strategy. Arrhythmias, valvular insufficiency and ventricular dysfunction are common. [9, 10] In addition there is growing evidence for a multitude of end-organ dysfunction, including poor somatic growth and development, increased risk of thromboembolism, peripheral venous insufficiency, and diabetes, protein losing enteropathy, plastic bronchitis and hepatic cirrhosis. [11-17]

Many have suggested that the combined effect of low cardiac output and increased central venous pressure are the cause of most late-complications associated with the Fontan operation. [15, 18] However, even though all Fontan patients have elevated central venous pressures and low to low normal cardiac output, these variables are not predictive of either when or which Fontan patient will develop a specific late complication.[19] For example, no all individuals with protein losing enteropathy have high central venous pressure and low cardiac outputs. [20, 21] We speculate that an alternate hypothesis for the cause of late-complications associated with the Fontan operation is that the chronic increase in central venous pressure produces generalized lymphedema, especially in the abdomen, that leads to chronic inflammation and resultant damage to many of the abdominal organs. Olszewski [22]has reported that the level of cytokines are elevated in lymphedema lymph. Olszewski also speculated that the high levels of cytokines are attributed to their local production by infiltrating immune cells. He reported that the lymph levels of cytokines, exceeded serum concentration by factors of 10 or more, and clearly point to an intensive inflammatory process in the tissues affected by the lymphedema [23]. Ostrow et al reported elevated inflammatory markers, increased TNF-alpha, CRP and C-reactive protein, in Fontan patients with protein-losing enteropathy [24]. Furthermore, Rychik reported that on endoscopic evaluation his group has found subtle evidence for inflammation/colitis in a number of individuals with protein-losing enteropathy following the Fontan operation [15]. Racz et al reported that the plastic bronchitis airway casts from children with Fontan physiology are composed of fibrin and are cellular and inflammatory in nature, providing evidence that their formation cannot be explained simply by lymph leak into the airways [25]. Consequences of cellular necrosis including extracellular histones and the apparent low number of T cells indicate that a derangement in inflammation resolution likely contributes to cast formation. There have been few reports of abnormal inflammatory markers in Fontan patients who are doing well. Zyblewski et al reported that after the Fontan operation, the plasma HDL-cholesterol levels were significantly reduced [26]. Since HDL-

cholesterol has been identified as an important anti-inflammatory mediator [27], Zyblewski et al have speculated that the low levels of HDL-cholesterol observed in their study raises the possibility that single-ventricle patients may be in a chronic inflammatory state. We have also [28] demonstrated an abnormal lipid profile in Fontan patients. We reported that Fontan patients have decreased total cholesterol, LDL-cholesterol and HDL-cholesterol, while triglycerides remain normal. In a recent study we have demonstrated that the decrease in cholesterol is related to a decrease in biosynthesis that may be mediated by inflammation (our Fontan patients had significantly higher CRP's compared to our control subjects).(unpublished data) A similar lipid profile has previously been reported in individuals with rheumatoid arthritis. Amezaga-Urruela et al [29] reported a continuous decline in total cholesterol and LDL-cholesterol has been demonstrated during the 5 years prior to the development of rheumatoid arthritis and an increase in the total cholesterol/HDL-cholesterol ratio was also observed. Increasing CRP has been negatively associated with total cholesterol and HDL-cholesterol.[30] Furthermore, in rheumatoid arthritis, as inflammations decreases with therapy, lipid levels rise. [31, 32] Based on the similar lipid profile in Fontan patients with rheumatoid arthritis patients, we hypothesis that abnormal lipids in Fontan patients are an early marker of chronic inflammation.

HDL-cholesterol levels may also relate to the pathogenesis of protein losing enteropathy. In the protein losing enteropathy patients in our study,[28]they had markedly low HDL-cholesterol and higher triglyceride levels. One determinate of HDL-cholesterol levels is lipoprotein lipase activity. [33] Blades et al [34]have reported that high hepatic triglyceride lipase and low lipoprotein lipase activity are both important contributors to low HDL-cholesterol levels in both normotriglyceride and hypertriglyceride subjects. In rheumatoid arthritis these is an inverse relation between lipoprotein lipase activity and inflammatory state. [35] Bode et al {Bode, 2005 #496} has demonstrated that loss of heparin sulfate proteoglycans from the basolateral surface of intestinal epithelial cells plays a central role in the pathogenesis of experimental meddles of protein losing enteropathy. Lipoprotein lipase is secreted by many tissues of the body, particularly metabolically active adipose tissue in the abdomen. It is transferred to the luminal surface of endothelial cells, where it is bound as homodimers to heparin sulfate proteoglycans and can be released by administration of heparin.{Lewis, 2005 #468} Therefore, if HDL-cholesterol levels are low in Fontan patients due to a decrease in lipoprotein lipases activity, based on Bode's report {Bode, 2005 #496} there may be a direct relationship between HDL-cholesterol level and protein losing enteropathy.

Abnormal lipoprotein lipase activity has also been speculated to relate to abnormal adipose tissue fatty acid trafficking and maybe part of the pathophysiological basis for ectopic fat deposition in the abdomen and heart. [36] We have recently demonstrated that Fontan patients have abnormally increased amounts of epicardial fat content when compared to age and body mass index adjusted group of patients with repaired tetralogy of Fallot. (Unpublished data)

Based on this review of the literature and our preliminary studies, we hypothesis that the abnormal lipid values in Fontan patient reflect the presence of chronic inflammation. Aspirin is a well-known agent that has been used to treat chronic inflammations associated with a number of diseases including Kawasaki's disease, rheumatoid arthritis and acute rheumatic fever. It has known to be well tolerated by both adults and children. Aspirin exerts some of its anti-inflammatory action by inhibiting the activity of IκB

kinases-β (IKKs-β). We and others have demonstrated that aspirin can prevent or correct the insulin resistance associated with obesity.[37, 38] Pharmacologic modulation of arachidonic acid metabolites, such as aspirin, can positively modify lipid metabolism, increase HDL cholesterol. [39-41] Therefore in an attempt to test our hypothesis that the abnormal lipid values in Fontan patient reflect the presence of chronic inflammation, we plan to determine if the anti-inflammatory agent , aspirin, will normalize the lipid abnormalities in Fontan patients.

Protocol:

Patient Population: We plan to study 20 young adult subjects who have had Fontan repair of single ventricle. All subjects will be over 18 years of age and in good health. Individuals will be excluded if they have had active protein losing enteropathy within the past three years, have congestive heart failure, active arrhythmias, or on Coumadin. Any individual with a bleeding disorder or known esophageal varicies will also be excluded. Subjects who known to have more than 10 drinks per week will be excluded. Females who are pregnant and /or planning become pregnant will be excluded.

Protocol: After informed consent is obtained. Subjects will have fasting blood drawn for measurement of lipids, total cholesterol, HDL-Cholesterol, LDL-cholesterol and triglycerides, a complete metabolic panel, GGT, Complete blood count and differential, plasma insulin, inflammatory markers including sedimentation rate, high sensitivity C-reactive protein and haptoglobin. Individuals will also be asked to fill out the Short-Form 36 Quality of Life Survery. Individuals will be told to stop their current 81 mg/day of aspirin, and then be started on 650 mg (two 325 mg tablets) of aspirin 2 times a day. All aspirin will be provided by use. After two weeks of aspirin therapy all individuals will have a blood salicylate level taken 6 hours after their morning aspirin dose. Goal aspirin levels will be 15-20 mg/dl. If the level is less than 10 or greater than 20 mg/dl the aspirin dose will be adjusted. All individuals will be instructed into the early symptoms of aspirin toxicity include nausea, vomiting, tinnitus, and hyperventilation. If they should experience any of these symptoms they will be instructed to immediately call us. In addition, if the individuals have any excess bleeding, blood in their stool or abdominal pain they will be told to immediately call. After 8 weeks of aspirin therapy the individual will be asked to return for repeat fasting blood test including a salicylate level and repeat the Short-Form 36 Quality of Life Survey. In addition to measuring salicylate levels, drug compliance will be monitored by pill count. All individuals will be provided with more aspirin pills than necessary for the study. They will be asked to return all the unused aspirin pills and the number or remaining pills will be counted.

Statistical analysis:

This is a pilot study to determine the safety and feasibility of a larger randomized trial. This study will form the basis for a statistically valid sample size for this planned larger trial.

Our primary outcome variable will be a change in total cholesterol and HDL-Cholesterol. It is our hypothesis that aspirin therapy will result in an increase of either total cholesterol and/or HDL-cholesterol.

Secondary outcomes: We would expect that aspirin therapy would improve the inflammatory markers (decrease high sensitivity CRP, decrease neutrophil to lymphocyte ratio, decrease sedimentation rate and decrease haptoglobin level). We also expect that aspirin will decrease plasma insulin levels and reduce the calculated HOMA-IR value [(Fasting glucose*Fasting insulin)/405; where glucose is in mg/dl and insulin is in mU/l]. We also hope that aspirin therapy might improve perception of quality of life and possibly improve liver function tests.

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