Tetralogy of Fallot

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Introduction

Tetralogy of Fallot (TOF) is a congenital cardiac defect in dogs that is characterized by four cardiac abnormalities. These four include a large ventricular septal defect (VSD), pulmonic stenosis, dextroposition of the aorta, and right ventricular hypertrophy.[9] Congenital heart disease in dogs has a prevalence of 27 cases per 4000 dogs; however, the prevalence of TOF has only been estimated to be 1/4000.[9] Deoxygenated blood is delivered to the systemic circulation due to the combination of the VSD and pulmonic stenosis, creating a right to left shunt. This results in systemic hypoxemia. The hypoxia is often severe enough to cause cyanosis, or bluish discoloration of the tissues and mucus membrane due to lack of oxygen delivery to the tissues. The cyanosis can occur with exercise or at rest and often necessitates emergency medical treatment. Medical therapy and surgical treatment options have both been explored; without palliative surgery the prognosis for this condition is poor.[9]

History and Presentation

Tetralogy of Fallot has been studied and described by many scholars, with the first description being in children in 1673 by Nicholas Sten.[9] In 1888 Etienne-Louis Arthur Fallot published a paper that described the classic four anatomical anomalies that now make up the tetralogy: (1) pulmonic stenosis; (2) interventricular communication; (3) deviation of the origin of the aorta to the right; (4) concentric right ventricular hypertrophy.[9] The main pathophysiologic consequences of tetralogy depend on the magnitude of the ventricular septal defect and pulmonic stenosis.[6] These defects allow deoxygenated blood to reach systemic circulation and cause hypoxemia. The deviation, or dextroposition, of the aorta allows blood to flow into the aorta from both the right and

left ventricles. The right ventricular hypertrophy is a consequence of the pulmonic stenosis.[6]

Certain breeds are predisposed to TOF including Keeshonds, English Bulldogs and Wirehaired Fox Terriers;[9] however other breeds have been described.[8] The embryology and heritability has been studied in Keeshond dogs,[8] and it has been discovered that the breed has an abnormal conotruncal septum.[9] This anatomical abnormality is inherited as a simple autosomal recessive trait. Normally the conotruncal septum forms the upper portion of the interventricular septum, but in TOF this portion of the septum forms too far cranial. The cranial displacement of the septum leads to misalignment with the lower portion of the interventircular septum and results in a ventricular septal defect.[9] Consequently, the misalignment of the conotruncal septum leads to a narrowed right ventricular outflow tract leading to pulmonic stenosis and dextroposition of the origin of the aorta.

The clinical presentation in dogs with TOF varies from no clinical signs to extreme dyspnea and cyanosis.[5] Most dogs present when they are young with the most common presenting age being between 2 and 8 months old;[9] however, young dogs often die before a veterinarian examines them. Owners report that the animal has exercise intolerance or is less active than they used to be. If the animal is brought in as a puppy, the owner may report that he is not as active as his littermates or has stunted growth. The hypoxia can often lead to syncope if severe enough, and central nervous system signs have also been reported including seizures due to polycythemia.[9]

Upon physical examination, the veterinarian often notes that the animal is smaller than normal. Cyanosis can be present at rest; or may be induced with exercise. Systolic

murmurs may be present, heard best at the left heart base and are usually associated with the pulmonic stenosis.[9]

Pathophysiology

The hemodynamic consequences caused by tetralogy of Fallot are dependent primarily on the degree of pulmonic stenosis, the size of the ventricular septal defect,[6] and ratio of pulmonary to systemic vascular resistance.[9] It must be understood that the clinical manifestations of TOF are due to the shunting defect that is caused by the four abnormalities.[11] In normal cardiac anatomy, blood flows to the right and left circulations proportional to systemic and pulmonary resistances. However, in TOF blood flow is no longer proportional due to the pulmonic valve being stenotic. The stenosis, or thickening, of the pulmonic valve causes the resistance in the pulmonic valve to be greater than systemic vascular resistance. Thus, deoxygenated blood flows from the right ventricle through the VSD and out through the aorta. The amount of blood that flows through the aorta is dependent upon the resistance between the two circulations.[9] In comparison to a normal animal the pulmonary blood flow is decreased in these patients because of the pulmonic stenosis. As the disease progresses, the body can no longer respond to decreased pulmonary blood volume because the compensatory mechanisms deteriorate.[11] It then becomes a domino effect; the decreased blood flow means decreased venous return to the left ventricle leading to a decreased left ventricular size and stroke volume. Stroke volume is the amount of blood pumped from the left ventricle with each contraction. Consequently, the amount of oxygenated blood that reaches systemic circulation is decreased.[9]

The blood from the right ventricle that is pumped through the aorta is venous, or deoxygenated, blood that is being pumped into the systemic circulation. Venous blood has a low partial pressure of oxygen whereas arterial blood has a high partial pressure of oxygen.[9] When these two mix in the aorta, it leads to decreases in oxygen tension and oxygen content of the systemic blood. This decrease leads to a net result of deoxygenated blood reaching the tissues or hypoxemia. The severity of hypoxemia is directly related to the severity of the right to left shunting that is occurring due to the pulmonic stenosis.[3] Hypoxemia is both a sensitive and specific means of evaluating the severity of a right-to-left shunt;[9] patients that have clinical signs associated with TOF often have arterial oxygen tensions of less than 40mmHg at rest or with exercise.[9]

In response to severe hypoxemia, the kidneys release erythropoietin.[8] Erythropoietin stimulates red cell production. In symptomatic patients, this increase in red cell production leads to polycythemia, or an increased concentration of hemoglobin in the blood. Hemoglobin is responsible for transporting oxygen; therefore this is beneficial to a hypoxemic patient if their hematocrit is in the 55-70% range.[9] However, as the hematocrit increases, the blood viscosity also increases. The thicker the blood is, the more resistant it is to flow which leads to decreased cardiac output as well as decreased tissue oxygen delivery. Decreased oxygen delivery causes symptoms that range from syncope to seizures.[9]

Diagnosis

Reaching a diagnosis of TOF often requires a myriad of diagnostics. These include clinical signs, radiographs, electrocardiograms, blood work, and ultimately a definitive diagnosis from echocardiography.[6]

Utilizing both two-dimensional and color flow Doppler echocardiography allows for a definitive diagnosis of TOF to be made as it demonstrates all four of the defects.[9] The overriding aorta and ventricular septal defect can often be appreciated from the right parasternal long axis view, and utilizing color flow Doppler at this site will demonstrate the laminar blood flow from the right ventricle into the aorta. Pulmonic stenosis can be visualized from a right parasternal short-axis view of the heart base. Examining the right ventricular outflow tract and VSD with color flow Doppler will help in determining the direction (usually right-to-left) and magnitude of the shunt.[9]

Thoracic radiographs can be variable in dogs with TOF, ranging from diagnostic to inconclusive. There are usually two main changes appreciated on radiographs in these patients. One being an enlarged right ventricle due to concentric right ventricular hypertrophy, and the second being decreased pulmonary vascular markings.[11] The decreased pulmonary vascular markings may only be appreciable in severe TOF. On the dorsoventral projection, the region of the main pulmonary artery can appear normal, be indented or may even be enlarged due to post stenotic dilatation.[9]

The main finding on electrocardiogram (ECG) is a right axis shift in the frontal plane and terminal orientation of QRS complex toward the right ventricle.[9] The right axis shift is characterized by a deep S wave in leads I, II, III, and aVF.[9] These findings are consistent with right ventricular hypertrophy. Arrhythmias can be seen, but they are infrequent.[9]

The most common finding on blood work is an increased packed cell volume, also known as polycythemia.[6] However, younger animals may not have polycythemia even though they are extremely hypoxic. This has been attributed to the fact that younger

animals normally have a lower PCV than older animals.[9] Along with the complete blood cell count, an arterial blood gas analysis can be performed to determine the severity of the disease. Normal arterial oxygen tension is approximately 90-110 mmHg. In animals with TOF, it is reported that arterial oxygen tension is usually less than 40mmHg.[9]

Treatment and Management

Treatment of TOF is broken down into medical management, interventional therapy and surgical therapy.[9] The goal of medical therapy is to alleviate clinical signs associated with polycythemia.[11] This can be achieved by performing a phlebotomy on symptomatic patients. Even a mild decrease in hematocrit can help alleviate clinical signs; however, there is a fine line in which decreasing the hematocrit too much will cause the patient to become even more symptomatic. Therefore, the goal of phlebotomy is to achieve a hematocrit between 60 and 65%.[9] The following formula has been developed to determine how much blood can safely be removed:

Blood to be removed (mL) = [body weight (kg) x 0.8] x [actual hematocrit – desired hematocrit / actual hematocrit].[9]

When performing a phlebotomy, a large bore catheter should be used and the blood removed must be replaced with a balanced crystalloid intravenous fluid, 1 to 2 times the blood volume removed.[9] In cases that require frequent phlebotomies, hydroxurea can be tried in attempt to suppress the bone marrow. Hydroxyurea is a myelosuppressive agent that produces reversible bone marrow suppression, which aids in reducing red cell production. A loading dose of 30 mg/kg/day for 7-10 days followed by 15 mg/kg/day thereafter is the suggested dose in dogs.[9] Complete blood counts and platelet counts should be performed every 1-2 weeks, and if leukopenia, thrombocytopenia, or anemia

are detected then the drug should be discontinued until blood counts normalize. Side effects of hydroxyurea include anorexia, gastrointesintal upset, bone marrow hypoplasia and sloughing of the nails.[9] Hydroxyurea should be used with caution and at lower doses in cats due to methemoglobinemia being reported at higher dosages (>500mg).[14]

Beta-adrenergic blocking drugs are another treatment option for symptomatic patients with TOF.[6] Propranolol is the beta-blocker of choice, and is often used during an acute episode of hypoxemia.[9] However, it can also be used chronically to prevent hypoxemia. Beta-blockers are thought to reduce the dynamic outflow obstruction, decrease the heart rate, increase systemic vascular resistance, and decrease myocardial oxygen demand.[6] The suggested starting dose for propranolol is 2.5 mg/kg every 8-12 hours.[9]

Other medical therapies that are being researched include morphine, arteriolar constricting drugs, and phenylephrine.[9] Morphine has been used in human patients with TOF; however, it has not been reported in veterinary medicine. The theory behind morphine in human medicine is that it decreases the release of catecholamines, which decreases the heart rate.[1] With a decreased heart rate, the period of right ventricular filling is increased.[1] Arteriolar constrictors would be beneficial in patients with right to left shunting defects by increasing systemic vascular resistance leading to less blood being shunted from right to left and more blood being pumped through pulmonary vasculature. Unfortunately, there are currently no available arteriolar constrictors that are long acting or orally available.[9] Finally, alpha-adrenergic agonists such as phenylephrine can be used in acute hypoxemic episodes.[10] Phenylephrine increases systemic blood

pressure, which produces increased pulmonary blood flow, thus improving arterial oxygenation.[12]

Balloon valvuloplasty of the pulmonary valve has been explored as an interventional therapy. The success has been varied,[9] but it has been shown to increase pulmonary blood flow and decrease right-to-left shunting. In one study by Weder, Ames, and others,[13] a 6-month-old beagle that had been diagnosed with TOF underwent a balloon valvuloplasty. His clinical signs and quality of life improved for approximately 9 months.[13] However, after 9 months the dog became symptomatic again so a shunt procedure (modified Blalock-Taussig) was performed. Potential reasons that the dog became symptomatic again include re-stenosis of the pulmonary valve, persistent annular hypoplasia, reduced function of the RV, worsening of right-to-left shunting, and/or progressive polycythemia secondary to chronic hypoxia.[13] Although a shunt procedure had to be performed after the balloon valvuloplasty, it was still concluded that balloon valvuloplasty in dogs with TOF seems to be feasible technique that may result in improvement of clinical signs. It also may allow for the delay of the more invasive surgical palliation and provide time for weight gain and development of the pulmonary vascular bed for greater ease of surgical shunt creation.[13] The 9 months between the two procedures in this study allowed for the beagle to gain body weight that may have allowed for growth of pulmonary vasculature. The main concern with balloon valvuloplasty is that if the right ventricle obstruction is too aggressively dilated, an overwhelming left-to-right shunt can be created and lead to pulmonary edema. In human infants a balloon-to-annulus ratio of 1.5 to 2 has been proven to be effective in resolving

TOF related symptoms; however, to avoid creating a right to left shunt, a more conservative 1:1 balloon-to-annulus ratio should be used in dogs.[13]

Medical therapy and interventional therapy have both been proven to be beneficial, and should be pursued to improve the patient's quality of life if surgery is not an option. However, it has been reported that approximately 25% of affected animals will not be controlled by conservative or medical means.[5] Objective indications for surgery include debilitating exercise intolerance, a hematocrit above 65%, and resting hypoxemia with arterial oxygen saturation below 70%. [11]

In human medicine, it is now standard practice to perform complete surgical repair of TOF.[13] This requires cardiopulmonary bypass and open-heart surgery. It has been described several times in veterinary literature; however, it requires advanced surgical skills and financial resources and has a high mortality rate.[13] Therefore, it has yet to become a common practice in veterinary medicine. Before complete surgical repair was performed in human medicine, several shunting operations were described as palliative therapy. These techniques have been adapted to veterinary medicine with the primary goal being to increase the oxygen tension in the systemic blood.[11]

The basis of palliative surgery in TOF patients consists of producing systemic to pulmonary anastomoses.[3] The goal is to increase pulmonary blood flow without causing a left-to-right shunt. Several procedures have been described including Potts anastomosis, Waterston anastomosis, Blalock-Taussig anastomosis (BT), and a modified Blalock-Taussig anastomosis (mBT).[3] Potts anastomosis is a side-to-side anastomosis involving the aorta to the left main pulmonary artery. Waterston anastomosis includes the aorta to the right pulmonary artery. Both the Potts and Waterston methods are no longer

recommended due to the direct central anastomosis to the aorta. This direct anastomosis allows for a high rate of blood flow through the anastomosis site and frequently resulted in congestive heart failure.[3]

In 1945, Helen Taussig and Alfred Blalock described what is now the most common anastomosis used in palliative TOF surgery.[9] A Blalock-Taussig (BT) shunt creates an artificial patent ductus arteriosus by connecting the left subclavian artery to a pulmonary artery using an end-to-end anastomosis.[9] This anastomosis allows for some of the blood that is shunted from right-to-left through the VSD to be redirected and shunted back into the pulmonary artery. This increases the pulmonary blood flow and venous return to the left heart with a net result of an increase in oxygenated blood returning to the left heart to be pumped into systemic circulation.[9] A common complication of this anastomosis was that the subclavian artery kinked at the junction with the aorta.[3] Modifications to the BT shunt using synthetic materials such as polytetrafluorethylene (PTFE) have decreased the risk of complications. The mBT allows for a larger-diameter shunt to be sutured in place, which reduces the risk of thrombotic complications and kinking.[3] In a study of 6 dogs that underwent a mBT shunt procedure due to having severe TOF-associated clinical signs, 5 of the 6 dogs survived the immediate post operative period.[2] Two dogs died of unknown causes six years after the mBT shunt procedure, and the remaining three dogs survived long term.[2]

All of the techniques described require meticulous surgical technique. Patients that are surgical candidates should be evaluated by a cardiologist if possible, and referred to a surgeon that has experience in performing TOF palliative surgery.[9] Complete surgical repair of TOF would be necessary for a normal quality of life;[11] however, as

previously discussed, in veterinary medicine it is not a common procedure and not financially feasible for most patients. Therefore, out of the many shunts that have been described, the mBT shunt procedure has been proven to be the most feasible in dogs and allows long-term palliation for symptomatic patients with TOF.[2]

Case Outcome

Tetralogy of Fallot is a complex congenital heart defect that results from developmental defects of the conotruncal region in dogs. It has been genetically linked to Keeshond breeds,[9] but is also documented in several other breeds. The conotruncal defects that lead to TOF include pulmonic stenosis, ventricular septal defect, overriding of the aorta, and secondary right ventricular hypertrophy. The pathophysiologic changes are dependent on the magnitude of pulmonic stenosis (right ventricular outflow obstruction) and the size of the VSD.[6] These defects lead to a right-to-left shunt, and deoxygenated blood being pumped throughout the systemic circulation. This leads to the clinical presentation of systemic hypoxia and cyanosis, polycythemia, exercise intolerance and weakness. Definitive diagnosis is made by echocardiography with use of color flow Doppler. Medical therapy can be instituted with beta-blockers, frequent phlebotomy, and bone marrow suppressive drugs such as hydroxyurea. Interventional therapy has also been explored with balloon valvuloplasty of the pulmonic valve.[9] However, due to the severity of the disease, surgery is often considered. Complete surgical correction with bypass and open-heart surgery is the standard of care in human medicine;[13] however, it is not practiced often in veterinary medicine due to risk and cost. Many shunt procedures have been described in the literature, and the modified Blalock-Taussig (mBT) shunt has been successful at providing increased oxygenation and quality

of life. In conclusion, long-term survival is variable with patients that have TOF and each patient's quality of life should be taken into consideration when managing TOF long term.[9]

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