Pathology with a Porpoise

A Case Report of Cetacean Patent Ductus Arteriosus

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Introduction

On April 20, 2010, one of the worst man-made environmental disasters in United States' history occurred when the British Petroleum Deepwater Horizon oil rig exploded off the Gulf of Mexico. Over a three-month period following the event, the waters of the Gulf Coast were subjected to contamination by an estimated 4.9 million barrels of oil (Shannon 2011). This unfortunate incident had catastrophic effects on the Gulf Coast's marine ecosystems, resulting in unusual mortality events for many aquatic species. Marine mammal species were some of the hardest hit, and Atlantic bottlenose dolphins (*Tursiops truncatus*) experienced a significant spike in die-off rates during the years following the oil spill.

The increase in stranded marine mammals following the Deepwater Horizon incident necessitated immediate response and investigation into the unusual mortality event. Many federal and private organizations, including the Institute for Marine Mammal Studies (IMMS), responded to the catastrophic event and helped investigate the resulting environmental impact on marine species. IMMS was established in 1984 as a non-profit organization with the goals of furthering marine mammal research and promoting public education and marine conservation efforts. In addition to its educational foundations, IMMS also has a long history with the National Stranding Network, which played an important role in its efforts following the Deepwater Horizon spill. The legal fallout from that incident resulted in the largest environmental damage settlement in United States history under the Clean Water Act and the Oil Pollution Act (NOAA, 2017). Although the unusually high mortality rates directly related to the oil spill officially ended in 2014, funding from the legal settlement has continued to provide enhancements in the rescue and conservation research of dolphins and other marine mammals. Under the Resources and Ecosystems Sustainability, Tourist Opportunities, and Revived

Economies (RESTORE) of the Gulf Coast States Act of 2012, allocations from the Deepwater Horizon settlement support a grant that allows collaborations between the Institute for Marine Mammal Studies and Mississippi State University College of Veterinary Medicine to enhance veterinary knowledge of aquatic marine mammals and further research efforts in marine conservation (NOAA, 2017). Part of this collaboration involves educational opportunities including performing post-mortem examinations on deceased stranded marine animals. These opportunities provide invaluable information and insight into normal anatomical variance and disease pathology in relatively unstudied species.

History and Presentation

On September 21, 2017, the Institute of Marine Mammals Studies was contacted regarding a dolphin stranding in Ocean Springs, Mississippi. The remains of a young adult female Atlantic bottlenose dolphin (*Tursiops truncatus*) were recovered by IMMS staff the same day, and the remains were determined to be a Code 2 stranding, or fresh dead stranding. The remains were frozen for later examination and necropsy evaluation.

Post Mortem Findings

On Monday, August 13, 2018, the remains of the young adult female Atlantic bottlenose dolphin, originally recovered on September 21, 2017, presented to Mississippi State University College of Veterinary Medicine for necropsy. According to the official necropsy report, the remains were determined to have advanced post mortem autolysis and were designated as early grade 3. The abdomen appeared significantly distended on gross observation. A moderate amount of dark red, watery fluid was noted within the abdominal cavity. The mesenteric veins within jejunal arcade were torturous and moderately distended. The stomach and intestines were determined to be within normal limits containing normal ingesta, and the liver was determined to

be severely autolyzed. Approximately 250ml of red tinged fluid was collected from inside the thoracic cavity. Examination of the lungs reveals clear red tinged fluid on cut surface. Approximately 15ml of red tinged fluid was collected from within the pericardium. The heart was determined to be enlarged with a mildly dilated right ventricle and a thickened right ventricular wall. A ductus arteriosus was observed extending between the descending aorta and the main pulmonary artery measuring approximately 2-3mm in diameter. All other post-mortem findings were determined to be within normal limits.

Based on the post-mortem findings, the official necropsy report cited the most likely cause of death as congestive heart failure, both right and left sided, secondary to patent ductus arteriosus. The presence of abdominal fluid and severe dilation of the veins within the jejunal arcade are consistent with signs of right sided heart failure. This venous congestion within the jejunal arcade is likely due to chronic passive congestion despite the liver being too autolytic to definitively identify changes consistent with hepatic congestion. Additionally, the pulmonary edema observed in the lung is strongly associated with changes seen in severe pulmonary hypertension suggesting left sided heart failure. Hypertrophic changes observed in the myocardium are also consistent with changes expected with chronic pressure overload of the right heart. The ductus arteriosus was patent at the time of necropsy, and the documented hemodynamic changes associated with PDAs explain the gross changes seen on the post-mortem examination of these remains.

Pathophysiology

The anatomy and physiology of marine mammals differ from their terrestrial counterparts in ways that allow them to function most efficiently within their aquatic environment. Because of these adaptations, a dolphin’s cardiovascular system is uniquely adept at accommodating the

physiological changes that are necessitated by their function and environment. Unlike terrestrial mammals, the anatomy of cetaceans must account for the physiological effects of a dive response and a lack of consistent access to useable oxygen. However, despite these differences, the heart of cetaceans is structurally similar to the hearts of other mammals. Cetaceans follow the general mammalian circulatory system of a four-chambered heart with a right ventricle pushing blood to the lungs and a left ventricle providing the output of blood to systemic circulation (Ponganis, 2009). Considering that few incidences of abnormal cardiac development in cetaceans have been published, the following information is largely drawn from studies focused on canine patent ductus arteriosus. Although some anatomical differences exist between the canine and dolphin heart, the pathophysiology and resulting sequelae of a patent ductus arteriosus are almost identical in both species.

A patent ductus arteriosus, or PDA, can be defined as the failure of the ductus arteriosus to close within an appropriate time frame after birth. The ductus arteriosus (DA) is a normal structure in the fetal heart that extends from the main pulmonary artery to the ventral portion of the descending aorta (Buchanan, 2008). It functions to shunt partially oxygenated blood from the right heart into the descending aorta to bypass the nonfunctional fetal lungs (Buchanan, 2008). This bypass creates a right-to-left shunting of blood that allows blood with a low oxygen concentration to be shunted from the right ventricle to the placenta via the descending aorta so that gas exchange can occur (Bhatia, 2007). In most cases, the ductus arteriosus functionally closes within 24-72 hours after birth (Bhatia, 2007). Failure or incomplete closure of the ductus arteriosus can often be diagnosed 72 hours after birth, and studies in human infants have cited fetal stress, respiratory distress, low oxygen tension, and premature birth as contributing factors to the ductus arteriosus remaining patent after parturition (Dierauf, 1984).

The ductus arteriosus remains open throughout fetal development due to low fetal oxygen tension and the circulation of prostanoids, like Prostaglandin E2 (PGE2), causing significant ductal relaxation (Bhatia, 2007). Mammalian ductus arteriosus closure is thought to be the product of two mechanisms. The first mechanism is an acute functional closure from smooth muscle contraction, and the second mechanism is a more chronic anatomical closure of the DA lumen (Akaike, 2014). The functional constriction that occurs immediately following birth is due to increased oxygen tension, decreased circulating levels of PGE2, increased destruction of PGE2 in the lung, decreased expression of PGE receptors in the DA wall, and a decrease in blood pressure within the DA (Akaike, 2014). Increased oxygen tension facilitates ductus closure through inhibition of smooth muscle voltage dependent potassium channels (Bhatia, 2007). The change from fetal to neonatal circulation causes this inhibition of several potassium channels within the DA, which leads to depolarization and activation of voltage-dependent calcium channels (Akaike, 2014). Activation of these calcium channels causes extracellular calcium to enter the cytosol of the DA smooth muscle cells ultimately resulting in DA constriction (Akaike, 2014). Additionally, the decreased numbers of prostaglandins in circulation following birth also contribute to the functional closure of the DA. Because PGE2 is a potent dilator, the decreased numbers in circulation combined with the decreased expression of PGE receptors in the DA help to facilitate smooth muscle constriction of the DA (Akaike, 2014). These mechanisms are vital to complete ductal closure, because the initial functional constriction of the DA is ultimately responsible for its anatomical closure. (Gournay, 2010).

The structural occlusion of the lumen occurs within days to weeks after birth and accounts for the anatomical closure of the DA. The loss of blood flow created by the functional constriction leads to an area of hypoxia within the muscle media of the DA (Gournay, 2010).

This zone of hypoxia results in smooth muscle death that incites hypoxia induced growth factors (Gournay, 2010). These growth factors are responsible for the endothelial proliferation that leads to extensive neointimal thickening within the DA (Gournay, 2010). A permanent seal is formed through fibrosis of the endothelial proliferation, and the ligamentum arteriosum remnant structure is completely formed in two to three weeks (Gournay, 2010).

A failure or incomplete closure of the ductus arteriosus after birth leads to inappropriate shunting of blood and multiple sequelae. Most of the initial consequences of a PDA result from the left-to-right shunting of blood. Within the closed circulatory system, pressure is greater within the aorta than within the pulmonary artery. This pressure difference causes inappropriate shunting of blood from the high-pressure aorta to the lower pressure pulmonary artery. Often this leads to left-sided volume overload, left ventricular eccentric hypertrophy, and left atrial enlargement (Rishniw, 2004). Left-to-right shunting can also contribute to hyperperfusion of the pulmonary vasculature resulting in pulmonary hypertension. This pulmonary hyperperfusion can cause hypertrophy of pulmonary arterioles that ultimately leads to right ventricular concentric hypertrophy (Rishniw, 2004). These irreversible changes eventually cause right ventricular and pulmonary pressures to exceed the pressures on the left side, and right-to-left shunting of blood occurs. This shunt reversal causes unoxygenated blood to enter systemic circulation (Rishniw, 2004).

Immediately following birth, all PDA shunts can be classified as left-to-right shunts, because of the higher pressures of the left side of the heart. Clinical signs typically associated with left-to-right PDA shunts include a continuous heart murmur, bounding peripheral pulses, and left sided heart enlargement with dilatation of the aortic arch (den Toom, 2016). The shunt causes increased blood volume within the left side of the heart leading to eccentric hypertrophy

of the left ventricle. This volume overload eventually leads to left-sided heart failure characterized by left atrial enlargement, pulmonary venous congestion, and pulmonary edema (LSU Veterinary Teaching Hospital, 2018). However, over time, the development of pulmonary hypertension can cause the shunt to reverse directions and become a right-to-left shunt due to the changes in vascular pressures. In these cases of reverse PDAs, unoxygenated blood is being shunted into systemic circulation leading to systemic hypoxia, exercise intolerance, and occasionally polycythemia (den Toom, 2016). The characteristic continuous holosystolic basilar "washing machine" murmur of the left-to-right shunt is noticeably absent and peripheral pulses palpate normally with reverse PDAs. If pulmonary hypertension becomes severe enough, the resulting changes can lead to right sided heart failure. Severe pulmonary hypertension leads to increased myocardial stiffness and diastolic dysfunction of the right heart (Brister, 2018). The increase in pulmonary arterial diastolic pressure leads to increased end-diastolic ventricular pressure of the right heart due to an inability to accommodate the current blood volume (Brister, 2018). An increase in right atrial pressure eventually develops leading to an elevation in central venous pressure that can result in portal hypertension, passive hepatic congestion, ascites, and peripheral edema (Brister, 2018). The consequences of the hemodynamics and changing pressures associated with the PDA result in an unrelenting tug of war between left and right heart failure. Unfortunately, without surgical correction of the patent ductus arteriosus, the inappropriate shunting of blood will ultimately result in death due to congestive heart failure.

Conclusion

For humans and the majority of domestic animals, surgical correction of a patent ductus arteriosus carries an excellent prognosis. Surgical ligation and occlusion devices are both considered curative, particularly when implemented within 2-4 months after birth (Rishiniw,

2004). Unfortunately, in the case of marine mammals, the diagnosis and subsequent surgical treatments of PDAs are currently impractical and unrealistic. Although current diagnostic methods make it theoretically possible to diagnose congenital heart abnormalities in captive dolphins, complex anesthetic considerations and strict marine mammal protection laws make invasive surgeries in these species difficult.

Anesthetizing bottlenose dolphins (*Tursiops truncatus*) often involves a rapid induction via intravenous propofol, followed by orotracheal intubation subsequent to the rostral disarticulation of the goosebeak (Bailey, 2016). Inhalation agents like isoflurane and sevoflurane are generally used for maintenance of an anesthetic plane (Bailey, 2016). However, the physiological and anatomical characteristics of cetaceans that allow their survival in aquatic environments create significant anesthetic challenges. The effects of cetacean dive reflex on cardiovascular and pulmonary function creates numerous complications for maintaining a steady plane of anesthesia. The dive reflex is an evolutionary response to apnea driven by an underwater environment and lack of access to consistent and useable oxygen. The cardiovascular component of the dive reflex causes controlled bradycardia and decreased cardiac output (Panneton, 2013). To prevent severe hypotension, the sympathetic nervous system responds by causing significant vasoconstriction and the shunting of blood to the heart and central nervous system (Panneton, 2013). These cardiovascular effects make appropriate dosing and monitoring of injectable anesthetics challenging. The dive reflex in cetaceans also results in apnea, making the use of inhalation anesthetics difficult. Additionally, the anatomy of cetaceans is especially susceptible to lung disease, which is a significant risk during anesthesia. Although successful anesthetic events have been reported in cetaceans, it is uncommon due to the inherent risk for complications.

Even though diagnosis and surgical correction of patent ductus arteriosus in an individual cetacean are unrealistic, the post-mortem finding has significance in terms of furthering scientific understanding of an understudied species. Congenital cardiac malformations are rarely seen in Atlantic bottlenose dolphins (*Tursiops truncatus*), and relatively few cetacean cardiac developmental anomalies have been published (Powell, 2009). Necropsy of stranded individuals can provide invaluable information about normal anatomical variance, common congenital abnormalities, and significant disease pathology in these elusive species. Since the Deepwater Horizon oil spill in 2010, anywhere from 40 to 110 marine mammal strandings have occurred annually on the Mississippi Gulf Coast (Institute for Marine Mammal Studies, 2018). The collaboration between IMMS and Mississippi State University, with the help of the RESTORE Act, allows each of these unfortunate stranding events to become an educational opportunity in marine mammal veterinary medicine. Through the findings and resulting publications, post-mortem examinations can aid in marine conservation and research efforts by furthering our understanding of marine mammal species.

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