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HEPATIC SYNDROMES IN DOGS

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Abstract

The liver plays a critical role in maintaining systemic metabolic and vascular balance. Hepatic failure can lead to serious complications in other organ systems. Hepatopulmonary syndrome, hepatorenal syndrome, and cirrhotic cardiomyopathy–hyperdynamic circulation syndrome are among these complications. Hepatopulmonary syndrome is characterized by pulmonary vasodilation and impaired gas exchange, arising as a consequence of portal hypertension. Increased levels of nitric oxide and prostaglandins lead to arterial hypoxemia, and pulmonary vascular dilatation, anatomical shunts, and ventilation–perfusion mismatches play important roles in the development of the syndrome. Hepatorenal syndrome is defined as functional and reversible renal failure that develops secondary to hepatic failure. As renal perfusion decreases, the renin–angiotensin–aldosterone system becomes activated and the glomerular filtration rate falls. This process results in increased renal vasoconstriction and decreased renal blood flow, ultimately leading to progressive renal failure. Cirrhotic cardiomyopathy is characterized by increased cardiac output due to impaired myocardial contractility, β-adrenergic receptor dysfunction, and systemic vasodilation. Cardiac dysfunctions that develop in chronic liver disease lead to reduced exercise tolerance and hemodynamic instability. Although there are some studies in the veterinary field demonstrating hepatorenal syndrome, more research is needed to determine the prevalence and prognosis of hepatopulmonary syndrome and cirrhotic cardiomyopathy. We believe that a better understanding of liver failure–related syndromes in dogs will contribute to the development of earlier diagnostic and treatment options.

Key words: hepatopulmonary syndrome, hepatorenal syndrome, hyperdinamic syndrome, dog hepatic disorders.

The liver is the second-largest organ in the body and undertakes more biochemical functions than other organs in the body. These functions are classified under the titles of vascular, immunological, metabolic and secretion/excretion (Mitra, V., & Metcalf, J., 2012). Due to this functional diversity, the liver is accepted as a basic organ that maintains systemic metabolic and vascular balance. Advanced hepatic diseases lead to disruption of systemic metabolic and hemodynamic order, paving the way for organ dysfunctions. This interaction especially manifests itself as hepatopulmonary syndrome (HPS), hepatorenal syndrome (HRS) and cirrhotic cardiomyopathy-hyperdynamic circulation syndrome (Öztaş & Oğuz, 2008; McCord & Webb, 2011; Low et al., 2015; Bansal et al., 2020; Mitra, V., & Metcalf, J. 2012). Respiratory symptoms caused by impaired arterial oxygenation due to the liver are called HPS (Şahan & Aksakal, 2009). HRS is a condition of acute renal failure that develops in patients with advanced liver disease without any other cause (Yılmaz et al., 2014). Cirrhotic cardiomyopathy is a cardiac disorder caused by liver disease (Semizel, 2010).

In this review, three major syndromes associated with liver disease in dogs hepatopulmonary syndrome, hepatorenal syndrome, and hyperdynamic circulation syndrome will be examined in sequence.

HEPATOPULMONARY SYNDROME (HPS)

In human medicine, hypoxemia and respiratory disturbances are frequently observed in patients with liver disease. Among the pulmonary complications specifically associated with hepatic disorders are hepatic hydrothorax, hepatopulmonary syndrome (HPS), and portopulmonary hypertension (POPH). The development of these conditions is often linked to portal hypertension (Machicao et al., 2014). Hepatic hydrothorax refers to the accumulation of pleural effusion, similar in nature to ascitic fluid, in patients with portal hypertension (Machicao et al., 2014). It is hypothesized that this condition results from the translocation of abdominal effusion into the thoracic cavity through unrecognized diaphragmatic defects (Buob et al., 2011). HPS is defined by abnormal pulmonary gas exchange resulting from pulmonary arterial vasodilation

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associated with portal hypertension and/or liver dysfunction (Şahan & Aksakal, 2009) (Figure 1).

HPS is thought to result from an imbalance between vasodilatory and vasoconstrictive mediator, and research on this subject is still ongoing (Bansal et al., 2020). Glucagon, which increases 3-6 times in patients with portal hypertension, is an important vasodilator in the development of the disease with its positive inotropic-chronotropic effect. It causes an increase in aortic, mesenteric artery and renal blood flow and a decrease in splenic and femoral blood flow. There is a correlation between increased glucagon levels and portosystemic shunt (Şahan & Aksakal, 2009). Atrial natriuretic factor (ANF) and substance P, which causes vasodilation, are other factors that affect HPS. Substance P levels have been reported to be approximately ten times higher in individuals with liver disease compared to controls (Rosell, S., 1981, Şahan & Aksakal, 2009). In addition, in liver disease, translocation of intestinal bacteria and endotoxemia and accumulation of macrophage and monocyte cells in the lungs are observed (Bansal et al., 2020). Macrophages cause an increase in nitric oxide (NO), an important vasodilator, by causing the secretion of TNF-alpha in the pulmonary vessels and the activation of inducible nitric oxide synthase (iNOS). While NO is effective in direct vasodilation in liver patients with its increase in splanchnic circulation; It increases the amount of GMP and CO production in smooth muscle cells and indirectly causes vasodilatation (Şahan & Aksakal, 2009; Bansal et al., 2020). Another cause of HPS is arteriovenous shunting, which occurs more frequently on the pleural surfaces of the lung. Anastomoses between portopulmonary, intrapulmonary, coronary vessels and pulmonary veins have been reported. Portal hypertension facilitates the formation of aberrant collaterals between pulmonary vascularity and splenic circulation. Diffusion disorders, ventilation-perfusion disorders, anatomical shunts, alveolar collapse, which can be seen in patients with HPS, increase the rate of pulmonary shunting (Şahan & Aksakal, 2009). The occurrence and severity of HPS are not necessarily correlated with the degree of hepatic dysfunction, and it may rarely be observed in acute liver disease (Bansal et al., 2020).

The most widely accepted hypothesis for portopulmonary hypertension (POPH) is the passage of vasoconstrictive substances into the pulmonary circulation through portosystemic collaterals and shunts (Alkım, 2014). Liver dysfunction is not a prerequisite for portopulmonary hypertension. This condition can also develop in cases with portal vein thrombosis and idiopathic portal hypertension but normal liver function. Large portosystemic shunts also increase pulmonary vascular resistance by increasing pulmonary flow and the mixing of vasoconstrictive substances into the circulation. Therefore, portosystemic shunts aggravate POPH (Alkım, 2014). The triad of this syndrome is liver dysfunction, hypoxia and/or high alveolar-arterial O2 gradient and pulmonary vascular dilatation (Şahan & Aksakal, 2009). In a study conducted on rats in which experimental cirrhosis was induced by ligating the bile ducts (Chang & Ohara, 1992), it was found that cardiac output increased, systemic-pulmonary resistance decreased, and alveolar-arterial gradient increased to 23 mmHg. Although hypoxemia is not necessary in every case for diagnosis, an increase in alveolar-arterial O2 gradient is definitely required (Şahan & Aksakal, 2009). When evaluating the triad of hepatopulmonary syndrome; (Grace & Angus, 2013)

1. Portal hypertension / liver dysfunction
2. Determination of hypoxia: the most sensitive marker is the increase in the alveolar-arterial oxygen gradient (PA-a O2). In studies conducted in human medicine, PA-a O2 is expected to be between 20-70 mmHg in HPS (Grace & Angus, 2013).
3. Demonstration of intrapulmonary vasodilation: there are 2 methods for this (Grace & Angus, 2013).

a) Contrast echocardiography (ECHO): In this method, after indocyanine green or saline is injected into the peripheral circulation, microtubules are normally deposited first in the right heart and then in the pulmonary capillaries and absorbed there. However, in the case of HPS, it is also seen in the left heart chambers 3-4 beats after being seen in the right atrium due to intrapulmonary shunts (Şahan & Aksakal, 2009). This method is used as the first choice because it is more sensitive, less invasive and excludes cardiac shunt (Grace & Angus, 2013).

b) Radioactive perfusion scan using macroaggregated albumin (MAA): In this method, a whole body scan is performed after venous injection of MAA particles radiolabeled with technetium-99 into the peripheral circulation. Detection of significant amounts of radiation in the brain and kidneys suggests intrapulmonary vasodilation or intracardiac shunt (Grace & Angus, 2013).

Transesophageal echocardiography, lung scintigraphy, and pulmonary angiography are also auxiliary imaging methods used for HPS diagnosis (Şahan & Aksakal, 2009). In studies conducted on

cirrhotic patients with HPS, its prevalence was found to be between 10-30% (Grace & Angus, 2013). HPS in dogs was first described in a case report reported by Kaneko et al. (2016). In this case report, ductal plate malformation and chronic active hepatitis were detected in a six-month-old Papillon dog, and a progressive increase in the alveolar-arterial oxygen gradient (PA-aO2) and the presence of intrapulmonary vasodilation were determined during the follow-up period. Intrapulmonary vasodilation was confirmed by transthoracic echocardiography performed with saline. In the study, although hypoxemia was not detected, it was reported that PA-aO2 gradually increased and intrapulmonary vasodilation became apparent. This case is the first to raise suspicion of HPS in dogs and suggests that gas exchange mechanisms may be impaired to a certain extent in dogs with chronic hepatitis and liver cirrhosis (Kaneko et al., 2016).

HEPATORENAL SYNDROME

Hepatorenal syndrome is a functional and potetially reversible renal failure that develops in the kidneys secondary to liver disease (Low et al., 2015). It is a syndrome characterized by impaired liver function, cirrhosis, portal hypertension, increased splanchnic blood flow, hyperdynamic state with increased cardiac output, systemic vasodilation, decreased central blood volume and systemic inflammatory response (Tandon et al., 2016) (Figure 1). Hepatorenal syndrome develops with decreased renal perfusion in advanced liver failure and is one of the most serious complications of patients with cirrhosis. This syndrome can also develop in patients with underlying kidney disease. In human medicine, renal dysfunction is frequently seen in patients with cirrhosis and HRS accepted as the most prominent and well-defined form of these disorders (Nadim et al., 2012).

There are **two principal hypotheses** explaining the development of HRS. These are; hepatorenal reflex and arterial vasodilation theory (Deepika, 2022). Splanchnic vasodilation developing as a result of liver failure and portal hypertension causes a decrease in arterial blood volume primarily through nitric oxide (NO) and to a lesser extent through carbon monoxide (CO), glucagon, vasodilator peptides, etc. (Low et al., 2015). Decreased blood pressure causes early activation of the baroreceptor-mediated renin angiotensin aldosterone system (RAAS) and the visceral sympathetic nervous system and secretion of antidiuretic hormone (ADH) (McCord & Webb, 2011; Deepika, 2022). Cardiac contractility and output increase as a compensatory mechanism (Low et al., 2015). Initially, vasodilators antagonize the renal effect of vasoconstrictors and renal perfusion can be kept within normal limits; In the advanced stages of liver disease, renal vasodilators cannot resist the activation of endogenous and/or intrarenal vasoconstrictors and develop uncontrolled vasoconstriction, reducing renal perfusion (Deepika, 2022) (Figure 1).

The developing renal failure is a result of a decrease in glomerular filtration rate (GFR) unrelated to tubular or interstitial damage and can lead to permanent renal damage with renal hypoperfusion if left untreated (McCord & Webb, 2011). In humans, HRS is classified as type 1 and type 2 depending on its severity. Type 1 HRS has a rapid course and a poor prognosis, while type 2 HRS develops more slowly and can be difficult to detect. According to findings reported in human medicine, the mortality rate in patients diagnosed with HRS reaches 50% within the first two weeks after diagnosis, and this rate increases in the following months. (Ruiz del Arbol et al., 2005; Low et al., 2015)

In an experimental study conducted on dogs, the relationship between obstructive jaundice and renal failure was examined by creating surgical extrahepatic biliary stasis and preventing other factors that could cause renal changes. Based on the findings of increased serum creatinine levels, low or no proteinuria, and decreased urine volume characteristic of HRS, it was concluded that obstructive jaundice and high bilirubin may contribute to HRS (Bayoumi et al., 2020). In a study conducted using 1066 dogs investigating the relationship between ascites and HRS, ascites was detected in 21 of the dogs and hepatorenal syndrome was confirmed in six of these cases (28.6%) (Phom et al., 2019). In another study conducted on 1509 dogs, hepatorenal syndrome was detected in 135 dogs. Dog breeds detected with HRS include German Shepherd, Spaniel, Poodle, Doberman and mixed-breed In addition, the highest incidence of HRS is seen in dogs aged 7 to 8 years, 14-12% and 11% in dogs under 1 year of age, respectively. While HRS is associated with chronic hepatopathies in dogs aged 7 to 8 years, it is more associated with toxic factors, infectious agents and gastrointestinal diseases in dogs under 1 year of age (Shulzhenko & Ryabik, 2017). In a reported case report, a 5-month-old, 7-kg, unvaccinated male poodle was diagnosed with leptospirosis. It was reported that the rapid course of the disease, histological findings such as widespread renal necrosis and glomerular atrophy, and the increase in serum urea and creatinine concentrations that occurred within a few days suggested and were assumed to be Type 1 hepatorenal syndrome. (Paz et al., 2021). It is

assumed that decreased vasopressor effect may be a cause of hypertension in animals and that this may also be the cause of renal vascular resistance. Renal vascular resistance, assessed by RI and PI, was observed to increase in some dogs with liver disease (Novellas et al., 2008). In another study conducted with dogs with ascites, renal RI (0.67±0.07) and PI (1.47±0.13) values were found to be significantly increased. At the same time, a positive correlation was found between serum GGT and hepatic PI and renal PI (Gonul et al., 2020).

In an experimental study to investigate the clinical signs and treatment methods of hepatorenal syndrome, 14 clinically healthy dogs weighing 14-32 kg, aged 2-5 years, were experimentally treated with bile ligation and liver cirrhosis due to obstructive type icterus. In animals with cirrhosis, the glomerular filtration rate was determined by serum cystatin C. It was found that serum cystatin C increased in all animals and the glomerular filtration rate decreased. As a result of this study, it was concluded that while serum urea and creatinine values were within normal limits in dogs with liver cirrhosis, early changes in the glomerular filtration rate could be detected by the increase in serum cystatin C concentration. (Gonul et al., 2003) Determination of glomerular filtration rate is important for the diagnosis of HRS, and while urea and creatine values used in veterinary medicine are insufficient for early diagnosis, and other classical methods are laborious and difficult to apply, biomarkers such as serum cystatin C and SDMA can be used instead. (Gonul et al., 2003; Pelander et al., 2019; Kim et al., 2020)

CIRROTIC CARDIOMYOPATHY-HYPERDYNAMIC CIRCULATORY SYNDROME

Portal hypertension, which is the most important complication of liver failure, and porto systemic shunts that develop secondary to it cause vasodilators (such as NO, CO, endocabinoids) to pass into the systemic circulation (Bolognesi et al., 2014). The increase in vasodilators leads to systemic vasodilation, causing arterial pressure to decrease. This situation triggers the central nervous system, renin-angiotensin-aldosterone system (RAAS) and antidiuretic hormone (ADH) release, increasing sodium retention and plasma volume, thus contributing to the development of hyperdynamic circulation syndrome. (Seo & Shah, 2012; Paz et al., 2021) (figure 1).

Other factors affecting the heart include impaired cardiac β-adrenergic receptor function, increased endocannabinoid activity, cardiodepressant substances, cardiomyocyte apoptosis, and inadequate tachycardic response to stress (Bátkai, S., 2001, Öztaş & Oğuz, 2008, Bahar, A. N., 2023). It has been reported that in the presence of liver failure, the inotropic and chronotropic responses that the heart is normally expected to show to stress are impaired (Öztaş & Oğuz, 2008). Endocannabinoid activity triggered by inflammatory mechanisms during liver failure causes a decrease in the contractile force of the heart muscle. Endogenous cannabinoids, especially anandamide (AEA), negatively affect cardiac function. AEA suppresses the cardiac contractile response via cannabinoid-1 (CB1) receptors (Bátkai, S., 2001, Öztaş & Oğuz, 2008). On the other hand, inflammatory cytokines such as TGF-β released by necrotic hepatocytes during liver injury can lead to apoptosis in heart muscle cells. This process results in cell death and loss of heart muscle function, facilitating the development of cardiomyopathy (Bahar, A. N., 2023). In addition, NO, TNF-α, bile acids and bacterial endotoxins can lead to impaired cardiac contractility. Bile acids have a cardiodepressant effect and have been associated with decreased ejection fraction and low heart rate (Møller & Henriksen, 2002; Desai et al., 2017) (figure 1). In humans, cirrhotic patients have impaired cardiac contractility during preload and afterload, reduced β-adrenergic receptor function, postreceptor dysfunction, and defective excitation contractions. This results in clinically significant cardiac dysfunction and latent heart failure (Møller & Henriksen, 2002). Myocardial hypertrophy in the heart causes diastolic dysfunction (reduced E/A ratio). While left ventricular end-diastolic pressure increases after exercise, cardiac stroke index and left ventricular ejection fraction (LVEF), which are used to measure systolic function, do not increase (Öztaş & Oğuz, 2008). Studies on cirrhotic rats have shown that there is a decrease in K+ currents in ventricular myocytes and the QT interval is prolonged (Campbell et al., 1993). Another abnormality seen in cirrhotic patients is the absence of a tachycardic response to stress (Öztaş & Oğuz, 2008). The left atrial diameter is usually seen as high in cirrhotic patients (Semizel, 2010). Due to limited data on cardiac output development, its true prevalence and prognosis in dogs are unknown (Williams et al., 2022).

In a case report, a 2-month-old female Retriever patient diagnosed with arterioportal malformation and congenital intrahepatic shunt by ultrasound showed normal troponin I level, left atrial dilatation (short-axis left atrium/aorta diameter ratio 1.9), and normal left ventricular systolic function (FS 46.6%; EF 70%) findings, and

the cardiac effects of hepatic malformation in dogs were reported for the first time outside of experimental studies (Williams et al., 2022). In another study, cardiac involvement was observed in 6 dogs with HRS. In echocardiographic examinations of these dogs, dilated cardiomyopathy, increased EPSS, increased LA:Ao ratio, decreased EF and FS ratios were found, and these decreased EF FS values were accepted as indicators of decreased cardiac output (Phom et al., 2019). Contrary to these findings, in another study, no significant cardiac changes were found in the examinations performed with M-Mode echocardiography to evaluate hepato-cardiac effects in dogs with an experimental cirrhosis model (Gonul et al., 2003).

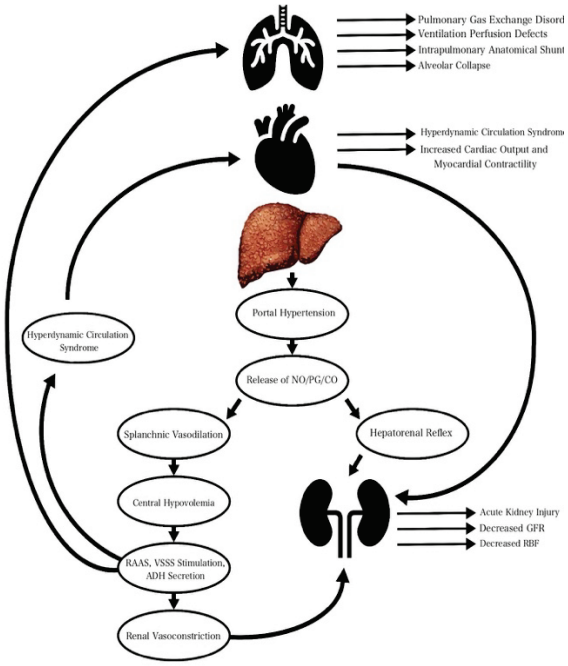

Figure 1: Pathogenesis of Hepatopulmonary Syndrome, Hepatorenal Syndrome and Cirrhotic Cardiomyopathy NO: Nitric Oxide PG: Prostaglandin CO: Carbon monoxide GFR: Glomerular filtration rate. RBF: Renal blood flow RAAS: Renin-angiotensin system VSSS: Visceral sympathetic nervous system ADH: Vasopressin hormone

CONCLUSION

Although systemic complications due to hepatic failure in dogs have been described in detail in human medicine, they are clinical conditions that have not been adequately investigated in veterinary medicine. HPS, HRS and cirrhotic cardiomyopathy-hyperdynamic circulation syndrome are among the important consequences of liver diseases affecting multiple organ systems.

HPS is characterized by pulmonary vascular dilatation, intrapulmonary shunts, and gas exchange disorders, and develops in association with portal hypertension and inflammatory processes. This syndrome, which is well-defined in human medicine, has only been documented in veterinary medicine with limited case reports. HRS is a functional renal failure in which renal vasoconstriction predominates, developing as a result of hemodynamic changes caused by hepatic insufficiency and portal hypertension. Current studies show that renal hemodynamics are affected due to liver failure in dogs. Cirrhotic cardiomyopathy includes cardiac dysfunctions that develop secondary to chronic hepatic diseases. It is a syndrome characterized by decreased myocardial contractility, loss of β-adrenergic receptor function, and systemic vasodilation.

In conclusion, more research is needed on the prevalence, pathophysiology and clinical management of systemic syndromes secondary to hepatic dysfunction in dogs. We believe that research on these syndromes will contribute to better management of diagnostic and therapeutic processes in veterinary medicine. We believe that a better understanding of hepatic syndromes, early diagnosis and development of effective treatment methods will improve the quality of life of dogs and contribute to the prevention of complications related to these diseases.

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