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Decreased Insulin Secretion in Dogs with Chronic Mitral Valve Insufficiency

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Abstract : Glucose metabolism abnormalities secondary to heart failure, including insulin resistance (IR) and impaired fasting glucose, have been gradually recognized as important prognostic factors in disease progression. However, to date, no study has investigated glucose abnormalities in dogs with chronic mitral valve insufficiency (CMVD). Thus, we hypothesized that glucose metabolism abnormalities due to heart failure may develop in dogs with CMVD. A prospective study was performed on 113 client-owned dogs with variable CMVD severities. Serum insulin, glucagon, fructosamine, and glucose concentrations were measured, and insulin resistance was determined using the homeostatic model assessment (HOMA) score. The serum insulin concentration had a significant inverse association with the heart failure severity. However, there was no significant association between the heart failure severity and fructosamine, HOMA score, and fasting blood glucose. Insulin, fructosamine, and HOMA had a significant positive association with body condition scores (BCS), whereas glucose had no association. This study found that insulin secretion in dogs with naturally occurring heart failure due to CMVD might be compromised as the disease worsens.

Key words **:** insulin resistance, impaired fasting glucose, heart failure.

Introduction

Chronic heart failure is a progressive disorder involving complex interactions between hemodynamic, neurohormonal, and metabolic disturbances (15,18). In addition to compensatory actions within the cardiovascular system, some cardiologists suggest that patients in heart failure may experience abnormal glucose regulation including diabetes, insulin resistance (IR), and impaired fasting glucose as the heart failure progresses (15,18,27,30). Most cardiologists accept that glucose imbalances during heart failure are a critical prognostic factor (15,18,30); heart function may become less energy efficient due to decreased glucose utilization and increased free fatty acid use (15). As a result, the heart may become more susceptible to injuries such as pressure or volume overload, hypoperfusion, oxidative stress, and damaging neurohormonal activation, including the renin-angiotensin-aldosterone system (15,18). As a result, cardiologists have recently stressed that glucose abnormalities in patients with heart failure, regardless of the type, should be closely monitored (15,18).

Insulin resistance secondary to heart failure has been identified in humans (18) and in dogs with experimentally induced heart failure (15). However, veterinary studies assessing potential glucose abnormalities associated with heart failure are rare, and previous canine studies have only investigated experimental heart failure models rather than natural disease (15). Despite reports of IR in obese or hypercholesterolemic dogs (15), IR secondary to heart failure has not been investigated.

Glucose abnormalities, including IR, can be diagnosed using fasting insulin or glucose blood concentration, homeostasis model assessment (HOMA) scores, glucose tolerance testing, and a modified suppression test (15). To date, few studies agree on consistent diagnostic criteria for IR. In the present study, fasting insulin concentration and impaired fasting glucose were measured using physiologic data from dogs in heart failure because these parameters are considered critical when diagnosing IR. The HOMA score, fructosamine concentration, and glucagon concentration were also measured to assess the presence of insulin abnormalities associated with heart failure. Fructosamine is a useful marker of glucose imbalances in dogs suspected to have diabetes (15). Glucagon is directly or indirectly linked to glucose regulation in the body (27,30), although it is not considered a diagnostic criterion for IR.

The present study sought to identify glucose abnormalities in dogs with naturally occurring chronic mitral valve insufficiency (CMVD).

Materials and Methods

Animals

A prospective study was conducted on 113 client-owned dogs with varying CMVD severity that presented to the

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Choong-Hyun Animal Medical Center from 2010 to 2011. All of the dogs received monthly heartworm prophylaxis and were negative for heartworm antigen. Medical management of heart failure was allowed, with the exception of phosphodiesterase inhibitors (e.g., theophylline or sildenafil). Potential influence from age and body weight on hematologic data was mitigated by including only small breed dogs (< 13 kg) older than 7 years of age. The physical condition of the animals was scored on a 9-point scale (body condition scores [BCS]) because canine waist circumference varies considerably by breed (27,30).

Heart disease diagnosis and classification

CMVD was diagnosed based on medical history, the presence of a heart murmur, chest radiography, and echocardiogram findings. Diagnostic guidelines for canine chronic valvular heart disease were adopted from those reported by the American College of Veterinary Internal Medicine (ACVIM) Specialty of Cardiology Consensus Panel (30). Dogs were included in the study if mitral regurgitation presumably secondary to CMVD was confirmed according to the guidelines. The CMVD diagnostic criteria were a left apical systolic murmur and mitral regurgitation on Doppler echocardiography along with valvular lesions such as leaflet thickening and prolapse. Dogs with CMVD were excluded from the study if they were also diagnosed with hyperadrenocorticism, diabetes, or any disorder that could influence serum cholesterol concentration.

The dogs were classified into one of five groups based on heart failure severity according to American College of Cardiology and the American Heart Association classification system (30).

Sampling and assays

Each 4-mL blood sample was obtained from the jugular vein after a 12-h overnight fast and collected into potassium EDTA and heparin tubes. The owners were instructed not to feed their dogs for at least 12 h prior to the scheduled blood collection. The plasma was separated by centrifugation at 4°C and shipped on ice to commercial laboratories (Seoul Clinical Laboratories, Seoul, Korea; IDEXX laboratory, USA) for analysis, which was completed within 3 days of collection.

Most commercially available immunoassays for measuring insulin and glucagon concentrations are based on human data. The slight amino acid differences between human and canine insulin does not influence measurement of this hormone in dogs, and the immunoassay used in this study had been validated for use in dogs. The insulin concentration was measured using a test assay kit (ADVIA Centaur™ Insulin Lite Reagent & Solid Phase, Siemens, USA) and detected by ADVIA Centaur™ XP (ADVIA Centaur® XP Immunoassay System, Siemens Healthcare Diagnostics Inc., DeerfieldDeerfield, USA). Glucagon concentration was measured by radioimmunoassay, gauged with a Gamma counter (Gamma counter, PacKard, USA). Colorimetric assay and ADVIA 2400 (ADVIA® 2400 Chemistry System, Siemens Healthcare diagnostics Inc., DeerfieldDeerfield, USA) were used to detect fructosamine. Glucose was assayed with a VetTest chemistry analyzer (IDEXX Laboratories Inc., USA; FUJI

Table 1. Population demographics of 113 dogs with heart failure classified according to the ISACHC from grade 1 to grade 5

Parameter	ISACHC grade 1-5					Total
	Grade 1 (n = 10)	Grade 2 (n = 20)	Grade 3 (n = 41)	Grade 4 (n = 25)	Grade 5 (n = 17)	n = 113
Sex						
Male	50.0% (5/10)	35.0% (7/20)	22.0% (9/41)	36.0% (9/25)	47.1% (8/17)	33.6% (38/113)
Female	50.0% (5/10)	65.0% (13/20)	78.0% (30/41)	64.0% (16/25)	52.9% (9/17)	66.3% (75/113)
Age	9.8 ± 1.78	10.3 ± 2.10	11.2 ± 2.26	12 ± 2.08	12.9 ± 2.64	11.3 ± 2.40
BW	5.6 ± 2.97	4.9 ± 2.54	5.3 ± 2.71	4.4 ± 1.52	4.9 ± 1.98	5.0 ± 2.43
Breed						
American Cocker Spaniel	0.0% (0/10)	5.0% (1/20)	4.9% (2/41)	0.0% (0/25)	0.0% (0/17)	2.7% (3/113)
Chihuahua	0.0% (0/10)	5.0% (1/20)	0.0% (0/41)	0.0% (0/25)	0.0% (0/17)	1.8% (2/113)
CKCS	0.0% (0/10)	0.0% (0/20)	4.9% (2/41)	0.0% (0/25)	0.0% (0/17)	1.8% (2/113)
Cross breeds	0.0% (0/10)	0.0% (0/20)	0.0% (0/41)	12% (3/25)	11.8% (2/17)	5.3% (6/113)
Maltese	50% (5/10)	55.0% (11/20)	35% (14/41)	32.0% (8/25)	52.9% (9/17)	41.6% (41/113)
Miniature Pinscher	0.0% (0/10)	0.0% (0/20)	2.4% (1/41)	0.0% (0/25)	5.9% (1/17)	0.9% (1/113)
Miniature Poodle	10.0% (1/10)	0.0% (0/20)	4.9% (2/41)	8.0% (2/25)	0.0% (0/17)	4.4% (5/113)
Pekingese	0.0% (0/10)	10.0% (2/20)	1.4% (6/41)	8.0% (2/25)	0.0% (0/17)	8.8% (10/113)
Pomeranian	0.0% (0/10)	0.0% (0/20)	7.3% (3/41)	4.0% (1/25)	0.0% (0/17)	3.5% (4/113)
Schnauzer	10.0% (1/10)	10.0% (2/20)	17.1% (7/41)	4.0% (1/25)	0.0% (0/17)	9.7% (11/113)
Shih-Tzu	20.0% (2/10)	10.0% (2/20)	9.8% (4/41)	20.0% (5/25)	17.6% (3/17)	14.2% (16/113)
Yorkshire Terrier	10.0% (1/10)	0.0% (0/20)	0.0% (0/41)	8.0% (2/25)	17.6% (3/17)	5.3% (6/113)

DRY-CHEM 3500i, Fuji Film Corporation, Japan).

The HOMA score, which provides endocrinologists a reliable method to assess IR, is commonly used in both human and veterinary medicine. The HOMA score was calculated using the following formula:

= [Basal serum insulin concentration (mU/L) × basal serum glucose concentration (mmol/L)]/22.5.

Statistical analysis

Statistical analyses were performed using SPSS version 19.0 for Windows (SPSS Inc., San Diego, CA, USA). Correlations between the heart failure severities, BCS, glucose profiles, HOMA scores, and hormone (insulin and glucagon) concentrations were determined by Pearson correlation analysis. For all comparisons, a $P < 0.05$ was considered statistically significant.

Results

The study included 113 dogs (75 males and 38 females) with CMVD. The majority was adult-age, male, and small breed (Table 1). The mean body weight was 5.0 (2.43) kg. The included breeds were as follows: Maltese (41%), Shih Tzu (14%), Miniature Schnauzer (9.7%), Pekingese (8.8%), cross breed (5.5%), Miniature Poodle (4.4%), Pomeranian (3.5%), American Cocker Spaniel (2.7%), Chihuahua (1.8%), Cavalier King Charles Spaniel (1.8%), and Miniature Pinscher (0.9%). The Maltese and Shih Tzu breeds were overrepresented.

As shown in Fig 1, serum insulin concentration had a significant inverse association with the heart failure grade. In contrast, no association was observed between glucagon and the heart failure severity. Fructosamine and fasting blood glucose also had no significant associations to heart failure

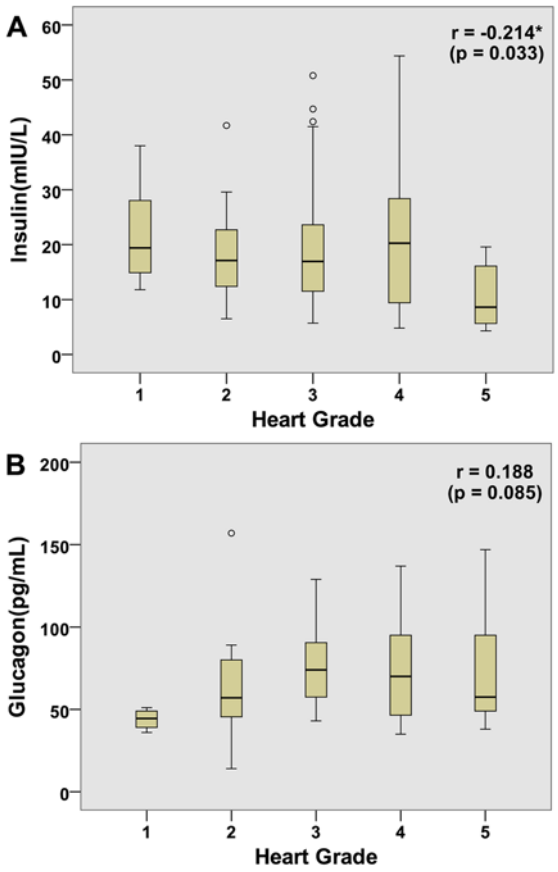

Fig 1. Box plots of insulin (A) and glucagon (B) concentrations according to the heart grade based on the ACVIM Specialty of Cardiology Consensus Panel. Associations between the serum hormone concentrations (A-D) and the heart failure severity in patients with CMVD are marked at the upper edge. The lines inside the boxes represent the median; the lower and upper edges of each box represent the 25th and 75th percentiles, respectively; and the lowest and highest lines represent the 10th and 90th percentiles, respectively.

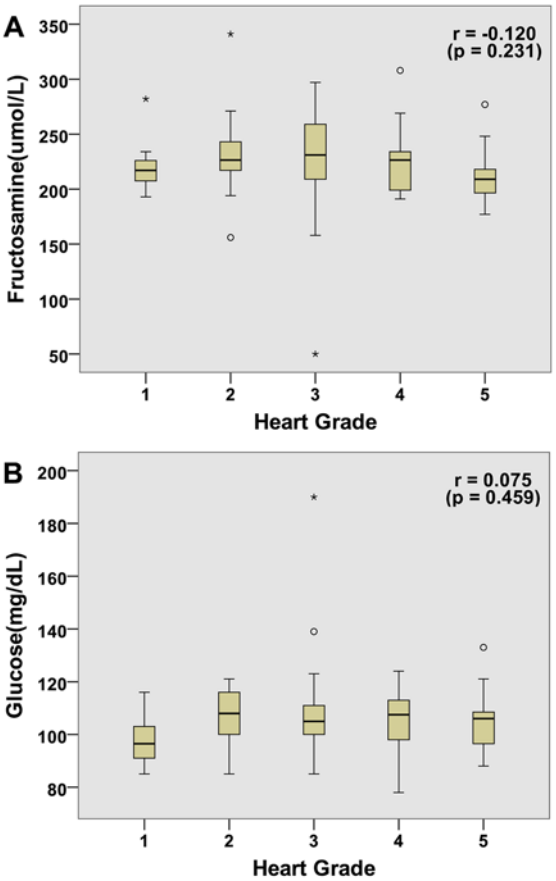

Fig 2. Box plots of fructosamine (A) and glucose (B) concentrations according to the heart grade based on the ACVIM Specialty of Cardiology Consensus Panel. Associations between the glucose profile concentrations (A or B) and the heart failure severity in patients with CMVD are marked at the upper edge. The lines inside the boxes represent the median; the lower and upper edges of each box represent the 25th and 75th percentiles, respectively; and the lowest and highest lines represent the 10th and 90th percentiles, respectively.

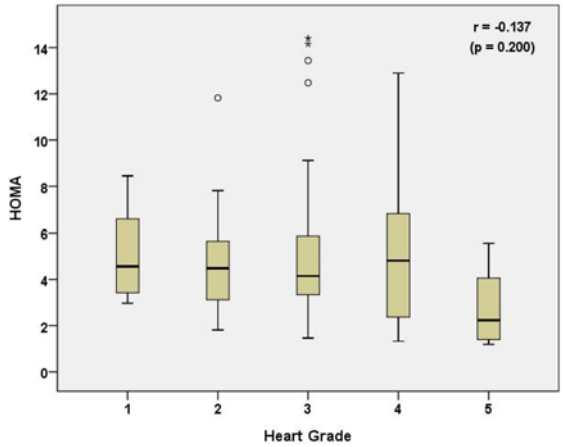

Fig 3. Box plots of the HOMA scores according to the heart failure grade based on the ACVIM Specialty of Cardiology Consensus Panel. Associations between the HOMA score and the heart failure severity in patients with CMVD are marked at the upper edge. The lines inside the boxes represent the median; the lower and upper edges of each box represent the 25th and 75th percentiles, respectively; and the lowest and highest lines represent the 10th and 90th percentiles, respectively.

grade (Fig 2). In addition to the glucose profiles, the HOMA score, a critical indicator of IR, was not associated with the heart failure grade (Fig 3).

There was a significant positive association between insulin and BCS (Fig 4); however, glucagon had no association. Fructosamine was positively associated with BCS, but glucose was not (Fig 5). Interestingly, the HOMA score had a significant positive association to BCS (Fig 6).

Discussion

The present study examined IR characteristics in dogs with heart failure according to the disease severity and has several notable advantages. All of the animals were prospectively investigated in a single hospital by trained practitioners using a standardized protocol and standardized radiography,

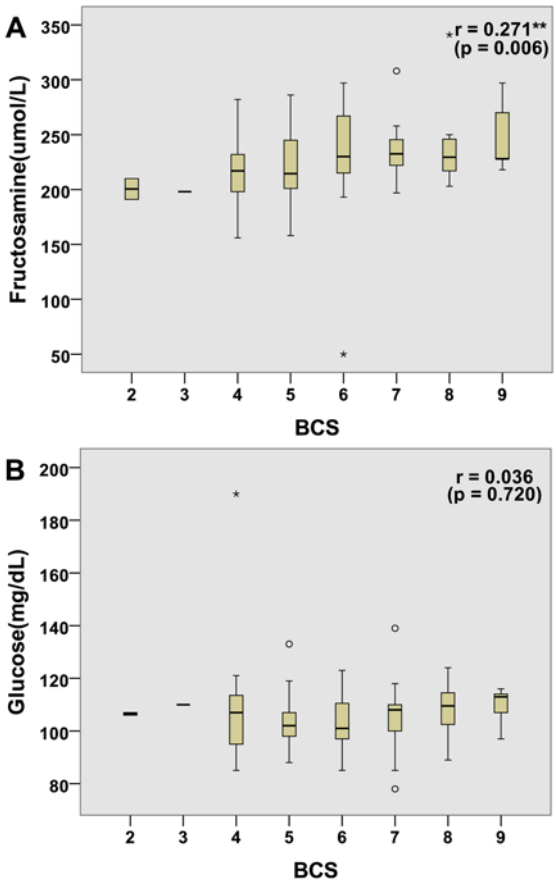

Fig 5. Box plots of fructosamine (A) and glucose (B) concentrations according to the BCS scores. Associations between the serum hormone concentrations (A-D) and the BCS scores in patients with CMVD are marked at the upper edge. The lines inside the boxes represent the median; the lower and upper edges of each box represent the 25th and 75th percentiles, respectively; and the lowest and highest lines represent the 10th and 90th percentiles, respectively.

ultrasonography, and hematologic diagnostic facilities. In addition, the number of dogs included was relatively high

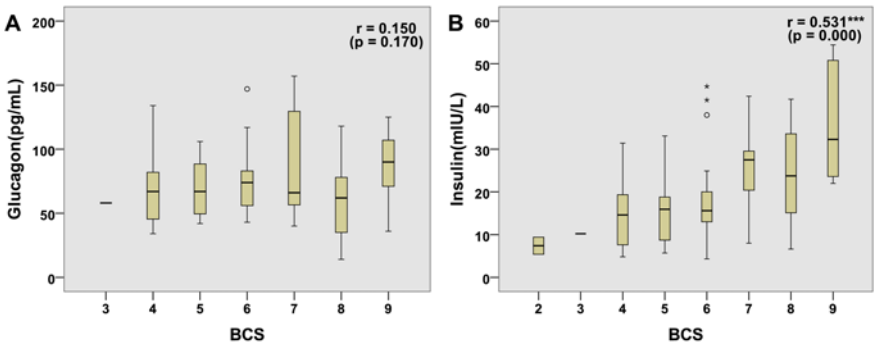

Fig 4. Box plots of glucagon (A) and insulin (B) concentrations according to the BCS score. Associations between the serum hormone concentrations (A and B) and the BCS scores in patients with CMVD are marked at the upper edge. The lines inside the boxes represent the median; the lower and upper edges of each box represent the 25th and 75th percentiles, respectively; and the lowest and highest lines represent the 10th and 90th percentiles, respectively.

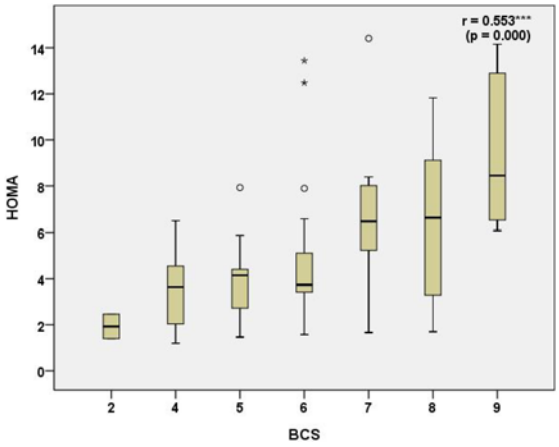

Fig 6. Box plots of the HOMA scores according to the BCS scores. Associations between the HOMA and BCS scores in patients with CMVD are marked at the upper edge. The lines inside the boxes represent the median; the lower and upper edges of each box represent the 25th and 75th percentiles, respectively; and the lowest and highest lines represent the 10th and 90th percentiles, respectively.

compared to other veterinary prospective studies. The included animals were limited to CMVD cases and small breed dogs to minimize factors affecting the clinical data. Furthermore, blood samples were analyzed by qualified commercial laboratories to measure glucose and hormone concentrations, including insulin, glucagon, and fructosamine.

In the current study, the epidemiologic characteristics of the CMVD population were inconsistent to those in previous veterinary reports (30). The results showed that female adult small-breed dogs predominated. Many veterinary studies have shown that male dogs are more prone to developing CMVD than females, and furthermore, the prognosis is poor and progression rapid (27,30). Among predisposed breeds, the Papillion, Poodle, Chihuahua, Dachshund, and Cavalier King Charles Spaniel are highly susceptible to CMVD. However, the demographics may have changed with geographic distribution. This may reflect the predominance of small breed dogs in South Korea. The dog population in Korea would be quite different from that in the United States, where large breed dogs predominate.

Overall, the serum insulin concentration decreased as the heart failure severity increased. Prior investigations of insulin dysregulation in heart failure patients have revealed that heart failure may be closely related to IR, and hyperinsulinemia and impaired fasting glucose are commonly identified comorbidities in heart failure patients. These abnormalities are caused by numerous pathologic mechanisms, including neurohormonal activation (18,27,30). The present data, however, showed an inverse association between insulin concentration and heart failure severity, which suggests that compromised insulin secretion increases as heart failure worsens. Hyperinsulinemia due to IR in patients with heart failure has been reported previously, possibly related to peripheral IR secondary to physical inactivity, increased systemic leptin and catecholamine concentrations, systemic hypertension, a hypermetabolic state, intracellular metabolic defects, poor muscle perfusion, or poor nutrition (1,18,27,30). Yet, there are far too few reports available to explain the inverse association between heart failure and insulin (30). Patients who develop type 2 diabetes generally experience IR and hyperinsulinemia phases, and eventually, insulin secretion declines due to progressive stress and damage to the pancreatic beta cells (30). Based on the pathophysiologic mechanisms of type 2 diabetes (27,30), we speculate that cardiac cachexia, progressive stress, and damage caused by chronic heart failure may compromise insulin secretion from the pancreatic beta cells in our study population. Although there is one prior report on hyperinsulinemia in dogs with heart failure (30), its study design is quite different from the present design; in the prior study, heart failure was artificially induced and was not naturally occurring. In addition, the previous study subjects experienced heart failure for a shorter period than the present patient population. Given these discrepancies, further study is needed to elucidate possible mechanisms causing reduced insulin secretion in dogs with heart failure.

In contrast to previous human studies (1,2527,30,44), our study found that impaired fasting glucose had no association with the heart failure severity in dogs. In human medicine, the importance of impaired fasting glucose in patients with heart failure has steadily increased (1,25,27), and the fasting serum concentration of insulin is one of the primary diagnostic criteria for IR (30). Despite the diagnostic accuracy of fasting insulin concentration, it is cost prohibitive as a routine test. Instead, impaired fasting glucose and glucose tolerance have been used as a substitute for measuring the serum insulin concentration. Compared to humans subjects in prior studies (1,25,27,30), in the canine subjects of this study, there was no association between the serum fasting glucose or fructosamine concentration and the heart failure grade. This finding may be due to the numerous other factors influencing blood glucose concentration, including obesity, diet, cardiac cachexia, hormones (e.g., glucagon and growth hormones) directly or indirectly associated with glucose metabolism, and hepatic function. For obesity specifically, this study differentiated the influences of heart failure from those of obesity. In assessing the effect of obesity on IR, we found that BCS was directly proportional to the IR diagnostic criteria such as insulin concentration and HOMA score. These results support those in previous veterinary and human studies of IR caused by obesity (1,3,25,27,30). Accordingly, we suspect that the varying BCS scores in the present study population may have influenced glucose metabolism.

Although this study benefits from its prospective design, single hospital site, and consistent practitioners between subjects, it also has several limitations. Finding candidates for enrollment was difficult, and as a result, the breeds varied in the study population. Despite limiting the body weight to less than 13 kg, certain breeds of dogs, such as Schnauzers, are

predisposed to familial dyslipidemias. Furthermore, IR was diagnosed using the serum fasting insulin, fasting glucose, glucose tolerance testing, modified insulin suppression test, and hyperinsulinemic euglycemic clamp. Additional diagnostic testing could have more accurately assessed IR in the study subjects. Finally, obesity should have been measured using an objective method rather than the subjective BCS scale. Despite these limitations, the present study results may assist in characterizing glucose abnormalities, including IR, and obesity in dogs with heart failure.

Conclusion

In conclusion, our results suggest that insulin secretion in dogs with naturally occurring heart failure secondary to CMVD may be compromised as heart failure worsens, rather than becoming hyperinsulinemic as supported by previous reports. In contrast, of the association between BCS and glucose abnormalities were similar to those reported in previous human and veterinary studies. Accordingly, it would be important to measure the insulin concentration in dogs with heart failure as a prognostic factor. Further studies are needed to elucidate the role of decreased insulin secretion in dogs with heart failure.

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만성 이첨판 폐쇄부전증 개에서 인슐린 분비기능 감소

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요 약 : 최근 사람연구에서는 심부전과 관련하여 발생하는 인슐린 저항성이나 공복혈당 이상과 같은 혈당 대사 이상 중요한 예후인자로 받아들여지고 있다. 그러나 심부전이 있는 개에서 이와 관련된 연구는 매우 드물다. 따라서 본 연구는 혈당대사이상이 이첨판 폐쇄 부전증이 있는 개에서도 나타날 것이라고 가정하였다. 총 113마리의 보호자가 있는 개를 대상으로 혈중 insulin, glucagon, fructosamine, glucose 를 측정하였으며, 인슐린 저항성은 homeostatic model assessment (HOMA) score를 이용하였다. 실험결과 혈중 인슐린 농도는 심장병이 심해짐에 따라서 유의성 있게 감소함을 확인하였다. 반면, fructosamine, HOMA score, and 공복 혈당은 심부전의 심각도와 어떠한 상관성도 보이지 않았다. 인슐린 농도, fructosamine, HOMA 의 경우 body condition scores (BCS)와 양의 유의적 상관관계를 보였으나, 혈당의 경우 그러지 않았다. 심부전과 BCS와의 음의 유의적 상관관계 또한 확인 되었다. 본 연구를 바탕으로 자연적으로 발생한 이첨판 폐쇄부전증에 따른 심부전 환자에서 심장 병이 심해짐에 따라서 인슐린 분비 기능이 감소함을 확인하였다.

주요어 : 인슐린 저항성, 공복 혈당 이상, 심부전