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Review article

Clinical applications of heart rate variability in dogs

Phurion Chueainta[1, 4], Wanpitak Pongkan[2, 4] and Chavalit Boonyapakorn[3,4,*]

[1] Veterinary Cardiopulmonary Clinic Small Animal Veterinary Teaching Hospital, Faculty of Veterinary Medicine Chiang Mai University, Muang, Chiang Mai 50200,Thailand
[2] Department of Veterinary Biosciences and Veterinary Public Health, Faculty of Veterinary Medicine, Chiang Mai University, Muang, Chiang Mai 50100,Thailand
[3] Department of Companion Animal and Wildlife Clinic, Faculty of Veterinary Medicine, Chiang Mai University, Muang, Chiang Mai 50100,Thailand
[4] Cardiopulmonary Clinic Small Animal Hospital, Chiang Mai University, Muang, Chiang Mai 50200,Thailand

Abstract

Heart rate variability (HRV) reflects the balance of the autonomic nervous system (ANS). There are two key HRV parameters: high frequency (HF), which is correlated with the parasympathetic nervous system, and low frequency (LF) which is correlated with sympathetic and vagal activity. In veterinary medicine HRV has proven to be an important tool for evaluation of cardiovascular events in patients and has provided useful clinical information in about different physiological systems. Changes in HRV are influenced by several physiological systems. HRV reflects the state of both the heart and the brain. For that reason, HRV is considered a surrogate parameter of the complex interaction between the brain and the cardiovascular system. Studies of the autonomic control of kidney disease, endocrinology disorders, respiratory disorders, and immunological disorders commonly include HRV. Additionally, HRV has shown an autonomic modulation effect following clinical treatment, indicating HRV is potentially more than just an indicator to identify disturbances of the ANS. Sympathetic activation is a poor prognostic predictor. On the other hand, parasympathetic activation is a good prognostic indicator in various conditions. HRV has become a significant predictor and a popular noninvasive tool as it is easy to perform. In conclusion, HRV measurement can be an essential tool for both scientific and clinical understanding.

Keywords: Clinical applications, Dogs, Heart rate variability, Veterinary

***Corresponding author:** Chavalit Boonyapakorn. Department of Companion Animal and Wildlife Clinic, Faculty of Veterinary Medicine, Chiang Mai University, Chiang Mai 50100, Thailand. Email: chavalit.b@cmu.ac.th

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INTRODUCTION

Heart rate variability (HRV) refers to variation in the beat-to-beat timing of heart rate (HR) or rhythmic variation between consecutive heartbeats (Billman, 2011). HRV can be used to assess activities of the autonomic nervous system (ANS) in investigations of the balance between parasympathetic and sympathetic function (Zanesco, 2016). Understanding the status of ANS provides good prognostic information for several diseases (Acharya et al., 2006). The present study reviewed various aspects of HRV, i.e., the association of HRV and the autonomic nervous system with health conditions, the parameters of HRV and the clinical usefulness of HRV in human and veterinary practice.

PHYSIOLOGICAL BACKGROUND

The physiological phenomenon of HRV is defined as oscillation between adjacent heartbeat intervals on an ECG. The modulation of the heart shows variations of heart rhythm which reflects interaction between the sinoatrial node and the autonomic tone. The input of the sinoatrial node is most affected by fluctuations in the parasympathetic (PNS) and sympathetic nervous system (SNS) leading to beat-to-beat variation of heart rate (Malliani et al., 1991). Other afferent inputs include sensory receptors and baroreceptors within the heart and great vessels, respiratory change, vasomotor regulation, the thermoregulatory system, alterations in endocrine function influence on the heart (Stein et al., 1994), actions of the renin-angiotensin system, and circadian rhythms (Stein et al., 1994).

Autonomic activities affecting heart variation can be approached by several methods. HRV has been considered to be a variation which allows estimation of cardiac autonomic modulation (Anaruma et al., 2016). The signal of HRV is usually obtained from continuous ECG monitoring (Holter monitoring) which records the interval between adjacent normal QRS complex. ECG data can be evaluated automatically by computer and provides analyses in the time domain and frequency domain parameters.

THE INFLUENCES OF HEART RATE VARIABILITY

Respiratory and heart rate variability

HRV is influenced by the respiratory cycle known as respiratory sinus arrhythmia (RSA). RSA is a heart rate pattern that rises during inspiration and falls during expiration. Negative thoracic pressure during inspiration causes a reduction in vagal tone and an increase in heart rate. During expiration, positive thoracic pressure causes an increase in vagal tone and decreases heart rate. RSA has been used as an index of cardiac vagal function (Billman, 2011). The fluctuation of blood pressure due to changes in intrathoracic pressure during the respiratory cycle is the most important mechanism of RSA (Roque et al., 2014). An experimental animal study demonstrated that the efficacy of gas exchange in alveoli was improved during RSA. (Hayano et al., 1996).

RSA is usually interpreted as a vagal activity which is highly dependent on the vagal tone in the heart. The respiratory drive is also influenced by oscillatory patterns in both vagal and sympathetic outflows (Eckberg, 2003). The major RSA observation in HRV measurement is the vagal influence known as the vasovagal tonus index (VVTI) (Doxey and Boswood, 2004). VVTI is a time domain analysis of HRV which is calculated from variations of R-R interval in natural logarithm (Haggstrom et al.,1996).

Baroreflex and heart rate variability

Baroreceptors in the aortic arch and carotid sheath detect stretching of the vessels that cause a changing of heart rate. If blood pressure falls, the heart rate will increase (Lehrer and Gevirtz, 2014). The nucleus of the tractus solitarius (NTS) is the main afferent fiber from the arterial baroreceptors when the NTS is activated. It has an effect on sympathetic and parasympathetic fiber modulation. In humans, HRV has been clinically documented in arterial baroreflex dysfunction to be a predictor of a greater risk of mortality, cardiovascular events and death from myocardial infarction, heart failure, particularly in diabetic patients (Parati et al., 2001).

HEART RATE VARIABILITY PARAMETERS

The two most commonly used HRV parameters are the time domain and the frequency domain.

Time domain analysis

The time domain is calculated from the interval between normal beats of a continuous ECG recording. With humans, normally in time domain analysis the ECG should cover a continuous 24 hour period, but with dogs it is difficult to obtain good quality continuous ECG recordings for that length of time. For that reason, a 2-hour HRV or short-term record is used rather than the conventional 24 hour period (Bogucki and Noszczyk-Nowak, 2015). The statistical parameters of the time domain consist of SDNN, SENN, SDSD, RMSSD, NN50 (%), and pNN50%. Table 1 shows the proposed reference values for analysis of time domain parameters. rMSSD and pNN50 correlate with HF in the frequency domain and illustrate parasympathetic activity.

Table 1 Time domain parameters of HRV for short term (60-min) records in healthy dogs (Bogucki and Noszczyk-Nowak, 2015).

Variable	Units	Statistical measurements	Range (mean ± 95% confidence interval)
SDNN	ms	Standard deviation of all R-R intervals	180-238
SDANN	ms	Standard deviation of the average normal R-R intervals calculated over short time periods (usually 5 minutes) of the entire 24 hours recording	60-82
rMSSD	ms	The square root of the mean difference between adjacent normal R-R intervals	214-305
SDNN index	ms	Mean of the standard deviation of the normal R-R intervals calculated over a short period (usually 5 minutes) of the entire 24 hours recording	162-220
NN50		The number of pairs of adjacent normal R-R intervals that differ by more than 50 milliseconds	630-725
pNN50	%	NN50 divided by the total number of normal R-R intervals x 100	66-77

Frequency domain analysis

The time domain methods are computationally simple but lack the ability to discriminate between sympathetic and parasympathetic contributions to HRV (Rajendra et al., 2006). Frequency domain techniques are more complex in terms of technical requirements, but provide more physiological information (Anaruma et al., 2016). The variable parameters of the frequency domain consist of TP, ULF, VLF, LF, HF, LFnu, HFnu, and LF/HF (Table 2). The power spectrum is a frequency band ranging from 0 to 0.5 Hz and can be classified into four bands: ULF, VLF, LF, and HF (Billman, 2011). The ULF and VLF are influenced by more long-term regulatory mechanisms, e.g., thermoregulation, renin-angiotensin system activity and physical activity (Serrador et al., 1999). The HF component is generally defined as a marker of vagal modulation (Calvert, 1998). HF is influenced by the sinoatrial node which responds to the parasympathetic and is influenced by respiration (Rasmussen et al., 2012). This component, respiratory mediation, is determined by the frequency of breathing (Sztajzel, 2004). The LF component is modulated by both the sympathetic and parasympathetic nervous systems (Calvert, 1998) and reflects the activities of both systems (Strauss-Blasche et al., 2000). In practical terms, an increment in the LF component (stress, sympathomimetic pharmacologic agents) has been generally considered to be a consequence of sympathetic activity (Billman, 2011). Consequently the LF/HF ratio reflects the global sympathovagal balance (Billman, 2013)

Table 2 Frequency domain parameters for short term (60-min) Holter monitoring in healthy dogs (Bogucki and Noszczyk-Nowak, 2015).

Variable	Units	Statistical measurements	Frequency range	Range (mean ± 95% confidence interval)
TP	ms2	Area under the entire power spectral curve (≤0.4),variance of all normal R-R intervals	(≤0.4)	9,600-12,500
ULF	ms2	Ultra low frequency power	(≤0.003 Hz)	Data not available
VLF	ms2	Very low frequency power	(0.003-0.04 Hz)	860-1,100
LF	ms2	Low frequency power	(0.04-0.15 Hz)	1,220-1,782
HF	ms2	High frequency power	(0.15-0.40 Hz)	4,735-6,950
LFnu	nu	Normalized low frequency power	(LF/LF+HF)	Data not available
HFnu	nu	Normalized high frequency power	(HF/LF+HF)	Data not available
LF/HF		Ratio of the low-to high frequency power	ND	0.24-0.33

The most widely applicable index of the time and frequency domains is based on assessment of the modulating factors as shown in Table 3. That widely used index reflects the vagal modulation, whereas the component reflects an interaction between sympathetic and parasympathetic (Kleiger et al., 2005).

Table 3 Relationship between frequency domain and time domain and their modulation (Buranakarl, 2017).

Frequency Domain	Modulating factors	Time Domain
TP	Total HRV	Data not available
ULF	Circadian HRV	Data not available
VLF	Vagal activity	Data not available
LF	Parasympathetic	SDNN SDNN index SDANN
HF	Sympathetic Baroreceptor	pNN50 rMSSD
LF/HF	Vagal tone	Data not available
LFnu	Sympathetic/Parasymathetic balance	Data not available
HFnu	Sympathetic	Data not available
HFnu	Parasympathetic	Data not available

HEART RATE VARIABILITY AND CLINICAL APPLICATION

HRV is a useful marker of autonomic homeostasis, known as the balance of the sympathetic and parasympathetic nervous systems (Lehrer and Gevirtz, 2014). Autonomic imbalance has been found not only in cases of cardiovascular disease but also in non-cardiovascular diseases (Montano, 2009). In addition, previous studies have demonstrated that the cardiac autonomic nervous system is related to many parameters of HRV (Bogucki and Noszczyk-Nowak, 2015).

In humans, HRV has been accepted for clinical use and has been demonstrated to be an early detection tool in cardiovascular disease patients (Billman, 2011; Thayer et al., 2010). Previous studies in humans have found that HRV impairment could be found prior to the appearance of coronary artery disease with arrhythmia (Bigger et al., 1992; Bigger et al., 1995; Shi, 2019). Consistent with previous studies, HRV impairment can be used as a diagnostic tool for acute myocardial infraction (Huikuri, 2012). Interestingly, HRV impairment can also be found in many non-cardiovascular diseases in human such as chronic kidney disease (Ferrario et al., 2014), cystic fibrosis in children (Florencio et al., 2013) and liver diseases (Ates et al., 2006).

In veterinary medicine, HRV is used more often in research studies than in clinical practice; analysis of HRV is an interesting tool for the researchers and cardiologists in the veterinary field (Frick et al., 2019). Not only is HRV related with cardiac autonomic regulation in animals, but this technique is also non-invasive and easy to perform. The HRV parameter is a practical and sensitive tool (Jarkovska et al., 2017). Reports include detailed studies of HRV in clinical application, in myxomatous mitral valve degeneration dogs, in heart failure dogs and the clinical use of HRV for treatment monitoring.

Heart rate variability in veterinary clinical applications

Several studies have used HRV for evaluating cardiac autonomic function in animals (Bogucki and Noszczyk-Nowak, 2015; Doxey and Boswood, 2004; Duerr et al., 2007; Manzo et al., 2009). A previous study found that HRV in dogs and calves was similar to human HRV and that it could be used as a model for the study of humans (Manzo, 2009). However, in veterinary medicine there are several factors that can affect the parameter of HRV, e.g., differences in species, breed, age, emotional and physiological activity (Haddad et al., 1987; Katayama et al., 2016; Manzo et al., 2009; Rasmussen et al., 2011). There have been few studies comparing HRV between species, although one study found no difference in HRV among dogs, calves and humans (Manzo, 2009). In addition, studies of differences among dog breeds have demonstrated that facial conformation in brachycephalic breeds can induce a greater decrease of HRV than in other dogs breeds (Doxey and Boswood, 2004), while age, sex and body weight were found to have no association with HRV in Cavalier King Charles Spaniels (Rasmussen et al., 2011). Previous studies have also reported that negative emotional stimulation such as stress can decrease HRV or induce HRV impairment (Katayama et al., 2016; Zupan et al., 2016). A study in healthy cats in a stressful environment were also found to have HRV impairment (Abbott, 2005). Differences in physiological activity, e.g., the milking process in cows, can also cause variation in HRV (Kovacs et al., 2019) (Table 4).

Table 4 Heart rate variability in veterinary clinical application

Model/Breed	Method	HRV parameter findings	Interpretation	Reference
Humans (n=9) Dogs (n=15) Calves (n=9) Rabbits and rats (n=9)	HRV data were collected and assessed ~ 11 minutes for each animal subject using ECG leads.	Decreased LF and HF in rabbits compared to humans. The values of LF, HF, LF/HF in dogs and calves were similar to humans.	The relation of HRV in dogs and calves can be used as a model for study of HRV in humans. HRV results in rabbits and rats were completely different from humans.	(Manzo et al., 2009)
Puppies (n=7) Young adult dogs (n=5)	Recorded RR intervals from polygraphic records with a bipolar ECG to get single-peak QRS complex. Electrodes were inserted subcutaneously on the anterior chest.	RR intervals in puppies during sleep are shorter than in adult dogs. RR intervals during apnea in puppies gradually increase compared to adult dogs.	The parasympathetic system changes with age. Puppies demonstrated decreased parasympathetic activation compared to adults as indicated by decreased RR intervals. Changes in respiration in both puppies and dogs fluctuated with RR interval.	(Haddad et al., 1987)
Clinically healthy (n=50) - CKCS (n=21) - Wirehaired Dachshunds (wD) (n=16) - Cairn Terriers (CT) (n=13)	Holter recordings were made twice within a 7-day period. Arrhythmia and heart rate variability (HRV) were analyzed for 4 periods (24 hours, 6-hour activity, 1-hour activity, and 1-hour inactivity)	CKCS had a lower HRV than wD, CT. • ↓ TP, ULF, VLF, LF, HF, LFnu, HF,HF/LF The breed of dog influenced HRV, but no association was found between HRV and sex, age or body weight.	HRV indices were influenced by breed but not by age, sex, body weight, recording artifacts or mitral valve prolapse.	(Rasmussen et al., 2011)

Table 4 Heart rate variability in veterinary clinical application (Cont.)

Model/Breed	Method	HRV parameter findings	Interpretation	Reference
Healthy vs congestive heart failure (92 dogs, 6 breeds) - German shepherd (n=17) - Labrador retriever (n=20) - Cocker spaniels (n=15) - Boxer (n=20) - Bulldog (n=8) - Cavalier King Charles Spaniel (CKCS) (n=12)	ECG recorded arrhythmia, sinus tachycardia, pacemaker HRV from 20 consecutive R-R intervals was measured to analyze time and frequency domains. VVTI was calculated and compared among groups.	VVTI was increased in brachycephalic dogs. CHF dogs demonstrated decreased VVTI both within and among breeds.	HRV was different in different types of dogs and was related with facial conformation. CHF can induce HRV impairment as indicated by decreased VVTI.	(Doxey and Boswood, 2004)
Healthy house dogs (n=33) Dogs were categorized from small to large breeds.	ECG recording was investigated for types of HRV change in situations causing positive and negative emotional states. For positive emotion, dogs were called by their name and petted gently. For negative emotion, dogs were left alone in an unfamiliar room. HRV parameters from each situation were recorded every 15 seconds.	Decrease in SDANN with positive emotion and RMSSD with negative emotion. • ↓ SDANN (positive emotion) • ↓ RMSSD (negative emotion)	Change in HRV was associated with the induction of positive or negative emotional state.	(Katayama et al., 2016)
Nine-year old Beagle research dogs (n=9)	ECG recorded for at least 15-minutes three times per day (10 A.M., 12 A.M., 3 P.M.) ECG was recorded continuously during rest and with different emotional stimuli, e.g., food and social rewards	Decreased RMSSD and HF in positive emotional state. • Increased heart rate and LF/HF were associated with emotional arousal.	Differences in physiological reactivity were related to the differences in experience. HRV indexes were used to investigate the aerosol valence dimension of emotional responses.	(Zupan et al., 2016)

Table 4 Heart rate variability in veterinary clinical application (Cont.)

Model/Breed	Method	HRV parameter findings	Interpretation	Reference
Healthy young cats (n=16)	Used ambulatory electrocardiograph to investigate HRV in 3-6 hour recording in a quiet cage at a teaching hospital then discharged the cats to the pet owner's home.	During hospital stay, HRV impairment was found. • ↑ LFn, LF/HF • ↓ HF, HFn	Differences in HRV indices between hospital environment and home environment were found to be associated with increased sympathetic and decreased parasympathetic activity.	(Abbott, 2005)
Healthy cats (n=7) randomly divided into 2 group with 7 day washout period. Group 1 (n=4) treated with placebo (week 1) and atenolol (week 2). Group 2 (n=3) treated with atenolol (week 1) and placebo (week 2).	ECG recorded in segments for HRV analysis.	No significant differences; differences may be significant with a larger number of cats. Atenolol administration decreased heart rate and increased LF/HF ratio.	Standard HRV technique in anesthetizing cats may be useful for investigating ANS in cases of abnormal cardiac condition or modulate of pharmacological challenges.	(Khor et al., 2014)
Dairy cows milked (n=49) 6 main stages - baseline - driving - pre-milking holding pen - preparation - milking - waiting after milking	Stress responses to the milking process studied using HRV. HRV was recorded using a Polar Equine T56H mobile recording system and Kubios HRV software.	During milking and waiting stages vagal response was predominant. • ↑ HF, ↓ LF/HF Driving, holding pen and preparation were found to decrease vagal tone. • ↓ HF	The milking process in cows could be investigated for welfare benefits using Holter monitoring.	(Kovacs et al., 2019)

Abbreviations: HRV, heart rate variability; HF, high frequency; LF, low frequency; LF/HF low frequency/high frequency ratio; HFnu, normalizing of high frequency; LFnu, normalizing of low frequency; SDNN, standard deviation of RR interval; SDANN, standard deviation average RR interval; CKCS, Cavalier King Charles Spaniel; wD, wire-haired Dachshund; CT, Cairn Terrier; VVTI, vasovagal tonus index; ARVC, arrhythmogenic right ventricular cardiomyopathy; MI, myocardial infraction; CME, canine monocytic ehrlichiosis; VPC, ventricular premature complex; NE, norepinephrine; SSS, sick sinus syndrome; MMVD, myxomatous mitral valve disease; iSGNA, integrated left stellate ganglion nerve activity; iVNA, integrated vagal nerve activity; HSET, high-speed treadmill standardized exercise test

Heart rate variability in myxomatous mitral valve degeneration dogs

Myxomatous mitral valve degeneration (MMVD) is the most common acquired heart disease in small dog breeds (Meurs et al., 2019). MMVD is classified by the American College of Veterinary International Medicine (ACVIM) in 4 basic stages according to the incidence of pathology and pathogenesis (Keene et al., 2019). In addition, HRV impairment has a positive correlation with the severity of MMVD (Rasmussen et al., 2012). Vasovagal tonus index (VVTI) is one of the parameters in time domain analysis of HRV (Doxey and Boswood, 2004). Decreased VVTI could indicated a sympathovagal imbalance (Doxey and Boswood, 2004; Haggstrom et al., 1996). VVTI is also an accurate prognostic parameter for evaluating the severity of heart failure (Pereira et al., 2008). Moreover, previous studies have used VVTI for detection of the severity of MMVD (Haggstrom et al., 1996) and have also found that decreased VVTI is related to an increased mortality rate in MMVD dogs (Lopez-Alvarez et al., 2014). Other studies of VVTI found decreased VVTI in CHF dogs (Doxey and Boswood, 2004) and DCM dogs (Pereira et al., 2008), whereas a previous study reported that VVTI measurement is not affected by the physical examination in dogs with heart disease (Moonarmart et al., 2012). Previous studies have also found that MMVD can exhibit impairment of both the time domain and frequency domain of HRV (Bogucki and Noszczyk-Nowak, 2017; Pirintr et al., 2017; Rasmussen et al., 2014). Previous time domain HRV studies have demonstrated that MMVD dogs can exhibit decreased SDNN, SDANN, SANNI, pNN50 and rMSSD (Chompoosan et al., 2014; Oliveira et al., 2012; Pirintr et al., 2017). Previous frequency domain HRV studies have demonstrated that MMVD dogs can exhibit increased LFn and LF/HF (Rasmussen et al., 2014; Pirintr et al., 2017). Thus, HRV impairment could be used as an indicator of cardiac autonomic imbalance and could also be used as a prognostic tool for MMVD dogs (Table 5).

Table 5 Heart rate variability in myxomatous mitral valve degeneration (MMVD) dogs.

Model/Breed	Method	HRV parameter findings	Interpretation	Reference
CKCS (n=81) - normal dogs (n=22) - dogs with MMVD (n=59)	HRV was analyzed using the vagal tonus index (VVTI), a time domain indicator, calculated by the formula $VVTI = (SD_{RR})^2$ The VVTI index was assessed in normal and MMVD dogs, classifying differences in severity using thoracic radiographs and echocardiographs.	HRV impairment indicated by decreasing VVTI index was found in dogs with severe left atrial and ventricular dilatation and clinical signs of congestion. No differences in HRV impairment were found in dogs with only cardiac murmur or in dogs with slight to moderate left atrial and ventricular dilatation compared to normal dogs.	HRV impairment was associated only with severe MMVD. HRV could be used to evaluate and inform the severity of MMVD.	(Haggstrom et al., 1996)
Healthy dogs (n=10) MMVD dogs (n=28) - no heart failure (n=15) - heart failure (n=13)	Holter examination was performed at different time frames: • 24-hour period • Four-hour period during sleep • Four-hour period while awake	MMVD dogs with heart failure had decreased SDANN and pNN50 pNN50 and SDNN correlated with LA/AO of echocardiographic indices.	MMVD was associated with HRV impairment MMVD dogs were demonstrated to have parasympathetic impairment and to develop heart failure.	(Oliveira et al., 2012)
CKCS with variable MMVD severity (n=70) Non-CKCS with MMVD secondary to CHF (n=20)	The group of CKCS and non-CKCS were divided base on history, physical examination, blood check and echocardiography. The echocardiographic indices included degree of MVP, MR, proximal isovelosity surface area (PISA) There was a 24-hour monitored Holter recorded and analysis of the HRV variable.	HRV impairment increased with MMVD severity. HRV impairment was correlated with echocardiographic parameters. Premature normal (PN) and triangular index) TI) had diagnostic potential.	HRV can be used to evaluate the severity of MMVD. HRV is reflected in the autonomic modulation of heart rhythm changes in CKCS with MMVD. HRV did not differ among breeds.	(Rasmussen et al., 2012)

Table 5 Heart rate variability in myxomatous mitral valve degeneration (MMVD) dogs (Cont.).

Model/Breed	Method	HRV parameter findings	Interpretation	Reference
MMVD dogs in heart failure stage B1 and B2 of ACVIM (n=14)	This study compared before and after parenteral dose of enalapril 0.5 mg/kg/day. Blood pressure, phenocardiograms, surface electrocardiograms, echocardiographic parameters and Holter monitoring for HRV indices were recorded. Holter monitoring of continuous ECG was recorded for at least 30 minutes.	After treatment there was increased HRV and decreased LFn, LF/HF. • ↑ TF, HFn, SDNN index, rMSSD • ↓ LFn, LF/HF A correlation among of LF, EDV and LVEDd was found before treatment.	14 day treatment with Enalapril as a short-term therapy in MMVD dogs improved cardiac parasympathetic tone but depressed cardiac sympathetic tone. Impairment of cardiac autonomic modulation was related to the stage of the heart disease and also to the effect of treatment.	(Chompoosan et al., 2014)
MMVD (n=102) - Dying/ euthanasia from cardiac disease; Group 1) n=28) - Dying/euthanasia from non-cardiac; Group 2 (n=40) - Dog alive Group 3 (n=34)	A prospective longitudinal study with follow-up at six-monthly intervals for at least 18 months. ECG was recorded for 1 minute to evaluate HR & VVTI.	Before death, dogs in group 1 and group 2 had increased HR and decreased VVTI.	The causes of death in MMVD dogs were mostly effect to HR and VVTI. HR and VVTI were different between dog breeds.	(Lopez-Alvarez et al., 2014)
Privately owned dogs (n=43) - Advance MMVD with a history of syncope (n=21) - Advance MMVD without a history of syncope (n=22)	This study included history taking, physical examination, echocardiography, arrhythmia measurement and 24-hour Holter recording.	Dogs with a history of syncope had decreased HRV, lower HFn and increased LFn. • ↑ LF/HF, LFn • ↓ RMSSD, SDNN, Mean NN, pNN50%	Advanced MMVD dogs with a history of syncope were not associated with arrhythmia but were correlated with depressed HRV with increased sympathetic and decreased parasympathetic activity.	(Rasmussen et al., 2014)

Table 5 Heart rate variability in myxomatous mitral valve degeneration (MMVD) dogs (Cont.).

Model/Breed	Method	HRV parameter findings	Interpretation	Reference
Sick sinus syndrome dogs (SSS) (n=20) Chronic MMVD dogs (n=20) Healthy control dogs (n=50)	Short term HRV within 60-minute (ST-HRV) was compared among the dog groups	Chronic MMVD dogs had decreased HRV • ↓ SDNN, SDANN, SDNN index, pNN50% In SSS and healthy subjects there was a significant difference in time and frequency domain in the ST-HRV parameter	Chronic MMVD dogs had decreased parasympathetic regulation. Dogs with SSS or MMVD could be identified from ST-HRV.	(Bogucki and Noszczyk-Nowak, 2017)
Private client-owned dogs (n=47) - healthy dogs (n=13) - asymptomatic mitral regurgitation dogs ACVIM class B1 or B2 (n=34) • MMVD control group (n=13) • MMVD sildenafil group (n=12) • MMVD enalapril group (n=9)	Holter was continuous – 1 hour at baseline day 0, day 30, day 90 and day 180 in dogs with MMVD stage B1 or B2 without CHF.	MMVD dogs receiving 90-day sildenafil treatment had increased NNA, SDNN, SDNN index, pNN50, rMSSD and decreased LF/HF ratio.	Dogs in long-term Sildenafil treatment (90 days) had increased cardiac modulation caused by an increase in parasympathetic activity over sympathetic activity.	(Pirintr et al., 2017)

Abbreviations: HRV, heart rate variability; HF, high frequency; LF, low frequency; LF/HF low frequency and high frequency ratio; HFnu, normalizing of high frequency; LFnu, normalizing of low frequency; SDNN, standard deviation of RR interval; SDANN, standard deviation average RR interval; CKCS, Cavalier King Charles Spaniel; wD, wire-haired Dachshund; CT, Cairn Terrier; VVTI, vasovagal tonus index; ARVC, arrhythmogenic right ventricular cardiomyopathy; MI, myocardial infraction; CME, canine monocytic ehrlichiosis; VPC, ventricular premature complex; NE, norepinephrine; SSS, sick sinus syndrome; MMVD, myxomatous mitral valve disease; iSGNA, integrated left stellate ganglion nerve activity; iVNA, integrated vagal nerve activity; HSET, high-speed treadmill standardized exercise test

The relationship between heart rate variability and heart failure in dogs

Congestive heart failure (CHF) is a condition that is demonstrated by cardiac dysfunction and/or abnormal cardiac structure (Schober et al., 2010). CHF is also related to left ventricular dysfunction (Wang et al., 2009). A previous study found that the adaptive contraction force of the left ventricular increases continuously from cardiac preload, known as the Frank-Starling mechanism (Komamura et al., 1993); too much preload can induce cardiac dysfunction, both systolic and diastolic (Wang et al., 2009). Studies have also found that CHF is the most common problem followed by MMVD (Bogucki and Noszczyk-Nowak, 2017; Oliveira et al., 2012) and DCM (Pereira et al., 2008). Interestingly, previous studies of different breeds of healthy and CHF dogs have found that CHF dogs show significant HRV impairment as indicated by decreased VVTI (Doxey and Boswood, 2004). In addition, a study of Boxers with CHF demonstrated that CHF can induce time domain HRV impairment as indicated by decreased mean NN, SDNN, ASDNN, and SDANN (Spier and Meurs, 2004). This is consistent with a study of CHF dogs which demonstrated that CHF can result in HRV impairment in the frequency domain caused by decreased TP, LF and LF/HF ratio (Piccirillo et al., 2009). In addition, a study in MI dogs which monitored time domain HRV for 30-minutes demonstrated that MI could induce a decrease in SDNN, mean RR interval, and the coefficient of variance (standard deviation/RR interval) (Hull et al., 1990). Thus CHF is related to HRV impairment in both the time and the frequency domains and can be used as a tool to classify the severity of CHF as well as for early detection or prediction of CHF in dogs (Table 6).

Table 6 Relationship between HRV and heart failure in dogs

Sample groups	Method	HRV parameter finding	Interpretation	Reference
92 healthy and congestive heart failure dogs of difference 6 breeds - German shepherd (n=17) - Labrador retriever (n=20) - Cocker spaniel (n=15) - Boxer (n=20) - Bulldog (n=8) - Cavalier King Charles Spaniel (CKCS) (n=12)	ECG recorded arrhythmia, sinus tachycardia, pacemaker HRV measured from 20 consecutive R-R intervals for analysis of time and frequency domains - VVTI compared among groups	VVTI increased in brachycephalic dogs CHF dogs demonstrated decreased VVTI both within and between breeds	HRV is different in different types of dogs and is related to facial conformation. CHF can induce HRV impairment as indicated by decreased VVTI.	(Doxey and Boswood, 2004)
Boxers with and without congestive heart failure (n=24) Clinically normal non-Boxer dogs (n=10)	Heart rate variability was analyzed by 24 hour Holter monitoring	Boxers with CHF demonstrated HRV impairment • ↓ mean NN, SDNN, ASDNN, SDANN No differences in HRV were detected between CHF Boxers with and without arrhythmogenic right ventricular cardiomyopathy (ARVC)	HRV impairment was observed in heart failure dogs ARVC was not associated with HRV impairment. HRV impairment could not predict ARVC in CHF dogs.	(Spier and Meurs, 2004)

Table 6 Relationship between HRV and heart failure in dogs (Cont.).

Sample groups	Method	HRV parameter finding	Interpretation	Reference
Implanted CHF dogs (n=6)	• Dogs were implanted with a radio transmitter to determine if integrated left stellate gangli on nerve activity (iSGNA) and integrated vagal nerve activity (iVNA) induce CHF • HRV was analyzed at baseline and after implanting the radio transmitter	Heart failure dogs were compared with baseline • ↓ total power (TP) • ↓ low-frequency (LF) component • ↓ LF/high frequency (HF) ratio • ↑ iVNA and iSGNA Only at baseline was there a positive correlation between iSGNA with LF power and between iVNA and HF	HRV impairment was observed in heart failure dogs	(Piccirillo et al., 2009)
Mixed breeds canine model (n=96) (2 to 4 years old). Dogs which developed ventricular fibrillation were separated into a susceptible group (high risk for sudden cardiac death) and a resistant group (low risk for sudden cardiac death).	HRV was measured 30 minutes before and 30 days after creation of myocardial infraction by left circumflex coronary artery (LAD) occlusion	At day 30 after LAD, HRV of dogs in the susceptible group had developed ventricular fibrillation • ↓ SDNN • mean RR interval • coefficient of variance (standard deviation/RR interval)	MI can induce HRV impairment as indicated by decreased RR interval HRV can be used as a tool to predict the risk of sudden death after MI	(Hull et al., 1990)

Abbreviations: HRV, heart rate variability; HF, high frequency; LF, low frequency; LF/HF low frequency and high frequency ratio; HFnu, normalizing of high frequency; LFnu, normalizing of low frequency; SDNN, standard deviation of RR interval; SDANN, standard deviation average RR interval; CKCS, Cavalier King Charles Spaniel; wD, wire-haired Dachshund; CT, Cairn Terrier; VVTI, vasovagal tonus index; ARVC, arrhythmogenic right ventricular cardiomyopathy; MI, myocardial infraction; CME, canine monocytic ehrlichiosis; VPC, ventricular premature complex; NE, norepinephrine; SSS, sick sinus syndrome; MMVD, myxomatous mitral valve disease; iSGNA, integrated left stellate ganglion nerve activity; iVNA, integrated vagal nerve activity; HSET, high-speed treadmill standardized exercise test

Clinical use of heart rate variability for treatment monitoring

HRV can be used not only to monitor the balance of the autonomic nervous system but also as a diagnostic tool to evaluate disease progression in cardiac diseases such as MMVD and DCM (Bogucki and Noszczyk-Nowak, 2017; Lopez-Alvarez et al., 2014; Pereira et al., 2008; Rasmussen et al., 2014). Additionally, it has been used in diabetes mellitus (DM) (Pirintr et al., 2012), the post-operative period (Pastarapatee et al., 2017), acupuncture treatment (Maccariello et al., 2018), rehabilitation programs (Frick et al., 2019; Munoz et al., 2019) and with infectious diseases (Gianfranchesco Filippi et al., 2019; Jarkovska et al., 2017).

A study of poorly controlled DM dogs demonstrated that DM dogs with autonomic neuropathy impairment showed decreased NNA and SDNN (Pirintr et al., 2012). HRV can be used as a tool for monitoring imbalance of the autonomic nervous system during the post-operative period of splenectomy patients (Pastarapatee et al., 2017). A previous study demonstrated that acupuncture can improve HRV by increasing HF, decreasing LF and decreasing the LF/HF ratio (Maccariello et al., 2018). Another study in athlete horses demonstrated that HRV can be used as a tool in a rehabilitation program to monitor recovery from a hypoxic condition which could induce increased SDNN, RMSSD and LF after 3 days of a hypoxic condition (Munoz et al., 2019). This is consistent with a study by Frick and colleague which compared healthy horses and horses with arrhythmias using a high-speed treadmill standardized exercise test. That study found that horses with arrhythmias had a greater decrease in RMSSD during the recovery phase compared to healthy horses and that the treadmill test could be helpful for monitoring and evaluating the risk of an arrhythmic event in healthy horses (Frick et al., 2019).

HRV has also been used for monitoring infectious diseases. A previous study demonstrated that peritonitis pigs exhibit HRV impairment as indicated by increased LF and decreased SDNN, SDSD, pNN50% and HF (Jarkovska et al., 2017). Additionally, a study in dogs demonstrated that ehrlichiosis can induce HRV impairment by increasing both the LF/HF ratio and LF power (Gianfranchesco Filippi et al., 2019) (Table 7).

Table 7 Clinical uses of HRV for treatment monitoring

Model/Breed	Method	HRV parameter finding	Interpretation	Reference
Healthy non-diabetic dogs (n=13) Healthy diabetic dogs (n=22) - well controlled DM (n=11) - poorly controlled DM (n=1)	The study protocol included a routine physical examination, blood check (plasma catecholamine) and urinalysis A 30-minute ECG was recorded for assessing HRV	Poorly control DM dogs had decreased HRV compared to the control group • ↓ NNA, SDANN • ↓ plasma norepinephrine concentration (NE) Poorly controlled DM dogs had decreased HRV compared to the well-controlled DM dogs • ↓ NNA, SDNN, SDNN index & pNN50% Poorly control DM dogs had greater depressed HRV compared to the well-controlled DM group • ↓ HF, TP • LF/HF	Impairment of autonomic neuropathy can be evaluated by HRV in poorly-controlled DM dogs Poorly-controlled DM dogs have suppressed HRV and decreased NE concentrations	(Pirintr et al., 2012)
Dogs (n=12) - low VPC (n=6) VPC <1000/d - high VPC (n=6) VPC >1000/d	30-minute continuous ECG waveforms were assessed for ventricular arrhythmias. Dogs were separated into 2 groups. The study was performed on: • Day 0 (preoperative day); (D0) • Day 1 to day 3 after splenectomy (D1,D2,D3) • Day 9 after splenectomy (D9)	The high VPC group had a greater decrease in HRV than the low VPC group • ↓ TP, HF • LF/HF	In splenectomy dogs enhancement of baroreceptor or ANS in low VPC was better than in high VPC	(Pastarapatee et al., 2017)

Table 7 Clinical uses of HRV for treatment monitoring (Cont.)

Model/Breed	Method	HRV parameter finding	Interpretation	Reference
Laboratory Beagle dogs (n=24) - control group (n=8) - no point group (n=8) - acupuncture point group (n=8)	HRV recorders were strapped on the chest during monitoring. In the stress protocol stimulation dogs heard thunder sounds for 150 seconds. The acupuncture point group were stimulated by a 20-minute session of needle insertion at acupuncture points.	The sound stress protocol induced group had depressed HRV • ↑ LF/HF • ↑ LF power • ↓ HF power The acupuncture point group had improved HRV • ↑ HF power • ↓ LF, LF/HF	Acupuncture reduces cardiac autonomic and behavioral responses without changing cortisol level in Beagles.	(Maccariello et al., 2018)
Healthy horses (H)) n=13) Horses with arrhythmia (A) (n=30) Poor performance, no arrhythmia (O) (n=11)	HRV was analyzed with the HSET exercise test (walk, trot, canter, recover) and horses were monitored for abnormal depolarization such as atrial premature complex (APCs) or VPCs	Increased maximum R-R interval variation in group A • ↑ RMSSD Arrhythmia was found in group O during the recovery phase	An increased R-R interval is likely to indicate an arrhythmic event. Treadmill exercise with HRV monitoring of horses can be helpful in assessing premature complex and abnormal pathological events.	(Frick et al., 2019)
Athlete horses (n=9)	HRV monitored for 6 days (Days 0, 1, 2, 3, 4, 5) for 6-hours each time. Horses were stimulated by a hypoxic normobaric device to adapt to a sealed environment.	Increased HRV in athlete horses at days 4 and 5. • ↑ SDNN, RMSSD • ↑ LF	Athlete horses need at least 3 days to adapt to avoid a hypoxic condition. Activated sympathetic tone was found in the hypoxic condition.	(Munoz et al., 2019)
Domestic pigs (n=16) experimental animal model - pigs with fecal peritonitis (n=11) - control (n=5)	Monitored HRV after 5-hours of induced fecal peritonitis for early indication of sepsis	After several hours of sepsis pigs had decreased HRV and increased LF • ↓ SDNN, SDSD, pNN50%, HF • ↑ LF	HRV can be used as an early indicator of sepsis. Sepsis inhibits the parasympathetic nervous system and induces HRV reduction.	(Jarkovska et al., 2017)

Table 7 Clinical uses of HRV for treatment monitoring (Cont.)

Model/Breed	Method	HRV parameter finding	Interpretation	Reference
Dogs with positive PCR assay for Ehrlichia canis afflicted by a chronic phase of cytopenia CME. (n=20) Healthy dogs (n=10)	24-hour HRV monitored and analyzed in the time domain	Dogs with Ehrlichia canis infection had decreased HRV • ↓ SDNN, SDANN, pNN50%	Cytopenic CME leads to autonomic imbalance through stimulation of the sympathetic nervous system	(Gianfranchesco Filippi et al., 2019)

Abbreviations: HRV, heart rate variability; HF, high frequency; LF, low frequency; LF/HF low frequency and high frequency ratio; HFnu, normalizing of high frequency; LFnu, normalizing of low frequency; SDNN, standard deviation of RR interval; SDANN, standard deviation average RR interval; CKCS, Cavalier King Charles Spaniel; wD, wire-haired Dachshund; CT, Cairn Terrier; VVTI, vasovagal tonus index; ARVC, arrhythmogenic right ventricular cardiomyopathy; MI, myocardial infraction; CME, canine monocytic ehrlichiosis; VPC, ventricular premature complex; NE, norepinephrine; SSS, sick sinus syndrome; MMVD, myxomatous mitral valve disease; iSGNA, integrated left stellate ganglion nerve activity; iVNA, integrated vagal nerve activity; HSET, high-speed treadmill standardized exercise test

CONCLUSION

HRV is related to the regulation of the autonomic nervous system. Impairment of HRV is correlated with many diseases in veterinary medicine such as cardiovascular and kidney disease which can result in increased activation of the sympathetic nervous system. HRV can be used to predict and monitor the progression of diseases. In cardiac diseases, HRV can be used to monitor and evaluate MMVD and congestive heart failure in dogs. HRV can also be used with other diseases, e.g., to evaluate the autonomic function in DM, during the post-operative period of splenectomy, to evaluate the effectiveness of acupuncture treatment and during rehabilitation programs as well as with canine ehrlichiosis infection and porcine peritonitis. In addition, HRV impairment resulting from these diseases increases sympathetic tone and induces impairment of both the time domain and the frequency domain. In the time domain, these diseases can induce the decrease of SDNN, SDANN, rMSSD and pNN50%, whereas LF and LF/HF ratios are increased in the frequency domain. HRV can also be used as a sensitive and non-invasive tool for evaluation of the autonomic nervous system and as a predictive tool in clinical veterinary medicine practice. Additionally, it can be used as a model in clinical research to increase knowledge and to help develop better clinical practices.

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