Spectral analysis of heart rate variability in dogs with mild mitral regurgitation

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Objective—To assess autonomic function in dogs with mild mitral regurgitation (MR) that did not have clinical signs of the condition.

Animals—6 healthy adult Beagles.

Procedure—Mild MR was experimentally induced. A 24-hour ambulatory ECG was recorded before and after induction of MR. Heart rate variability was analyzed in frequency domains by use of the ambulatory ECG. Low-frequency (LF) and high-frequency (HF) power were calculated by integrating over their frequency intervals, and the ratio of LF to HF was also calculated. Measurements of frequency domains were analyzed for 4 time periods (midnight to 6 AM, 6 AM to noon, noon to 6 PM, and 6 PM to midnight).

Results—Dogs with experimentally induced MR were classified as International Small Animal Cardiac Health Council class Ia. The HF power of dogs with MR was significantly decreased between 6 AM and noon. The ratio of LF to HF in dogs with MR was significantly increased for the periods between midnight and 6 AM, 6 AM and noon, and noon and 6 PM.

Conclusions and Clinical Relevance—Compensatory response through autonomic modulation was observed in dogs with mild MR that did not have abnormalities, except for cardiac murmur, during clinical examination. This result suggests that treatment during the early stages of mild MR may be beneficial. Additional studies are necessary to determine whether such treatment will delay the onset of congestive heart failure and prolong survival in dogs affected with mild MR. (Am J Vet Res 2003; 64:145–148)

Mitral regurgitation (MR) is 1 of the most common heart diseases in older dogs. It has been documented that angiotensin-converting enzyme (ACE) inhibitors prolong survival time and improve quality of life in humans and dogs with moderate to severe chronic heart failure. Therefore, it is clear that treatment is beneficial during those stages.

Studies have been conducted on treatments administered during the early stages of congestive heart failure (CHF). In a study that involved 229 dogs with naturally developing MR that did not have clinical signs of the condition, long-term treatment with ACE inhibitors did not delay the onset of CHF. On the other hand, it has been reported that there is early activation of the renin-angiotensin system and effects on circulating catecholamines in some dogs with mild MR. Therefore, treatment during the early stages of CHF may be beneficial in these dogs, although treatment for mild MR is still a controversial issue in the field of veterinary medicine.

The current concept for treatment of CHF is to suppress activated neurohormonal factors. Assessment of the altered autonomic system in the early stages of MR is important to determine whether treatment during the early stages is necessary. The purpose of the study reported here was to assess autonomic function in dogs with mild MR (ie, International Small Animal Cardiac Health Council [ISACHC] class Ia).

Materials and Methods

Animals—Six healthy Beagles (1 male, 5 females) that were between 1 and 5 years of age were used in the study. Dogs were housed separately in stainless-steel cages in a temperature-controlled room (approx 25°C). Dogs were placed in the room at least 1 week before the study began to enable them to acclimate to the environment. Lights were turned on at 8 AM and turned off at 8 PM each day. Feeding of the dogs and cleaning of the cages were performed twice each day at approximately 8 AM and 8 PM. Nobody entered the room except the investigators who provided care for the dogs. This study was approved by the Animal Research Committee at Azabu University, School of Veterinary Medicine.

Induction of MR—General anesthesia was induced in all dogs, and left lateral thoracotomy was then performed. Bupivacaine hydrochloride was injected locally into the chest wall of the incision site for analgesic purposes. A hook device was inserted into the left ventricle and used to transect the chordae tendineae. The chordae tendineae of the cusps parietalis were transected, and echocardiography was used to confirm and monitor the regurgitant jet. Transection of the chordae tendineae was considered sufficient when left atrial pressure increased to 15 mm Hg. A few dogs required medical treatment for pulmonary edema after surgery; this treatment was discontinued when clinical signs resolved.

Recording of ambulatory electrocardiography—Prior to the surgery to induce MR, a Holter recorder was placed on each dog to enable it to become acclimated to the experimental device. Each dog was allowed an acclimation period of 1 week. Then beginning at 8 AM, a 24-hour ambulatory ECG was recorded for 3 consecutive days. Approximately 1 month after recovery from surgery to induce MR, a 24-hour ambulatory ECG was begun at 8 AM, and data were recorded for 3 consecutive days. Data recorded for the 2 groups were used to analyze heart rate variability (HRV).

Twenty-four hour ambulatory ECG monitoring was recorded by use of a portable tape recording system (Holter recorder). The ambulatory ECG was recorded on 2 channels by use of an AB lead (CC5R lead) and MX lead (NASA lead).

Received July 15, 2002.
Accepted October 7, 2002.
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Power spectral analysis of HRV—Tapes were digitized by use of an analogue-digital converter. Spectral indices of HRV were computed by fast-Fourier transformation on each 20-minute segment of the recording; a Hanning window was applied to minimize spectral leakage. Low-frequency (LF) power (0.01 to 0.1 Hz) reflects modulation of sympathetic and parasympathetic tone, whereas high-frequency (HF) power (0.10 to 0.60 Hz) reflects modulation solely of parasympathetic tone by breathing. Both LF and HF power were calculated by integration over their frequency intervals. In addition, the ratio of LF to HF was calculated as a measure of sympathovagal balance. Mean values for measurements of the frequency domains and heart rate were determined for 4 time periods (midnight to 6 AM, 6 AM to noon, noon to 6 PM, and 6 PM to midnight).

Statistical analysis—All values were reported as mean ± SD. Comparisons between values for the control and MR groups were made by use of the Wilcoxon signed-rank test. A value of \( P < 0.05 \) was considered significant.

Results
Characteristics of dogs with MR—None of the dogs with induced MR had clinical signs of the condition. Furthermore, abnormalities were not detected during physical examination, except for a regurgitant murmur heard at the left apex. Although a turbulent flow signal was observed during Doppler echocardiography, measurements of the left atrium and left ventricle (LV) (ie, LV end-diastolic diameter, LV end-systolic diameter, thickness of interventricular septum at end of diastole, thickness of LV caudal wall at end of diastole, and fractional shortening) of these dogs were not significantly different from measurements obtained before MR was induced. Dogs were considered normal on the basis of evaluation of thoracic radiographs and results of the ECG. Therefore, dogs with MR were classified as ISACHC class Ia.

Comparison of HRV before and after MR—Heart rate did not differ significantly in dogs before and after induction of MR for any of the 4 time periods (Fig 1). The HF power for the period between 6 AM and noon decreased significantly (\( P = 0.01 \)) from 7,615 ± 5,418 milliseconds² before induction of MR to 4,246 ± 2,469 milliseconds² after induction of MR (Fig 2). The ratio of LF to HF increased significantly (\( P = 0.01 \)) for the periods between midnight and 6 AM (before MR, 32.3 ± 15.45%; after MR, 51.6 ± 28.21%), 6 AM and noon (before MR, 40.2 ± 19.03%; after MR, 70.7 ± 37.51%), and noon and 6 PM (before MR, 41.0 ± 22.42%; after MR, 65.5 ± 39.69%; Fig 3).

Discussion
Abnormal autonomic control of cardiovascular function is believed to provide an important contribution to the pathophysiologic process in patients with CHF. A significant relationship between alteration of the autonomic nervous system and cardiovascular mortality has been revealed during the past 2 decades. It is meaningless to evaluate hemodynamics for the assessment of the early stages of MR, because failure of the pumping action of the heart would be too mild to affect hemodynamic variables. In addition, improvement of hemodynamic variables does not always equate with a better prognosis. Therefore, evaluation of neurohormonal modulation is an appropriate method for assessment of whether medical treatment could improve survival.

The use of HRV is widely accepted for the evaluation of cardiac autonomic modulation. Time-domain
analysis and frequency-domain analysis are 2 major methods used to evaluate HRV. Time-domain indices are measurements of the dispersion of individual cycles around their mean. On the other hand, frequency-domain analysis includes calculations of frequency transformations for the R–R interval, such as power spectral analysis. In general, short-term (a few seconds) fluctuation of R–R intervals is referred to as HF variability (the HF component). The calculated waveform from long-term fluctuations of R–R intervals is an LF component.

The SD of normal sinus R–R intervals (SDNN) is probably the simplest time-domain index of HRV, and SDNN has been considered useful as a prognostic indicator in some studies. Reduced SDNN reflects autonomic modulation of the sinus node characterized by sympathetic predominance or reduced vagal tone.

In contrast, frequency-domain analysis allows HRV to be dissected into its specific frequency components. For example, the HF component is synchronous with respiratory sinus arrhythmia and is mainly supported by vagal activity. The LF component correlates with pharmacologically measured vagal activity. The HF component is largely correlated with sympathetic efferent activity. Consequently, the ratio of LF to HF is considered by some investigators to mirror sympathetic balance or to reflect sympathetic modulation. Therefore, frequency-domain analysis was selected for use in the study reported here to assess autonomic modulation as well as to evaluate the components that were most greatly influenced.

One of the main targets of current medical treatment of heart failure is neurohormonal activation of the sympathetic nervous system and the renin-angiotensin-aldosterone system. Drugs such as ACE inhibitors and β-blockers improve survival in humans and dogs with CHF. However, medical intervention for mild MR is still controversial. In a study of Cavalier King Charles Spaniels, investigators did not find significant differences in HRV (calculated from short-term ECGs) between normal dogs and dogs with a cardiac murmur. However, it is known that autonomic function clearly has circadian variations in dogs. In the dogs reported here, HF power increased at night, and the ratio of LF to HF was high in the morning and low during the night. This tendency was similar to results in another study. Because a significant difference in HF power was not always detected during an entire day in the dogs of our report, autonomic modulation may be masked if it is evaluated only by using short-term ECG recordings.

Abnormalities in HRV have been associated with an adverse prognosis in humans and dogs with heart disease. In a study of humans with chronic severe MR, the SD of the mean R–R interval was the most potent prognostic indicator. In the study reported here, HF power was significantly lower and the ratio of LF to HF was significantly higher in dogs with MR, compared with healthy dogs before the induction of MR. Analysis of our results indicates that the index of vagal tone decreased, whereas the index of sympathetic tone increased, even in dogs with mild MR that did not have clinical signs of the condition. In patients with CHF, parasympathetic activity immediately decreases during the early stages of cardiac dysfunction, and the more cardiac dysfunction progresses, the more sympathetic tone increases. Results of our study were similar to results in those studies. However, an increase in sympathetic tone does not always indicate the severity of CHF. A decrease in the number of β-receptors in the myocardium and abnormalities in G-proteins has been observed as CHF progresses. Therefore, HRV may appear too low in some patients because of a lower responsiveness of the sinus node, even though sympathetic activity is high.

Mild MR in some dogs is reportedly associated with high plasma renin activity and high plasma aldosterone concentration, which documents early activation of the renin-angiotensin-aldosterone system. Modulation of autonomic function seen in the study reported here could have been associated with activation of the renin-angiotensin-aldosterone system in addition to response of baroreceptors.

In the study reported here, compensatory neuroendocrine responses by autonomic modulation were observed in dogs with MR that did not have clinical signs of the condition and did not have abnormalities during clinical examination, except for cardiac murmur. These results imply that early treatment of dogs with MR by use of ACE inhibitors, angiotensin-II receptor blockers, β-blocking agents, or other drugs may be beneficial. Parasympathetic activity increases in human patients with heart failure who are treated with ACE inhibitors. In 1 study, a prevention trial was designed to determine whether enalapril would reduce mortality and morbidity in humans with LV dysfunction that did not have clinical signs of the condition. Those investigators found that the combined end point of death or the development of CHF was reduced significantly. However, in a multiple-center study for the evaluation of ACE inhibitors in dogs, it was concluded that long-term ACE inhibition in dogs with MR that did not have clinical signs of the condition did not delay the onset of CHF. Other studies have documented a benefit with regard to mortality for β-adrenergic blockade in humans with mild to moderate heart failure. Additional treatment with carvedilol in humans with moderate heart failure improves vagal activity and baroreflex control of heart rate. Long-term effects of β-blocking agents in dogs with mild MR have not yet been proven. Additional studies are needed to determine whether early treatment delays the onset of CHF and prolongs survival in domestic animals.

The study reported here had several limitations. Although HF power is widely accepted as an indication of parasympathetic activity, other factors influence the HF component as well as parasympathetic activity, such as breathing-related changes in atrial transmural pressure or the cardiac axis. In 1 study, it was suggested that the nonneurohormonal portion of HF power increases when parasympathetic tone decreases because of CHF, such that HF power may overestimate parasympathetic tone in this situation. Even though the respiratory rate should be controlled to diminish these artifacts, it was impossible in our study design.
The ratio of LF to HF has been used as a measure of sympathetic activity. Because the ratio of LF to HF is inversely proportional to HF, an increase in the ratio of LF to HF could be caused by a decrease of HF (ie, a decrease of parasympathetic tone) and may not be caused by an increase in sympathetic tone.\(^9\)\(^{10}\) Other types of measures of sympathetic activity, such as circulating concentrations of catecholamines, may be needed in addition to HRV analysis for a more accurate evaluation.

References