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Original article

Study of autonomic modulation by non-linear analysis of heart rate variability in different age groups and analysis of health status, disease and risk of death in dogs

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Abstract

The symbolic analysis of heart rate variability (biomarker of cardiac autonomic homeostasis) is a nonlinear and effective tool for pattern extraction and classification in a series analysis, which implies the transformation of an original time series into symbols, represented by numbers. Autonomic heart rate control is influenced by different factors, and better indicators of heart rate variability are found in healthy young individuals than in older and sicker individuals. The aim of this study was to compare the indicators of heart rate variability among healthy dogs in different age groups and in health status using the nonlinear method of symbolic analysis to evaluate the diagnostic accuracy of this method for the risk of death in dogs. An increase in cardiac sympathetic modulation was observed in puppies and dogs at risk of death, which was evidenced by a marked increase of 0 V% (without variation – associated with sympathetic modulation) and a decrease in patterns of 2 V% (two variations – associated with parasympathetic modulation), while the opposite was observed in young adult dogs with increased parasympathetic modulation. Elderly dogs showed a gradual decrease in parasympathetic activity, which tended to worsen with loss of health. It is concluded that the variables of symbolic analysis may be useful to evaluate autonomic modulation in dogs and assist in the differentiation between health states, advanced disease and death throughout the life cycle and have been shown to be indices with high specificity, sensitivity and diagnostic accuracy to help identify dogs at risk of death.

Keywords: dogs, sympathetic system, parasympathetic system and heart rate variability

Introduction

Physiological time systems, such as the series of successive intervals between heartbeats, contain valuable information. Different linear and nonlinear approaches have been proposed to characterize the dynamic peculiarities of autonomic homeostasis (Cysarz et al. 2013). Non-linear analysis of heart rate variability (HRV) provides a non-invasive way of investigating cardiac autonomic modulation in the presence of rhythmic variability (Guzzetti et al. 2005, Vanderlei et al. 2009, Moïse et al. 2020).

Symbolic analysis is a nonlinear and effective tool for the extraction and classification of patterns in temporal systems, which implies the transformation of an original time series into symbols and the creation of patterns with them (Porta et al. 2001). Different criteria can be applied for the transformation of series into symbolic representations and the creation of patterns of analysis (Valencia et al. 2015). The full dynamics of the series (the minimum-maximum range) are distributed over six sections, each identified by a number or symbol from 0 to 5. Original values within each section are replaced by the symbol that defines it in a specific way, thus obtaining a symbolic series. The symbolic series is converted into several patterns of three symbols. Four different categories of patterns can be identified: 0 V (without variation – associated with sympathetic modulation) when there are no variations between three successive symbols, i.e., all three symbols are the same (e.g., 555); 1 V (one variation – no predominance) when a variation between three successive symbols exists, i.e., two symbols are equal (e.g., 755); 2 LV (pattern with two equal variations forming ascending or descending ramps) in which there are two similar variations between successive symbols, i.e., two successive decreases or increases (e.g., '456' or '654'), and 2 UV (pattern with two different variations, forming peaks or valleys) when there are two different variations between successive symbols, i.e., a decrease followed by an increase or vice versa (e.g., '252' or '847') (Tobaldini et al. 2009, Cysarz et al. 2015, Valencia et al. 2015, Silva et al. 2017, Corrêa et al. 2019, Moura-Tonello et al. 2019). The results of the 2 LV% and 2 UV% patterns added together and presented as 2 V% are associated with parasympathetic activity (Guzzetti et al. 2005).

A study by Guzzetti et al. (2005) showed that after high doses of atropine (parasympathetic), there was a significant increase in 0 V patterns (without variation – associated with sympathetic modulation) and a decrease in 2 V (two variations – associated with parasympathetic modulation), while phenylephrine infusion (receptor-specific adrenergic agonist 1) showed a significant increase in the percentage of 2 V, and

the infusion of nitroprusside (mixed vasodilator) (reflex increase in cardiac sympathetic modulation) caused a significant increase in 0 V dynamics. Changes in 1 V patterns did not reach the significance threshold during the autonomic tests in this study, concluding that the increase in cardiac sympathetic modulation determines the increase in 0 V and the decrease in 2 V patterns, while opposite results are observed during an increase in cardiac parasympathetic modulation.

Hyperactivity of the sympathetic nervous system (SNS) is triggered by central and peripheral pathways that are associated with abnormal cardiovascular reflexes observed in a variety of disease states. Patients with congestive heart failure (CHF) have evidence of sympathetic nervous system activation, reflected by increased plasma levels of norepinephrine. It is important to highlight that in the senescent heart, sympathetic activity is increased (Valencia et al. 2015, Lucia, Eguchi and Koch 2018).

Autonomic heart rate control is influenced by different factors, and better HRV indicators are found in healthy young individuals than in elderly and sick individuals. However, most studies on HRV were conducted in populations of extreme ages, young and old, usually without information and comparisons of the initial, intermediate and end-of-life periods (Kleiger et al. 2005, Costa et al. 2017).

To date, there are no published data on symbolic analysis in dogs. Thus, the aim of the present study was to compare HRV indicators between healthy dogs in different age groups, dogs with chronic diseases and dogs at risk of death using the nonlinear method of symbolic analysis and to determine whether this method of analysis presents good diagnostic accuracy to identify dogs at risk of death.

Materials and Methods

Study animals

A total of 126 dogs examined at the hospital between August 2017 and October 2018 were included in the study, 66 males and 60 females of different breeds, separated into five groups.

This study was conducted according to animal welfare standards after approval by the Ethics Committee on the Use of Animals of the Faculty of Veterinary Medicine of UNESP - FMVZ - Botucatu (protocol no. 204/2017) and after the free written consent of the tutors. Group 1 (n=30) was composed of healthy dogs under 1 year of age, group 2 (n=30) was composed of healthy dogs aged between 1 and 8 years, and group 3 (n=30) was composed of healthy dogs older than 8 years. Group 4 consisted of 14 animals with chron-

Table 1. Diseases manifested by dogs in groups 4 and 5.

Group 4 - Chronic diseases	Group 5 - State of imminent death
Stage C myxomatous mitral valve disease	Neoplasia in the terminal stage: <ul style="list-style-type: none"> • Multicenter lymphoma • Cutaneous mastocytoma • Lung carcinoma • Renal carcinoma • Neof ormation in cardiac base (caudal vena cava obstruction)
Stage III chronic kidney disease	Stage D myxomatous mitral valve disease
Diabetes Mellitus	Stage IV chronic kidney disease
Pulmonary Neoplasia	Refractory pneumonia
Chronic pancreatitis	Status epilepticus
Cardiorenal syndrome	

ic compensated diseases (asymptomatic patients with controlled underlying disease), with a mean age of 12.07 years. Group 5 consisted of 22 dogs at risk of death, with an average age of 12.14 years. HRV indices analyze an individual's homeostasis regardless of disease, so groups 4 and 5 represent dogs with different conditions. Group 4 and 5 diseases are shown in Table 1.

Experimental procedure

All dogs in the study were preliminarily selected through electrocardiographic examinations to visualize possible arrhythmias and subsequent inclusion or exclusion from the study, and in the first three groups, brachycephalic animals or animals that presented any other clinical condition were excluded. Dogs in group 4 that had decompensated chronic diseases were excluded. The animals in group 5 died a maximum of 15 days after analysis with the frequency meter.

The analysis was performed by the heart rate monitor, and the RR intervals were captured by a Polar device®, model V-800, already validated for animals for this purpose (Jonckheer-Sheehy et al. 2012, Essner et al. 2013). A sequence of RR intervals with 660 consecutive beats and with the highest stability was selected to perform all analyses, according to the methodology previously proposed by Martinello et al. (2022). To perform the examination, the animals were released during the recording period in a room only with their owners to suffer the least possible influence of stress in the clinical environment; the heart rate monitors were only switched off at the end of a period of five to eight minutes, and all collections were performed during the day.

Heart rate variability

The HRV was evaluated from the symbolic analysis using symbolic analysis software (fast version),

developed in the Department of Pre-Clinical Sciences of Università Di Milano, Italy, of the RR interval series (Perseguini et al. 2011, Valencia et al. 2015), which separated the RR intervals into 6 levels (0 to 5) and ordered them into sequences of 3 symbols that in turn were classified into 4 categories:

- 1-0 V% - pattern without variation (3 symbols equal);
- 2-1 V% - pattern one variation (2 equal symbols followed by a different symbol);
- 3-2 LV% - pattern with two equal variations (3 symbols form ascending or descent ramps);
- 4-2 UV% - standard with two different variations (3 symbols form peaks or valleys).

The results of the 2 LV% and 2 UV% patterns were summed and presented as 2 V%, as performed by Guzzetti et al. (2005).

Statistical analysis

Descriptive analysis of all quantitative variables, such as the mean, standard deviation and quartiles for each group, was performed. The efficiency of the discrimination of the variations found for the patients and death groups against the G2 group was performed by calculating sensitivity, specificity, positive predictive value, negative predictive value and accuracy (with the respective confidence intervals) and constructing the ROC curve. The values of the area under the curve were used to choose the most efficient variables (area above 80%). The assumption of normality of the distribution of variables for each group was made by the Shapiro-Wilk test. For the comparison of the mean/median between all groups, ANOVA (when the assumption of normality was met) and the Kruskal-Wallis test (when the assumption of normality was not met) were used. Multiple comparisons were applied to detect which groups differed from each other. A p value lower

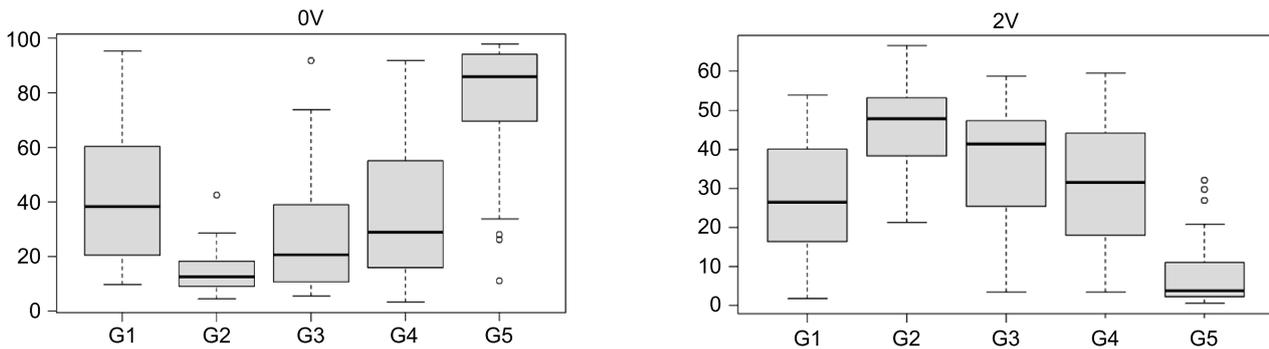


Fig. 1. Graphic representation of the positional value of the symbolic analysis of each variable 0 V% and 2 V% in the different groups of dogs analyzed (G1, G2, G3, G4 and G5). A parabolic pattern of the acquired values is perceived.

Table 2. Mean ± standard deviation and [median] of the indices (mean RR, 0 V%, 1 V% and 2 V%) of HRV in dogs in the different groups analyzed.

Variables	Group 1 < 1 year (n=30)	Group 2 1.1-7.9 years (n=30)	Group 3 >8 years (n=30)	Group 4 Chronic diseases (n=13)	Group 5 Risk of death (n=14)
Mean RR	378.56±89.13 ^a [351.24]	580.57±11.74 ^b [542.57]	537.53±131.74 ^{cb} [558.35]	463.76±95.635 ^{ad} [437.50]	379.18±79.94 ^{ad} [371.00]
0 V (%)	40.37±22.93 ^a [38.32]	14.02±7.97 ^b [12.47]	26.91±22.23 ^{abc} [20.61]	36.50±24.64 ^{acd} [28.85]	75.82±26.26 ^d [85.79]
1 V (%)	32.05±10.01 ^a [36.71]	40.08±4.98 ^b [39.91]	35.95±8.57 ^{cab} [37.55]	32.69±10.61 ^{dabc} [36.03]	15.75±16.55 ^e [10.34]
2 V (%)	27.53±14.29 ^a [26.49]	45.87±10.35 ^b [47.84]	37.09±15.05 ^{cab} [41.39]	30.93±16.31 ^{dac} [31.48]	8.41±9.80 ^c [3.82]

Mean RR (mean normal RR intervals), 0 V% – pattern without variation, 1 V% – pattern with a variation, 2 V% – standard with two variations. Different letters in the same line represent significant differences between the groups (one-way ANOVA and Tukey – Kramer, $p \leq 5\%$).

than 0.05 was considered to indicate a significant difference between the respective groups.

Results

Table 2 describes the means, medians and standard deviations of each variation analyzed. It was verified in the present study that dogs in group G2 (healthy dogs aged between 1 and 8 years) presented higher values of 2 V and less than 0 V compared to the other groups, showing that young adult animals presented higher parasympathetic predominance. There was a significant difference in the correlation of group G2 with groups G1 (< 1 year of age), G4 (compensated chronic diseases) and G5 (death) in most of the symbolic variations. There was no significant difference ($p > 0.05$) between groups G2 and G3 (healthy > 8 years) (Table 3), but group G3 presented lower values of 2 V and higher values of 0 V.

There was no significant difference between groups G1 and G3, G1 and G4, and G3 versus G4 in all symbolic analyses; however, the values of 0 V were higher than the values of 2 V in groups G4 and G1, showing a sympathetic predominance in these groups.

Dogs in group G5 that presented risk of death, as predicted, had significantly lower values of 2 V and higher values of 0 V compared to all other groups, indicating progression toward the equilibrium state, thus revealing an absolute sympathetic predominance at this stage. The mean death of these animals was 6.28 days.

This differentiation between all groups was displayed as a parabolic pattern in box-plot charts (Fig. 1). Table 2 shows the significant differences in the indices between the analyzed groups in bold ($p < 0.05$).

The 0 V index showed a sensitivity of 90.91% and specificity of 93.33%, while the 2 V index showed a sensitivity of 95.45% and specificity of 93.33%, revealing that they are sensitive and specific indices to assist in the identification of dogs at risk of death, in addition to presenting good diagnostic accuracy to assess risk 0 V (96.5%) and 2 V (99.4%). The sensitivity, specificity, positive predictive value, negative predictive value, diagnostic accuracy and cutoff of each index are shown in Table 4.

The AUROCs of the 0 V and 2 V indices overlapped and did not differ completely from the intersection at certain points, indicating little difference between them (Fig. 2).

Table 3. Comparison between groups and p values for each variable.

Groups	Mean RR	0 V (%)	1 V (%)	2 V (%)
G1XG2	0.0000	0.0001	0.0126	0.0005
G1XG3	0.0000	0.2012	1.0000	0.3440
G1XG4	0.1493	1.0000	1.0000	1.0000
G1XG5	1.0000	0.0311	0.1067	0.0044
G2XG3	1.0000	0.3454	0.5455	0.5582
G2XG4	0.1950	0.0189	0.1515	0.0795
G2XG5	0.0000	0.0000	0.0000	0.0000
G3XG4	1.0000	1.0000	1.0000	1.0000
G3XG5	0.0003	0.0000	0.0021	0.0000
G4XG5	0.3147	0.0369	0.2559	0.0058

Table 4. Values of SE, SP, PPV, NPV, diagnostic accuracy and cutoff for dogs at risk of death of each index evaluated (0 V and 2 V).

Indices	SE for risk of death, % (IC95%)	SP for risk of death, % (IC95%)	PPV for risk of death, % (IC95%)	NPV for risk of death, % (IC95%)	Accuracy, % (IC95%)	Cutoff
0 V	90.91 (70.84-98.88)	93.33 (70.88-98.88)	90.91 (70.84-98.88)	93.33 (77.93-99.18)	96.5 (91.0-100.2)	> 26.18% > RM
2 V	95.45 (77.16-99.88)	93.33 (77.93-99.18)	91.30 (71.96-98.93)	96.55 (82.24-98.79)	99.4 (98.2-100.6)	< 32.04% > RM

Sensitivity (SE), specificity (SP), positive predictive value (PPV), negative predictive value (NPV), accuracy and cutoff of each index were evaluated. Sensitivity to risk of death, % (CI95%) Specificity for risk of death, % (95% CI%) PPV for risk of death, % (95% CI%) VNP for risk of death, % (CI95%) Accuracy, % (95% CI%). Risk of death (MR) and cutoff values < (lower) or > (higher).

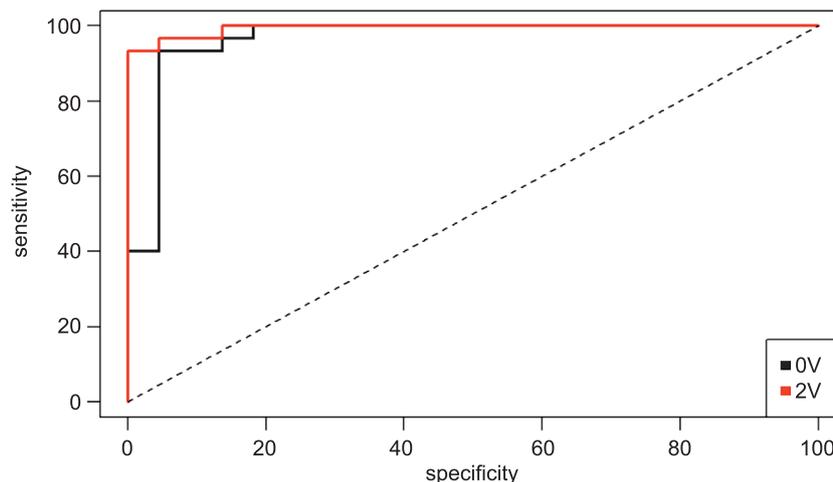


Fig. 2. Receiver operating curves of diagnostic accuracy of symbolic analysis indices for risk of death in dogs. 0 V (index that evaluates the sympathetic nervous system) and 2 V (index that evaluates the parasympathetic nervous system).

In Fig. 3, we contemplate the most representative cases of each analyzed group. We can see higher values of 0 V in the puppy dog (group 1), in the dog with chronic disease (group 4) and in the dog at risk of death (group 5) and higher values of 2 V in the young adult dog (group 2) and old dog (group 3).

Discussion

The purpose of this study was to evaluate whether the short-term symbolic analysis of RR intervals, opted for the use of the heart rate monitor, which is widely used for HRV analysis in humans (Vanderlei et al. 2008,

Heitmann et al. 2011, Barbosa et al. 2016), is a noninvasive method and very accessible for the analysis of HRV, advantageous in relation to Holter, because it is more comfortable for the patient and presents a good level of agreement already described in humans between the two methods (Min et al. 2008), in addition to being already a validated method for dogs (Jonckheer-Sheely 2012, Essner et al. 2013, Essner et al. 2015).

The heart rate monitor is a small device that captures the RR intervals without having to contain the patient or stay close to him, it is known that the approach of the veterinarian for a simple cardiac auscultation can cause the release of catecholamines and consequently increase the HR (Tebaldi et al. 2015).

It was observed that dogs younger than one year old (G1) showed sympathetic predominance, with values greater than 0 V and less than 2 V, but this group of animals did not present significantly different values in relation to the dogs in groups 3 and 4; however, the animals that make up G3 (healthy dogs > 8 years) showed values greater than 2 V, showing parasympathetic predominance in these stages of life, but it was noticed that dogs in group 3 and 4, the values of 0 V increased progressively and the of 2 V have decreased. The immaturity of the autonomic nervous system shows a clear physiological decrease in HRV, but aging and the presence of diseases at different stages cause progressive deterioration of autonomic function, gradually reducing HRV (Godoy and Gregório 2019).

Several studies in humans have shown that the aging process interferes with cardiac autonomic modulation and decreases HRV (Perseguini, et al. 2011, Nascimento et al. 2013, Godoy and Gregory 2019). In the present study, elderly dogs (G3) showed values lower than 2 V and greater than 0 V compared to young adult dogs (G2), i.e., lower HRV and high sympathetic modulation, slightly more evidenced in G3 (healthy dogs > 8 years), although not significant, which could be explained by the clinical aspect of G3 animals, as cardiac function and structure are initially preserved.

The results revealed that animals with chronic diseases (G4) presented statistically higher values of the 0 V index, displayed by increased cardiac sympathetic modulation, than young adult dogs (G2). HRV translates into a balance or homeostasis between sympathetic and parasympathetic activity, and disease states undoubtedly cause an imbalance between these two systems, promoting more evident sympathetic modulation. The results of the present study are similar to those previously described, which also showed an increase in sympathetic activity in sick dogs (Peripherr et al. 2012, Bogucki and Noszczyk-Nowak 2017, Baisan, Vulpe and Ohad 2021).

A human study based on an extensive amount

of data published in the literature combined several individuals with different diseases into the same group and showed that these people had low HRV. The present study also observed that dogs with different diseases have low HRV values compared to healthy dogs (Godoy and Gregório 2022).

Group 5 included a dog with pneumonia, and a decrease in HRV was observed in this patient, corroborating a study carried out on humans diagnosed with pneumonia which showed that sympathetic activity is dominant in this group of people. Diseases in general, and pneumonia in particular, are associated with a balance of pro-inflammatory and anti-inflammatory processes, leading to an immune response. Pneumonia causes fever, tachypnea, tachycardia and hypoxia, which reflects sympathetic modulation and leads to the expected change in HRV (Izhaki et al. 2022).

The SNS is fundamental for the so-called “fighting or flight response” and is activated under physiological conditions of stress in cardiovascular and noncardiovascular diseases. The action of the SNS takes place through the release of catecholamines (norepinephrines) and plays a crucial role in the regulation of homeostasis, but its chronic stimulation is particularly harmful in the case of multiple comorbidities and negatively influences the clinical phenotype (Lucia et al. 2018, Goldberger et al. 2019).

In the present study, the analysis of AUROCs (sensitivity and specificity) to assess the efficiency of these indices in discriminating patients at risk of death showed a good diagnostic accuracy and a high sensitivity and specificity to assist in the identification of these dogs. In addition, the cutoff value was obtained for each of these indices, and dogs with values of 0 V greater than 26.18% and 2 V lower than 32.04% had a higher possibility of dying.

Thus, the symbolic analysis proved to be a viable and reproducible method that can be very useful to direct the veterinarian clinician in therapeutic monitoring and even prognostically with the data obtained. During the study, we contemplated the monitoring of symbolic analysis for one year and nine months in a patient with MVMD evolving until his death. Even under treatment, hemodynamic changes that occurred as a consequence of CHF caused a cascade of changes in neurohumoral activity as a response to the state of the disease. This can lead to a vicious cycle, promoted by the release of catecholamines and inflammatory cytokines, which in turn lead to exacerbation of heart disease. From that moment on, the hyperactivity of the SNS becomes a major complicator in heart failure, conferring significant toxicity to the heart in insufficiency and increasing intensely to death (Lymperopoulos et al. 2013).

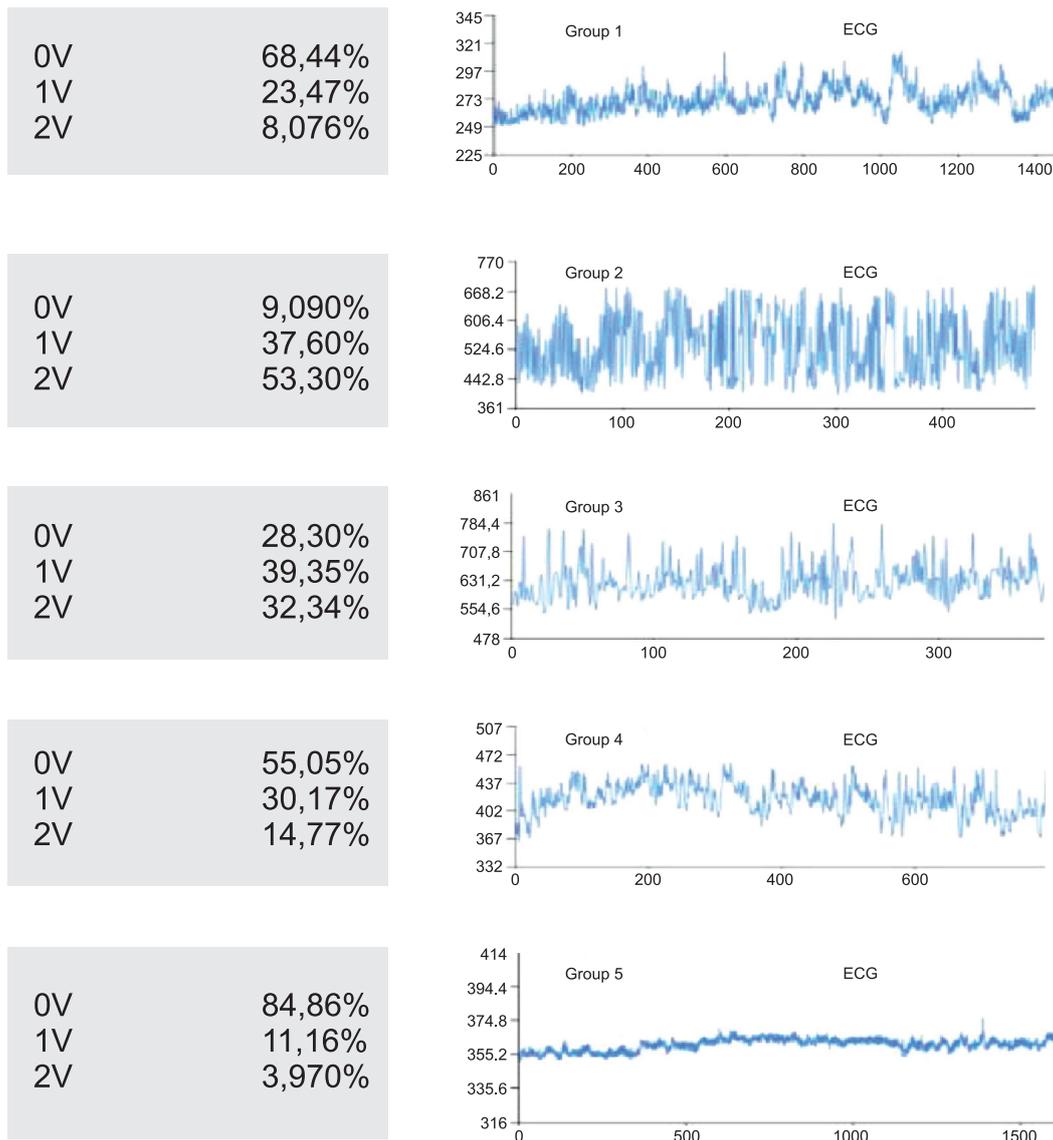


Fig. 3. Symbolic analysis of dogs chosen to represent each of the groups: G1- puppies group, G2: young adults group, G3: elderly group, G4: dogs with chronic diseases (stage C myxomatous mitral degenerative disease; and G5- dogs at risk of death (stage D mitral myxomatous degenerative disease).

In another patient in stage C [ACVIM Consensus – 2019] of MVD, the symbolic analysis of the patient still untreated showed a significant increase of 0 V% and decrease of 2 V%. When the therapy for CHF (Pimobendan, enalapril and furosemide), was instituted, there was a probable decrease in oxygen and metabolic demands of the heart, generating suppression of compensatory neurohormonal systems and restoration of cardiac and circulatory reflex controls, thus improving, in the long term, myocardial function and performance.

The two examples show different profiles of patients who are found in our clinical routine. Some patients are responsive to the treatment instituted, and the symbolic analysis can clearly illustrate the dynamic balance of SNA being restored with therapy, thus establishing

a better prognosis. Some patients, even instituting the therapeutic protocols recommended for stage D [ACVIM Consensus - 2019], do not respond adequately, and we can visualize in the symbolic analysis that gradually the hyperactivity of the SNS occurred and thus indicated a worse prognosis. Figures 4 and 5 show the graphical representation of the tachogram and the value of symbolic analysis (0 V% and 2 V%) of the mentioned patients.

With the symbolic analysis, the clinician can perfectly visualize the percentages of the activity of the autonomic nervous system, being an ally for therapeutic and clinical monitoring of patients, since small changes in these percentages may indicate an improvement or worsening of the clinical condition, helping in the next strategy.

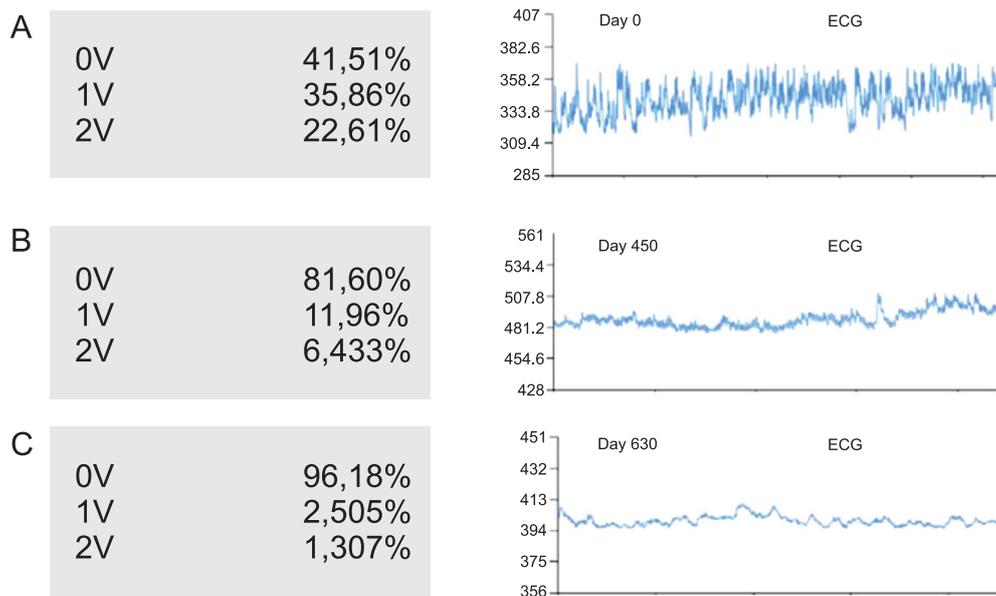


Fig. 4. Graphical representation of the tachogram and value of the symbolic analysis of each variable 0 V% and 2 V% of the follow-up for one year in a patient with MVMD. A- Patient in stage C of MVMD [ACVIM Consensus - 2019], B- The same patient in evolution to stage D of MVMD [ACVIM Consensus - 2019], C- Six hours before death. Figure A shows a sympathetic predominance and reduction in parasympathetic activity. Figure B- Even in therapy, the patient evolved to stage D of the disease, showing a more evident sympathetic predominance. Figure C shows the same patient 6 hours before his death, with the negligible absence of the parasympathetic component.

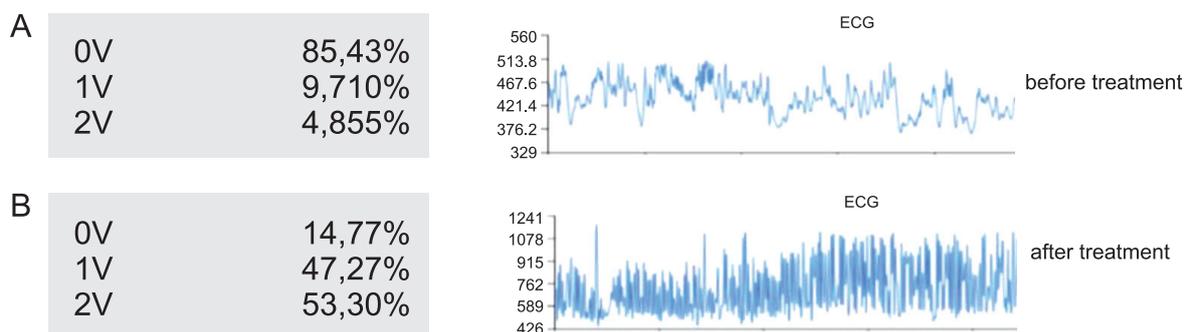


Fig. 5. Graphic representation of the tachogram and value of the symbolic analysis of each variable 0 V% and 2 V%. A- Patient with CHF before therapy, B- The same patient after 30 days of treatment for CHF (Pimobendan, enalapril and furosemide). Figure A shows a sympathetic predominance and a reduction in the parasympathetic component, and after therapy for CHF in figure B, the predominance returned to parasympathetic, showing that the therapy instituted had the desired effect.

I regret that this study could not differentiate between the group of elderly animals and the group of animals with chronic diseases, which was a limitation, possibly because aging is characterized by the activation of several neurohormonal pathways, the most important of which is the SNS. SNS hyperactivity is initially a compensatory mechanism to stimulate contractility and maintain homeostasis, but unfortunately, this chronic stimulation becomes harmful and causes a decrease in cardiac function (Lucia, Eguchi and Koch 2018), consequently decreasing the VFC and this differentiation between the groups.

To date, the authors are unaware of any studies using symbolic analysis in dogs and its diagnostic accuracy for risk of death in dogs; we observed that dogs at risk of death (G5) physiologically present an exacer-

bated sympathetic predominance. The decrease in HRV indicates a lower ability to maintain homeostasis, which may predispose the patient to the disease (Takakura et al. 2017) and, if uncontrolled, cause body balance and, consequently, death.

Conclusion

We concluded the efficacy of the symbolic analysis with diagnostic precision for the identification of dogs at risk of death and in the differentiation between the state of health in younger individuals from morbid states in dogs because healthy animals presented better behavior of the ANS in relation to animals with chronic diseases and with risk of death. Thus, symbolic analysis

in the clinical routine can contribute to the investigation of a possible disease in patients with sympathetic predominance. In addition, it was very clear that animals at risk of death have hyperactivity sns compared to all other groups, which can help in the prognosis and clinical management of dogs.

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