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Myocardial injury in dogs: a retrospective analysis on etiological, echocardiographic, electrocardiographic, therapeutic, and outcome findings in 102 cases☆

G. Romito [a,*], L. Palatini [a], M.C. Sabetti [b], M. Cipone [a]

[a] *Department of Veterinary Medical Sciences, Alma Mater Studiorum - University of Bologna, via Tolara di Sopra 50, 40064, Ozzano dell'Emilia, Italy*
[b] *Department of Veterinary Sciences, University of Parma, Strada del Taglio 10, 43126, Parma, Italy*

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Abstract *Introduction:* In dogs, myocardial injury (MI) is a poorly characterized clinical entity; therefore, this study aimed to provide a detailed description of dogs affected by this condition.
Animals, materials, and methods: Dogs diagnosed with MI according to the concentration of cardiac troponin I (cTnI) were retrospectively searched. Signalment, diagnostic, therapeutic, and outcome data were retrieved. Dogs were divided into six echocardiographic (dilated cardiomyopathy phenotype; hypertrophic cardiomyopathy phenotype; hypertrophic cardiomyopathy phenotype with systolic dysfunction; abnormal echogenicity only; endocarditis; and no echocardiographic abnormalities suggestive of MI), four electrocardiographic (abnormalities of impulse formation; abnormalities of impulse conduction; abnormalities of ventricular repolarization; and no electrocardiographic abnormalities suggestive of MI), and nine etiological (infective; inflammatory; neoplastic; metabolic; toxic; nutritional; immune-mediated; traumatic/mechanical; and unknown) categories. Statistical analysis

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* Corresponding author.
E-mail address: giovanni.romito2@unibo.it (G. Romito).

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was performed to compare cTnI values among different categories and analyze survival.
Results: One hundred two dogs were included. The median cTnI value was 3.71 ng/mL (0.2—180 ng/mL). Echocardiographic and electrocardiographic abnormalities were documented in 86 of 102 and 89 of 102 dogs, respectively. Among echocardiographic and electrocardiographic categories, the dilated cardiomyopathy phenotype (n = 52) and abnormalities of impulse formation (n = 67) were overrepresented, respectively. Among dogs in which a suspected etiological trigger was identified (68/102), the infective category was overrepresented (n = 20). Among dogs belonging to different echocardiographic, electrocardiographic, and etiological categories, cTnI did not differ significantly. The median survival time was 603 days; only eight of 102 dogs died due to MI.
Conclusions: Dogs with MI often have an identifiable suspected trigger, show various echocardiographic and electrocardiographic abnormalities, and frequently survive to MI-related complications.

Abbreviations

2D	two-dimensional
AVB	atrioventricular blocks
bpm	beats per minute
BW	body weight
CHF	congestive heart failure
cTnI	cardiac troponin I
DCM	dilated cardiomyopathy
EDV	end-diastolic volume
EF	ejection fraction
ESV	end-systolic volume
FS	fractional shortening
HCM	hypertrophic cardiomyopathy
HR	heart rate
LV	left ventricular
LVDd	end-diastolic left ventricular diameter
LVDs	end-systolic left ventricular diameter
MI	myocardial injury

In human medicine, the term myocardial injury (MI) is conventionally used to identify patients in whom at least one cardiac troponin concentration is above the 99th percentile upper reference limit without overt myocardial ischemia (i.e. a pathologic condition caused by a mismatch between myocardial oxygen demand and myocardial blood-flow supply), whereas the term myocardial infarction is reserved for patients with MI related to myocardial ischemia [1,2]. Although reports designed to formally define MI are lacking in veterinary medicine, the definition provided by human medicine may be reasonably adapted in dogs [3,4].

In dogs, MI [4—12] seems more common than myocardial infarction [13,14], possibly due to the low predisposition of this species to coronary artery disease. However, there are still many areas of uncertainty about canine MI, also because the available literature mainly consists of isolated case reports [9,10], small case series [11], and original studies that included only dogs affected by a single predisposing condition (e.g. MI exclusively due to snake envenomation [6] or pancreatitis [12]). To date, only one study has analyzed a population of dogs with MI of various etiologies, providing data not strictly related to a single etiological trigger [15]. This inevitably limits our current knowledge on canine MI and our therapeutic and prognostic considerations in affected dogs.

Therefore, the aim of this study was to retrospectively evaluate a large cohort of dogs with MI diagnosed at our institution regardless of the underlying suspected etiology and to provide a detailed description of selected etiologic, diagnostic, therapeutic, and outcome data.

Materials and methods

Study population

For this observational retrospective study, data were collected from the internal database of one university veterinary hospital. Dogs that underwent diagnostic evaluation that led to a final

diagnosis of MI between 2014 and 2023 were included in the study. For the purpose of this study, dogs were considered affected by this condition if they had elevation of cardiac troponin I (cTnI) levels exceeding the upper hospital limit[c] (<0.15 ng/mL), along with concomitant documentation of ≥1 echocardiographic and/or ≥1 electrocardiographic abnormality(ies) that could be considered suggestive of MI according to previous literature [4,6,8–12,16–18]. Concerning echocardiographic abnormalities, these were considered suggestive of possible MI in the case of (a) diffuse left ventricular (LV) systolic dysfunction (i.e. fractional shortening [FS]: <25% and ejection fraction [EF]: <40% [19]) in breeds not reported to be genetically predisposed to primary dilated cardiomyopathy (DCM; e.g. Doberman pinscher [20]); (b) LV segmental akinesia (i.e. a segment of the ventricular wall that shows no contractile function during systole [21]) or dyskinesia (i.e. a segment of the ventricular wall that exhibits a paradoxical outward movement during systole [21]); (c) LV diffuse/segmental wall thickening (i.e. thickness of the LV free wall and/or interventricular septum over the upper body weight (BW)–dependent prediction intervals [22]) in dogs not affected by diseases able to cause LV hypertrophy (e.g. systemic arterial hypertension [23]) or mimic it (e.g. decreased LV preload in hypovolemic subjects, leading to pseudohypertrophy [24]); and (d) LV heterogeneous echogenicity due to the presence of ≥1 linear/patch-like hyperechoic area(s) (which were noted only when consistently observable in high-quality two-dimensional [2D] images by different echocardiographic views) [4,25]. Concerning electrocardiographic abnormalities, these were considered suggestive of possible MI in the case of (a) ventricular and/or supraventricular arrhythmias in breeds not reported to be genetically predisposed to arrhythmogenic heart diseases (e.g. Boxer [26]); (b) atrioventricular blocks (AVBs) in dogs not affected by diseases that may induce these disturbances of impulse conduction (e.g. advanced heart diseases associated with severe cardiac remodeling [27], neoplastic disorders clearly infiltrating the interventricular septum on echocardiography [28], and severe electrolyte disturbances [29]); and (c) abnormalities of ventricular repolarization in dogs not affected by electrolytes abnormalities capable of inducing modifications of the ST segment, T wave, and QT interval (e.g. hyperkalemia [29]).

[c] IMMULITE 2000, Siemens, Erlangen, Germany.

Since DCM and arrhythmogenic right ventricular cardiomyopathy can induce echocardiographic and electrocardiographic abnormalities similar to those identifiable during MI (e.g. LV systolic dysfunction, ventricular arrhythmias), dogs with high levels of suspicion of these primary myocardial diseases were purposefully excluded from this study. Enrollment of dogs with myxomatous mitral valve degeneration at the stages B1 and B2 [30] was permitted since the early stages of this disease usually do not cause remarkable increase of cTnI associated with reduced LV systolic function or abnormalities of cardiac rhythm. In contrast, dogs with myxomatous mitral valve degeneration at stages C and D [30] were excluded since these stages may be associated with a relevant increase of cTnI, a decline of LV systolic function, and arrhythmias [31–33]. The use of drugs capable of reducing LV systolic function (e.g. sedatives/anesthetic drugs such as α2 agonists and propofol) or promoting disturbances of cardiac rhythm (e.g. dobutamine and epinephrine) at the time of echocardiographic and electrocardiographic analysis represented an additional exclusion criterion. The type of diet did not represent an exclusion criterion, although diet history was noted for each dog.

Echocardiographic data

Echocardiographic exams were reviewed by a board-certified cardiologist at the time of study entry to ensure the inclusion criteria were met. In addition to the aforesaid echocardiographic variables, particular attention was paid to the following measurements:

- left ventricular end-diastolic and end-systolic diameters (LVDd and LVDs, respectively) measured using a 2D-guided M-mode leading edge-to-leading edge technique from the right parasternal short-axis view at the level of the papillary muscles;
- left ventricular FS calculated from LV diameters using the following formula: $FS = [(LVDd - LVDs)/LVDd] \times 100$;
- left ventricular end-diastolic diameters normalized for BW (LVDdn) calculated using the following formula: $LVDdn = LVDd\ (cm)/BW\ (kg)^{0.294}$ [22];
- left ventricular end-systolic diameters normalized for BW (LVDsn) calculated using the following formula: $LVDsn = LVDs\ (cm)/BW\ (kg)^{0.315}$ [22];
- left ventricular end-diastolic and end-systolic volumes (EDVs and ESVs, respectively)

measured using the Simpson's method of discs from a 2D right parasternal long-axis four-chamber view and then indexed to body surface area;
- left ventricular EF calculated from LV volumes using the following formula: EF = [(EDV−ESV)/EDV] × 100;
- end-diastolic thickness of the LV free wall and interventricular septum measured using a leading edge-to-leading edge technique from a 2D right parasternal short-axis view at the papillary muscle level;
- left atrial and aortic root diameters measured in 2D from the right parasternal short-axis view at the level of the heart base in early diastole to calculate the left atrium-to-aorta ratio [34].

In dogs with sinus rhythm, for each variable, an average of three measurements was determined from three consecutive cardiac cycles within the same video loop. In dogs with arrhythmias, at least five consecutive cardiac cycles were considered necessary for calculating the average of echocardiographic measurements. In addition to the aforesaid echocardiographic abnormalities suggestive of MI and measurements, attention was also paid to the presence of echocardiographic signs suggestive of infective endocarditis as this condition can progress from the valvular tissue to the surrounding myocardium, leading to MI [35]. The echocardiographic suspicion of infective endocarditis was based on the detection of vegetative lesions/abscesses; the final diagnosis was made according to standardized minor and major criteria [35].

Electrocardiographic data

Electrocardiographic exams (including both surface six-/12-lead electrocardiograms and 24-h Holter recordings) were reviewed by a board-certified cardiologist at the time of study entry to ensure the inclusion criteria were met. The same operator performed further electrocardiographic analysis, including specific rhythm characterization and measurements of waves, segments, and intervals. Initially, the cardiac rhythm was analyzed and classified as sinus or pathological rhythm. Then, the heart rate (HR) in beats per minute (bpm) was calculated by determining the number of QRS complexes in a three-second interval and multiplying this number by 20 at a paper speed of 50 mm/s. For the purpose of this study, the classification of abnormalities of heart rhythm included [33,36,37] the following:

- supraventricular premature complexes: premature normal-appearing QRS complex not preceded by any P wave or conducted by a P wave with abnormal morphology;
- supraventricular tachycardia: ≥4 supraventricular ectopic complexes at an HR of >160 bpm;
- ventricular premature complex: premature, wide, and bizarre-looking QRS complex, not associated with a P wave;
- accelerated idioventricular rhythm: ≥4 ventricular ectopic complexes at an HR of 60−180 bpm;
- ventricular tachycardia: ≥4 ventricular ectopic complexes at an HR of >180 bpm;
- first-degree AVB: a P wave associated with a QRS through a prolonged PQ interval;
- second-degree AVB: a P wave without an associated QRS complex;
- third-degree AVB: evidence of P waves dissociated from QRS complexes with a ventricular rate less than 60 bpm;
- left bundle branch block: sinus rhythm with QRS complexes showing a normal axis in the frontal plane (i.e. between +40° and +100°) and a duration exceeding 80 ms due to a wide R wave;
- right bundle branch block: sinus rhythm with QRS complexes showing a duration exceeding 80 ms due to a wide S wave and a right deviation of the mean electrical axis in the frontal plane that can reach −110°.

Moreover, supraventricular/ventricular ectopic complexes were also characterized as follows [37].

- couplet: two consecutive supraventricular/ventricular ectopic complexes;
- triplet: three consecutive supraventricular/ventricular ectopic complexes;
- bigeminy: a supraventricular/ventricular ectopic complex following every sinus beat.

Lastly, a modified Lown−Wolf grading system was adopted for the classification of ventricular arrhythmias as follows [17]:

- grade 1: isolated ventricular premature complexes;
- grade 2: ventricular bigeminy;
- grade 3: accelerated idioventricular rhythm;
- grade 4: ventricular couplets or triplets;
- grade 5: ventricular tachycardia or R-on-T phenomenon.

If multiple types of ventricular arrhythmias were documented in the same dog, the highest grade of arrhythmia organization was recorded for patient classification (e.g. if both ventricular bigeminy and tachycardia were documented in a dog, a grade 5 was ultimately noted).

The analysis of ventricular repolarization included assessment of the ST segment, T wave, and QT interval. The presence/absence of the ST segment was initially evaluated; then, in dogs with ST-segment deviation, its amplitude was measured, and the type of deviation was classified as previously described [38]. Morphology, duration, amplitude, and mean electrical axis of the T wave were assessed and interpreted in the light of previous canine literature [4,39]. The duration of the QT interval was measured and considered normal if between 150 and 240 ms; moreover, the QT corrected for the HR was calculated according to the logarithmic formula (the QT corrected for the HR = log600 × QT/logRR) [40].

Diagnostic tests, diagnosis, treatment, and outcome data

The medical records were also reviewed to note the following: the type and number of cardiovascular drugs prescribed before the diagnosis of MI; cTnI value at the time of MI diagnosis; the type and number of additional diagnostic tests performed to identify the cause of MI; hypothesized cause of MI; the type and number of cardiovascular treatments prescribed after the diagnosis of MI; and outcome data. Outcome data included the status of dogs at the time of data analysis (i.e. dead/alive); for dead dogs, the cause of death was also noted (i.e. spontaneous/euthanasia, cardiac/non-cardiac), and survival time was calculated.

Statistical analysis

All continuous variables were tested for their distribution using a Shapiro—Wilk normality test.[d] Initial descriptive statistics included mean ± standard deviation for normally distributed data and median and range (minimum to maximum) for data that were not normally distributed. For the purpose of statistical analysis, dogs were initially divided into cases with and without echocardiographic abnormalities and cases with and without electrocardiographic abnormalities. Then, the value of cTnI was compared between the aforesaid groups (i.e. echocardiographic abnormalities vs. no echocardiographic abnormalities and electrocardiographic abnormalities vs. no electrocardiographic abnormalities) using the Mann—Whitney test. For further statistical analysis, echocardiographic and electrocardiographic findings, as well as hypothesized triggers of MI, were subsequently subclassified. Specifically, echocardiographic findings were arbitrarily classified into the following six categories: (1) DCM phenotype, which included dogs showing diffuse LV systolic dysfunction and/or LV segmental akinesia/dyskinesia (with/without concomitant LV dilatation); (2) hypertrophic cardiomyopathy (HCM) phenotype, which included dogs showing diffuse/segmental thickening of LV walls without concomitant LV systolic dysfunction; (3) HCM phenotype with systolic dysfunction, which included dogs showing diffuse/segmental thickening of LV walls associated with concomitant LV systolic dysfunction (with/without concomitant LV dilatation); (4) abnormal echogenicity only, which included dogs with heterogenicity of LV echogenicity associated with neither LV systolic dysfunction nor thickening of LV walls; (5) endocarditis, which included dogs with valve endocarditis not associated with other echocardiographic abnormalities (i.e. lack of concurrent LV systolic dysfunction, LV wall thickening, and LV heterogeneous echogenicity); and (6) no echocardiographic abnormalities suggestive of MI. Moreover, electrocardiographic findings were arbitrarily classified into the following four categories: (1) abnormalities of impulse formation, which included dogs with ventricular and supraventricular arrhythmias regardless the type of organization; (2) abnormalities of impulse conduction, which included dogs with AVBs and bundle branch blocks; (3) abnormalities of ventricular repolarization, which included dogs with abnormalities of the ST segment, T wave, and QT interval; and (4) no electrocardiographic abnormalities suggestive of MI. Additionally, hypothesized triggers of MI were arbitrarily classified into the following nine etiological categories: (1) infective; (2) inflammatory; (3) neoplastic; (4) metabolic; (5) toxic; (6) nutritional; (7) immune-mediated; (8) traumatic/mechanical; and (9) unknown. Then, the Kruskal—Wallis test was used to compare the cTnI value between the dogs belonging to different echocardiographic, electrocardiographic, and etiological categories. Among dogs with ventricular arrhythmias, the Kruskal—Wallis test was also used to compare the cTnI value between dogs belonging to different severity grades. Furthermore, the same test was

[d] MedCalc version 19.5.1; MedCalc Software Ltd, Ostend, Belgium.

used to compare selected echocardiographic measurements between dogs belonging to different electrocardiographic categories. Spearman's correlation coefficients between cTnI value and continuous echocardiographic variables were calculated. Survival curve, median survival time, and 95% confidence intervals were obtained by the Kaplan–Meier method. Survival time was counted from the day of diagnosis to either the day of death or the last available follow-up. Endpoint of the study was death (all causes). Furthermore, a subanalysis was performed including only deaths that were considered cardiac related. Dogs for which the timepoint of death was not available or those that were still alive were censored. Lastly, univariate Cox survival model was used to analyze the effect of selected cardiovascular complications such as congestive heart failure (CHF), electrocardiographic abnormalities, and systolic dysfunction on survival. Results were considered significant when P values were <0.05.

Results

Study population and echocardiographic and electrocardiographic data

The study population included 102 dogs; the demographic characteristics are reported in Table 1. All dogs underwent echocardiographic and electrocardiographic analyses. The latter analysis consisted into a six-/12-lead surface electrocardiogram in 67 of 102 (65.7%) dogs and a combination of six-/12-lead surface electrocardiogram and Holter monitoring in 35 of 102 (34.3%) dogs. On the basis of these tests, echocardiographic and electrocardiographic abnormalities hypothesized to be associated with MI were found in 86 of 102 (84.3%) and 89 of 102 (87.3%) dogs, respectively, with 62 of 102 (60.8%) dogs showing concomitantly both types of abnormalities. Details on echocardiographic categories are reported in Table 2 (Video 1 and 2). In addition to the abnormalities described in Table 2, five of 102 (4.9%) dogs showed intracardiac spontaneous echocontrast. Selected echocardiographic measurements are reported in Table 3. Details on electrocardiographic categories are reported in Table 4. With specific regard to abnormalities of impulse formation, ventricular and supraventricular arrhythmias were found in 53 of 67 (79.1%) and 14 of 67 (20.9%) dogs, respectively (Figs. 1 and 2).

Table 1 Selected demographic data of dogs with enrolled in this study.

Variable	
Number of dogs	102
Age (years)	8 (1–16)
Body weight (kg)	25 (4.8–62)
Sex (EM/NM/EF/NF)	45/12/30/15
Breed (number of dogs)	Mixed breed (35) Labrador retriever (10) German shepherd (6) American Staffordshire terrier (5) Boxer, cocker spaniel (4) Corso, Dogue de Bordeaux, German shorthaired pointer, miniature pinscher, pit bull (2) Australian shepherd, basset hound, beagle, border collie, Bracco Italiano, Cavalier King Charles spaniel, Czechoslovakian Wolfdog, Dalmata, Doberman pinscher, Dogo, English Pointer, English Setter, fox terrier, giant schnauzer, golden retriever, Gran Bleu de Gascogne, Great Dane, Jack Russell terrier, Lagotto, Leonberger, Maltese, miniature schnauzer, Newfoundland, rottweiler, Saint Bernard dog, Segugio Italiano, vizsla, West Highland white terrier (1)
Concurrent cardiac diseases other than MI (Y/N)	41/61
Type of concurrent cardiac diseases (number of dogs)	ACVIM stage B1 MMVD (29) ACVIM stage B2 MMVD (9) Atrial septal defect, small heart base tumor, mild mitral dysplasia (1)

ACVIM: American College of Veterinary Internal Medicine; EF: entire female; EM: entire male; MI: myocardial injury; MMVD: myxomatous mitral valve disease; NF: neutered female; NM: neutered male.

According to the modified Lown–Wolf grading system, ventricular arrhythmias were classified as grade 1, 2, 3, 4, and 5 in 21 of 53 (39.6%), two of 53 (3.8%), two of 53 (3.8%), 12 of 53 (22.6%), and 16 of 53 (30.2%) dogs, respectively. In addition to echocardiographic and electrocardiographic abnormalities, further cardiovascular complications likely associated with MI included CHF (17/102 [16.7%] dogs).

Table 2 Details on echocardiographic categories of dogs enrolled in this study.

Category	
DCM phenotype (number of dogs)	52
Type of abnormality in dogs with the DCM phenotype (Number of dogs)	Diffuse LV systolic disjunction (50) LV segmental akinesia/dyskinesia (2)
HCM phenotype (number of dogs)	22
Type of abnormality in dogs with the HCM phenotype (number of dogs)	Diffuse LV wall thickening (19) Segmental LV wall thickening (3)
HCM phenotype with systolic dysfunction (number of dogs)	4
Abnormal echogenicity only (number of dogs)	4
Endocarditis (number of dogs)	4
Type of valve affected in dogs with endocarditis (number of dogs)	Mitral and aortic (2) Only aortic, only mitral (1)
No echocardiographic abnormalities suggestive of MI (number of dogs)	16

DCM: dilated cardiomyopathy; HCM: hypertrophic cardiomyopathy; LV: left ventricular.

Diagnostic tests, diagnosis, treatment, and outcome data

In line with criteria for study enrollment, in all dogs, at the time of study inclusion, cTnI was measured and was found to be above the upper hospital limit (3.71 ng/mL [0.2–180 ng/mL]). Additional diagnostic tests are listed in Table 5. Based on diagnostic tests, hypothetical triggers of MI were suspected in 68 of 102 (66.7%) dogs (Table 6).

According to statistical analysis, cTnI differed significantly neither between dogs with and without echocardiographic abnormalities (P=0.06) nor between dogs with and without electrocardiographic abnormalities (P=0.14). Moreover, cTnI did not differ significantly between dogs belonging to different echocardiographic (P=0.35), electrocardiographic (P=0.17), and etiological categories (P=0.1). Additionally, cTnI did not differ significantly between dogs belonging to different severity grades of ventricular arrhythmias (P=0.15). Furthermore, no significant differences were found when selected echocardiographic measurements were compared between dogs belonging to different electrocardiographic categories (LA/Ao, P=0.98; LVDdn, P=0.4; LVDsn, P=0.4; FS, P=0.48; EDV indexed to body surface area, P=0.15; ESV indexed to body surface area, P=0.39; EF, P=0.39). Lastly, no significant correlations were found between selected echocardiographic measurements and cTnI value (Spearman's correlation coefficients = from −0.19 to 0.14).

Concerning cardiac treatments, some dogs were already receiving cardiovascular drugs before the diagnosis of MI (according to the prescriptions of referring veterinarians). Having completed the cardiologic evaluation at our institution, cardiovascular therapies were updated on the basis of the ongoing clinical condition of the dogs, primarily to treat MI-related complications (Table 7). With specific regard to dogs with infective diseases, antimicrobials included marbofloxacin (six dogs); amoxicillin-clavulanic acid (five dogs); ceftazidime and clindamycin (three dogs each); ampicillin-sulbactam and piperacillin-tazobactam

Table 3 Selected echocardiographic measurements in dogs enrolled in this study.

Variable	DCM phenotype	HCM phenotype	HCM phenotype with systolic dysfunction	Abnormal echogenicity only	Endocarditis	No echocardiographic abnormalities suggestive of MI
LA/Ao	1.5 (1–2.7)	1.2 (1–1.8)	1.4 ± 0.1	1.4 ± 0.1	1.4 ± 0.4	1.4 (1.2–1.5)
LVDdn	1.9 (1.6–2.6)	1.2 (0.9–1.7)	1.4 ± 0.2	1.4 ± 0.4	1.5 (1.4–2)	1.4 (1.1–1.6)
LVDsn	1.3 (1.1–2.3)	0.9 (0.7–1.1)	1.1 ± 0.3	1 ± 0.3	1 (0.9–1.4)	0.9 (0.8–1.1)
FS (%)	18 (5–24)	44 (26–69)	20 ± 4	35 ± 1	32 ± 5	30 (27–59)
EDVI (mL/m^2)	82 (48–233)	50 (19–69)	72 (47–95)	65 ± 3	75 (63–172)	65 (56–80)
ESVI (mL/m^2)	47 (11–208)	19 (6–30)	35 (12–62)	22 ± 8	30 (20–50)	24 (18–28)
EF (%)	40 (9–48)	64 (52–89)	47 ± 2	65 ± 7	60 ± 9	62 (52–87)

DCM: dilated cardiomyopathy; EDVI: end-diastolic volume index; EF: ejection fraction; ESVI: end-systolic volume index; FS: fractional shortening; HCM: hypertrophic cardiomyopathy; LA/Ao: left atrial-to-aortic root ratio; LV: left ventricular; LVDdn: end-diastolic diameter normalized for body weight; LVDsn: end-systolic diameter normalized for body weight; MI: myocardial injury.

Table 4 Details on electrocardiographic categories of dogs enrolled in this study.

Category	
Abnormalities of impulse formation (number of dogs)	67
Type of abnormality impulse formation (number of dogs)	Isolated ventricular ectopic complexes (21) Ventricular tachycardia (16) Ventricular couplet (10) Isolated supraventricular ectopic complexes, supraventricular tachycardia (6) Accelerated idioventricular rhythm, supraventricular couplet, ventricular bigeminy, ventricular triplet (2)
Abnormalities of impulse conduction (number of dogs)	14
Type of abnormality of impulse conduction (number of dogs)	Second-degree AVB (8) First-degree AVB (3) Left BBB, right BBB, third-degreed AVB (1)
Abnormalities of ventricular repolarization (number of dogs)	8
Type of abnormality of ventricular repolarization (number of dogs)	Giant negative T wave (5) Deep negative T wave, depression of ST segment, QT (and concomitant QTc) prolongation (1)
No electrocardiographic abnormalities suggestive of MI (number of dogs)	13

AVB: atrioventricular block; BBB: bundle branch block.

(two dogs each); and amikacin, doxycycline, and teicoplanin (one dog each).

Complete follow-up data were available for 88 of 102 (86.3%) dogs. Among these dogs, at the time of study's data analysis, 42 of 88 (47.7%) and 46 of 88 (52.3%) dogs were alive and dead, respectively. Among dead dogs, euthanasia and spontaneous death were documented in 34 of 46 (73.9%) and 12 of 46 (26.1%) dogs, respectively. The causes of death were classified as cardiac and noncardiac in eight of 46 (17.4%) and 38 of 46 (82.6%) dogs, respectively. All cardiac deaths were hypothesized to be a consequence of MI-related complications and included spontaneous death due to CHF (4/8 [50%] dogs); sudden cardiac death (3/8 [37.5%] dogs); and euthanasia for relapsing CHF (1/8 [12.5%] dog). Non-cardiac deaths were due to neoplastic, renal, hematologic, neurologic, and infective disorders in 14 of 38 (36.8%), 13 of 38 (34.2%), seven of 38 (18.5%), three of 38 (7.9%), and one of 38 (2.6%) dogs, respectively. The median survival time, regardless of cause of death, was 603 days (133–791 days) (Fig. 3). When only cardiac-related deaths were considered, the median time to event could not be calculated because >50% of dogs remained event-free by the end of the study. The presence of CHF (hazard ratio: 1.3, 95% confidence interval: 0.58–2.9, P=0.5), electrocardiographic abnormalities (hazard ratio: 0.7, 95% confidence interval: 0.36–1.4, P=0.3), and systolic dysfunction (hazard ratio: 1.4, 95% confidence interval: 0.8–2.5, P=0.2) was not associated with a significantly increased risk of death (considering all causes).

Discussion

To date, this study represents one of the largest studies of MI in dogs. Our findings not only support some findings from previous reports on this topic but also provide additional information to expand our knowledge on this clinical entity.

Regarding hypothesized triggers of MI, it is important to underline that we based our etiological hypothesis on the results of numerous diagnostic tests and the identification of at least a disease able to induce MI in dogs according to previous literature [3–12,41–44]. Our results show that the two most common categories were the infectious and the inflammatory ones, primarily represented by sepsis and systemic inflammatory response syndrome, respectively. These findings are not completely surprising as these two conditions are relatively common in small-animal practice [45] and can induce MI by several mechanisms [46]. Another relatively common infective trigger was infective endocarditis, which may lead to MI due to the extension of the infective process from the valvular tissue to the surrounding myocardium [35]. Interestingly, the third most common suspected infective trigger was represented by toxoplasmosis. Although sepsis and endocarditis are somewhat unpredictable conditions, the relatively high prevalence of dogs tested positive for

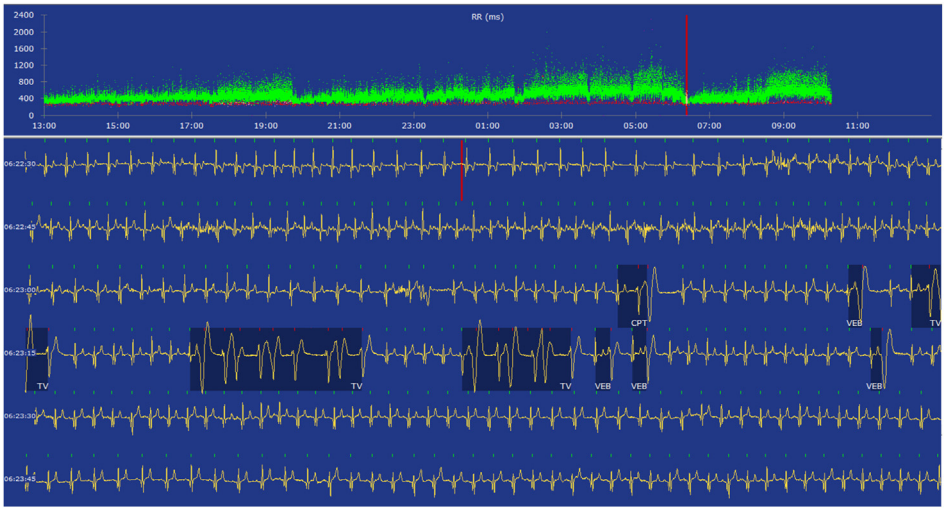

Figure 1 Holter monitoring obtained at the time of diagnosis of myocardial injury from a dog belonging to the electrocardiographic category of abnormalities of impulse formation (specifically, the dog was affected by ventricular arrhythmias). A. Tachogram is presented above the selected portion of Holter recording. On tachogram, the time of day and the RR intervals are represented on the X-axis and Y-axis, respectively. Variations of the heart rate are depicted as increases and decreases of the band of RR intervals. Based on the QRS duration, the software identifies 'typical beats' ($\leq$70 ms; i.e. sinus beats) and 'atypical beats' ($>$70 ms; i.e. ventricular ectopic complexes) and represents them on tachogram as green and red dots, respectively. In the case described herein, the diffuse presence of red dots with RR intervals largely $<$400 ms indicates frequent premature ventricular premature ectopic complexes (total count: 3,180/Holter monitoring). On both tachogram and electrocardiographic tracing, a red line indicates the moment analyzed. B. The selected portion of electrocardiogram shows premature ventricular ectopic complexes, both isolated (i.e. VEB) and organized into a couplet (i.e. CPT) and runs of ventricular tachycardia (i.e. TV) associated with R-on-T phenomenon (minimum coupling interval: 170 ms; maximum instantaneous heart rate: 353 beats per min). Paper speed: 33.9 mm/s. Amplitude: 5 mm/1 mV. Channel: X-axis. CPT: couplet; VT: ventricular tachycardia.

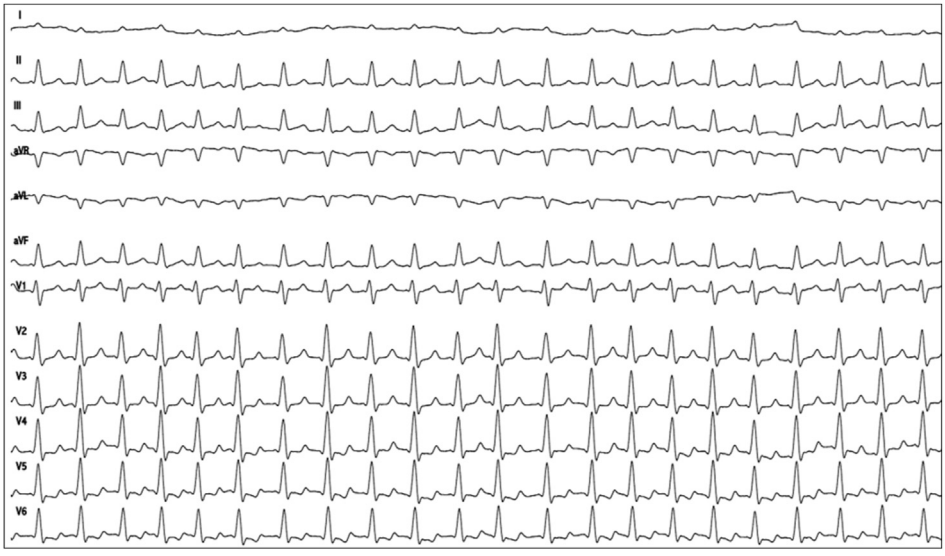

Figure 2 Twelve-lead surface electrocardiogram obtained at the time of diagnosis of myocardial injury from a dog belonging to the electrocardiographic category of abnormalities of impulse formation (specifically, the dog was affected by supraventricular arrhythmias). In the electrocardiographic tracing, a run of supraventricular tachycardia is present. Note the lack of clearly identifiable sinus P waves and the normal configuration of QRS complexes. The coupling intervals are mildly variable (from 222 to 228 ms). The heart rate varies between 263 and 270 beats per min. Paper speed: 50 mm/s. Amplitude: 5 mm/1 mV.

Table 5 Diagnostic tests performed in dogs enrolled in this study in addition to echocardiography, electrocardiographic analysis, and measurement of cardiac troponin I.

Test	Number of dogs (%)
CBC	102/102 (100%)
Serum biochemistry	102/102 (100%)
Venous blood gas analysis	85/102 (83.3%)
Coagulation profile	60/102 (61.2%)
Abdominal ultrasound	54/102 (52.9%)
Thoracic radiography	45/102 (44.1%)
Tests for *Dirofilaria immitis* (serology with/without microfilariae test)	32/102 (32.6%)
Serology for *Anaplasma phagocytophilum*, *Ehrlichia canis*, and *Borrelia burgdorferi*	29/102 (28.4%)
Serology for *Toxoplasma gondii*	19/102 (18.6%)
Blood culture	10/102 (9.8%)
Measurement of plasma taurine concentration	9/102 (8.8%)
Tests for *Bartonella henselae* (serology and/or PCR)	6/102 (5.9%)
Tests for *Angiostrongylus vasorum* (serology and/or Baermann test)	5/102 (4.9%)
Thyroid tests (T4 and TSH)	4/102 (3.9%)
Measurement of catecholamine concentrations (plasmatic and/or urinary)	3/102 (2.9%)
Serology for *Neospora caninum*	3/102 (2.9%)
Urine culture	2/102 (2%)
Tests for COVID-19 (serology and PCR)	2/102 (2%)

CBC: complete blood count; COVID-19: coronavirus disease 2019 due to severe acute respiratory syndrome coronavirus 2; PCR: polymerase chain reaction; T4: thyroxine; TSH: thyroid-stimulating hormone.

Table 6 Hypothesized causes of myocardial injury of dogs enrolled in this study.

Category	
Unknown (number of dogs.)	34
Infective (number of dogs)	20
Type of infective trigger (number of dogs)	Sepsis (12) Endocarditis (4) Toxoplasmosis (3) COVID-19 (1)
Inflammatory (number of dogs)	18
Type of inflammatory trigger (number of dogs)	SIRS (17) Anaphylactic shock (1)
Metabolic (number of dogs)	8
Type of metabolic trigger (number of dogs)	CKD (5) AKI (3)
Neoplastic (number of dogs)	8
Type of neoplastic trigger (number of dogs)	Hemangiosarcoma, pheochromocytoma (3) Lymphoma (2)
Toxic (number of dogs)	6
Type of toxic trigger (number of dogs)	Snake envenomation (4) Dicoumarol poisoning, doxorubicin toxicity (1)
Nutritional (number of dogs)	3
Type of nutritional trigger (number of dogs)	Grain-free diet (3)
Immune-mediated (number of dogs)	3
Type of immune-mediated trigger (number of dogs)	Immune-mediated anemia (3)
Traumatic/mechanical (number of dogs)	2
Type of traumatic/mechanical trigger (number of dogs)	Cardiopulmonary resuscitation, vehicular trauma (1)

AKI: acute kidney injury; CKD: chronic kidney disease; COVID-19: coronavirus disease 2019 due to severe acute respiratory syndrome coronavirus 2; SIRS: systemic inflammatory response syndrome.

Toxoplasma gondii may not necessarily be incidental (of note, these three dogs had serological titers indicating an active infection, as previously documented in a case series reporting details of these subjects [11]). Indeed, cases of MI in *T. gondii*—positive cats have been reported in the same geographical area as the dogs from this report [47,48]. Furthermore, epidemiological studies performed in different animal species have documented a relatively wide diffusion of this protozoal disease in Italy [49,50]. Concerning the only case of MI associated with coronavirus disease due to severe acute respiratory syndrome coronavirus 2 (a case already documented as a case report [10]), it was diagnosed in 2021 during a local wave of the ongoing pandemic. In addition to systemic inflammatory response syndrome, another suspected inflammatory trigger of MI was

Table 7 Cardiovascular drugs prescribed before and after the diagnosis of myocardial injury dogs enrolled in this study.

Drug prescribed before the diagnosis of MI	Number of dogs
Pimobendan	5
Angiotensin-converting enzyme inhibitor	4
Spironolactone	3
Drug prescribed after the diagnosis of MI	**Number of dogs**
Pimobendan	42
Sotalol	18
Furosemide	17
Lidocaine	8
Angiotensin-converting enzyme inhibitor	6
Amiodarone	4
Clopidogrel	4
Mexiletine	3
Spironolactone	3
Taurine supplementation	3
Enoxaparin	1

MI: myocardial injury.

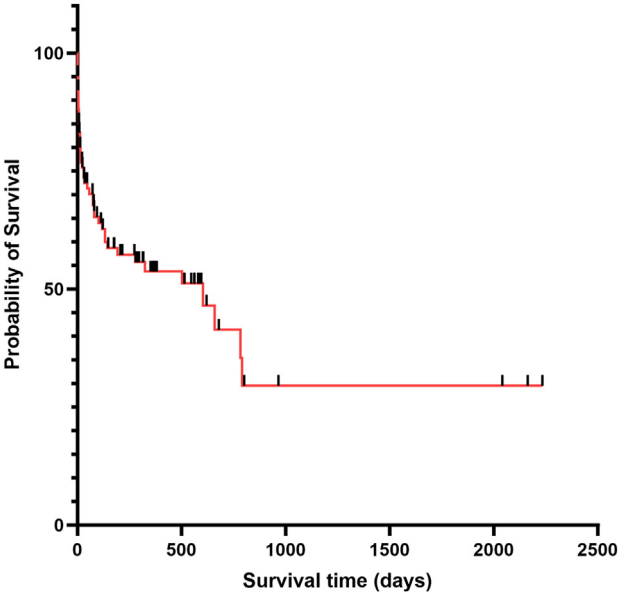

Figure 3 Kaplan-Meier survival curve displaying all-cause mortality for dogs with myocardial injury. The median survival time was 603 days (133—791 days). Censored animals are indicated by vertical hash marks.

anaphylactic shock (due to multiple wasp stings). According to human literature, MI in the setting of anaphylaxis in an otherwise apparently healthy subject can be due to Kounis syndrome (allergic angina) [51].

The third most common etiological category of MI was represented by metabolic processes, namely renal diseases (of note, all dogs from this group had severe azotemia, with a median creatinine of 7.5 mg/dL [3.6—11.1 mg/dL]). This finding agrees with previous publications documenting a high prevalence of MI among dogs with advanced renal diseases (e.g. ~80% in a study including 31 dogs with renal failure [5]), potentially due to the pro-inflammatory, pro-thrombotic, and apoptotic effects of uremic toxins [52].

The fourth most common etiological category of MI included malignant neoplasia, namely hemangiosarcoma, lymphoma, and pheochromocytoma. The first two neoplasia can induce MI by infiltration of the heart, whereas the third one is induced by the cardiotoxicity of massively released catecholamines [28,42,43].

The fifth most common etiological category of MI was the toxic one, primarily snake envenomation. In this condition, MI is caused by the toxic mixture of the snakes' venom, which contains several hemotoxic and cytotoxic proteases [6]. Additionally, one dog from this category experienced MI during dicoumarol poisoning, a condition already documented to be a potential source of MI in this species [41]. In the last dog from this category, MI was documented after five doses of doxorubicin. This finding is in line with previous literature as the risk of doxorubicin cardiotoxicity has been reported to be higher after the fifth dose of this chemotherapy [53].

Less common etiological categories of MI included the nutritional, immune-mediated, and traumatic/mechanical ones. Interestingly, all dogs from the nutritional category were dogs fed with grain-free diets that had a DCM phenotype on echocardiography. These results agree with previous studies in dogs, documenting LV systolic dysfunction and increased cTnI in some dogs fed with grain-free diets [44]. Concerning dogs from the immune-mediated category, immune-mediated anemia was diagnosed in all cases. In this condition, MI results from direct cardiomyocyte damage due to hypoxia and development of cardiac thromboemboli [7]. Concerning dogs from the traumatic/mechanical category, one developed MI after vehicle trauma (primarily as a result of the mechanical damage) and the remaining one, after cardiopulmonary resuscitation (of note, this case has been already described in a previous publication, where a detailed explanation on the related pathophysiology is provided [9]).

It should be also noted that, in ~one-third of our study population, a possible cause of MI could not be determined despite the numerous diagnostic tests performed, highlighting the elusive nature of canine MI. Regarding diagnostic procedures performed in addition to those considered essential to assess cardiac condition (e.g. echocardiographic and electrocardiographic analysis, cTnI measurement), the type and number of tests we performed need to be contextualized in light of the hypothesized systemic triggers of MI and geographic areas in which the dogs lived (as the prevalence of some infectious diseases depends on the latter factor). Based on our experience, we believe that there is no universal list of extra-cardiac diagnostic tests that should be systematically adopted for all dogs with MI, but the diagnostic process should be evaluated on a case-by-case basis.

In addition to investigating possible etiological trigger, we aimed at evaluating if cTnI levels varied according to the suspected cause of MI. Our results demonstrate that the concentration of this biomarker did not differ significantly among different etiological categories of MI. Accordingly, veterinarians should not hypothesize a specific etiology just because of a particularly high cTnI value but should instead keep any hypothesis open and carry out the appropriate diagnostic tests to confirm/exclude the various differential diagnoses of MI. For example, the five dogs with the highest value of cTnI from our study population (i.e. 180 ng/mL) belonged to five distinct etiological categories (i.e. infectious, neoplastic, metabolic, immune-mediated, and unknown).

We also compared the concentration of cTnI among dogs with and without echocardiographic changes, and among dogs with and without electrocardiographic changes, finding no significant differences. Additionally, we found no relevant differences when comparing cTnI values among dogs belonging to different echocardiographic and electrocardiographic categories. In this study, there was also a lack of significant difference between cTnI value and the severity grade of ventricular arrhythmias and lack of correlation between cTnI value and selected echocardiographic measurements. As a matter of fact, in our study population, it was possible to document a remarkably high cTnI value (e.g. >15 ng/mL) in dogs with normal echocardiographic measurements as well as in dogs with no electrocardiographic abnormalities or low-grade ventricular arrhythmias (e.g. isolated ventricular ectopic complexes). At the same time, it was also possible to document a mildly increased cTnI (e.g. <2 ng/mL) in dogs with abnormal echocardiographic measurements (e.g. reduced FS and EF) as well as in dogs with electrocardiographic abnormalities, including high-grade ventricular arrhythmias (e.g. ventricular tachycardia).

A possible explanation for the aforesaid findings is that timings of changes of cTnI concentration are not necessarily identical to those needed by the heart to manifest overt structural and electrocardiographic abnormalities. Indeed, after an acute cardiac insult, cTnI concentration changes rapidly (i.e. it reaches a peak within 24 h and then decreases rapidly once the underlying source of injury has resolved since the cTnI half-life in dogs is <2 h) [3]. In contrast, after a triggering stimulus/insult, the heart typically needs days to weeks to develop histological changes at the basis of echocardiographic and electrocardiographic abnormalities (e.g. fibroblast proliferation and collagen deposition) [54]. Another explanation concerns the number of cTnI measurements as only a single cTnI measurement was analyzed herein (i.e. that performed at the time of MI diagnosis). Regrettably, the fact that cTnI was not measured serially made it impossible to properly characterize the phase of MI and, therefore, to temporally associate it with the echocardiographic and electrocardiographic abnormalities.

Concerning electrocardiographic abnormalities, we investigate not only disturbance of impulse formation and conduction (both already well documented in dogs with MI [6,11,12,15,17]) but also abnormalities of ventricular repolarization, given the importance of changes of the ST segment and T wave in humans with MI [1]. Interestingly, only a few dogs showed abnormalities of ventricular repolarization, primarily expressed as deep/giant negative T waves (an electrocardiographic abnormality already described in dogs with MI [4]). It could be hypothesized that dogs are more resistant than humans to the development of impairments of repolarization during MI. Alternatively, this may be secondary to the imprecision in identifying repolarization abnormalities in dogs, given the limited veterinary data published on this topic to date [4,38,39].

Concerning echocardiographic abnormalities, it is interesting to note that the DCM phenotype was overrepresented, followed by the HCM phenotype. In the acute phase, the first echocardiographic pattern may be a result of impaired contractility due to the massive release of inflammatory cytokines, especially tumor necrosis factor α and interleukin 1β [55], whereas, in the chronic phase, it is a consequence of a maladaptive remodeling associated with cardiomyocyte necrosis and fibrosis [54]. In contrast, the HCM phenotype may be

caused by interstitial edema and infiltration of inflammatory cells during acute myocardial inflammation [47,48,56].

In this study, cardiac complications such as CHF, electrocardiographic abnormalities, and systolic dysfunction were not associated with an increased risk of death, and only a few dogs experienced cardiac death. Admittedly, a speculative hypothesis, but yet plausible, is that the low MI-associated death rate was due, at least in part, to the attention we paid to performing comprehensive diagnostic tests in dogs affected by systemic diseases able to induce MI and the prompt introduction of the appropriate therapies.

This study has some limitations. First, the retrospective design of our analysis precluded the standardization of timing of diagnostic procedures and therapeutic interventions. Moreover, we cannot completely exclude a possible effect, albeit likely modest, of cardiovascular drugs previously prescribed by the referring veterinarians on cardiological assessment at the time of MI diagnosis (e.g. possible changes in systolic function in the five dogs already receiving pimobendan to treat myxomatous mitral valve degeneration). Second, we classified dogs arbitrarily into different echocardiographic, electrocardiographic, and etiological categories, and categories were not equally represented. Third, our decision to exclude dogs with DCM and arrhythmogenic right ventricular cardiomyopathy could have introduced a bias. Indeed, there is a possibility that a Doberman pinscher with DCM or a Boxer with arrhythmogenic right ventricular cardiomyopathy could also be secondarily affected by MI due to comorbidities. Additionally, it could be hypothesized that some of the enrolled dogs showing an HCM phenotype could actually be affected by primary HCM (although this disease is rare in this species [57—59]). However, in our opinion, the observed cTnI values make the risk of misclassification limited. Indeed, the cTnI levels we documented in dogs with an HCM phenotype (median value of 12.1 ng/mL) are remarkably higher than those described in canine HCM (1.7 ng/mL according to a case report [58]; median value of 3.94 ng/mL according to a retrospective study [59]), suggesting the presence of a pathological process associated with MI different from primary HCM. Fourth, we focused our echocardiographic assessment on the left-sided cardiac chambers, although MI could also lead to right-sided cardiac abnormalities. Fifth, advanced echocardiographic modalities, which could have helped to more comprehensively address LV function, were not assessed in our study population. Sixth, as an FS of 20—25% could be physiologically found in some large-breed dogs, the echocardiographic cut-offs adopted to identify LV systolic dysfunction could have been inaccurate in some subject. Moreover, our way of indexing EDV and ESV, although conventionally used, may have been partially imprecise as this method is based on a false dimensional premise. Seventh, no dog underwent invasive diagnostic procedures to gain further information on the nature and extent of myocardial compromise (e.g. endomyocardial biopsy). Lastly, only the initial measurement of cTnI was considered for our statistical analysis; therefore, further studies on canine MI evaluating the role of serial cTnI controls are required to validate and expand on our findings. Despite this last limitation, we believe that our results can be anyway clinically useful since not all dogs undergo repeated cTnI rechecks in clinical practice (e.g. due to economic restraints of the owners). Therefore, our findings can act as a guide for those cases where only the initial cTnI value is available.

In conclusion, this study provides a detailed description of echocardiographic and electrocardiographic abnormalities as well as therapeutic and outcome data of dogs with naturally acquired MI of different etiologies diagnosed at our institution. The results provided here should be interpreted in the light of the diagnostic criteria we adopted to define MI. Further studies are needed to provide information on dogs with different clinical characteristics, including those with an increase in cTnI not associated with the echocardiographic or electrocardiographic abnormalities we investigated.

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Conflict of Interest Statement

The authors do not have any conflicts of interest to disclose.

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Italiana delle Scienze Veterinarie, Bari, Italy, 21st—23rd June 2023.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.jvc.2024.03.004.

Video	Title	Description
1	Transthoracic echocardiographic video clip obtained from a right parasternal long axis four-chamber view at the time of diagnosis of myocardial injury from a dog belonging to the echocardiographic category named dilated cardiomyopathy phenotype.	Note the diffuse left ventricular systolic dysfunction and dilatation.
2	Transthoracic echocardiographic video clip obtained from a right parasternal long axis four-chamber view at the time of diagnosis of myocardial injury from a dog belonging to the echocardiographic category named hypertrophic cardiomyopathy phenotype.	Note the asymmetric left ventricular wall thickening, which is more pronounced at the level of intraventricular septum, and the preserved systolic function.

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