Transient deep and giant negative T waves in dogs with myocardial injury

Abbreviation table

cTnI	cardiac troponin I
LV	left ventricular
MI	myocardial injury
NTWs	negative T waves
QTc	QT interval corrected for the heart rate

Introduction

In human medicine, the definition of myocardial injury (MI) and its distinction from myocardial infarction has evolved over time to accommodate the development of increasingly sensitive markers of myocardial damage and imaging methods [1,2]. In humans, the term MI currently identifies any patient in whom at least one cardiac troponin concentration is above the 99th percentile upper reference limit without overt myocardial ischemia, whereas the term myocardial infarction is specifically reserved for patients with MI related to myocardial ischemia [1,2]. Although reports purposefully designed to formally define MI are lacking in veterinary literature, the increase in cardiac troponins, especially cardiac troponin I (cTnI), is acknowledged to have a clinical role in dogs similar to that described in human medicine [3]. In humans and dogs, a variety of cardiovascular or non-cardiovascular conditions may lead to MI, often due to a mismatch in myocardial oxygen supply and demand or a direct cardiomyocyte damage [1-3]. In both species, MI may be defined as acute if there is a dynamic pattern in cTnI concentrations, characterized by an initial rise and a subsequent fall, or chronic if cTnI levels remain persistently elevated [1-3]. In addition to the measurement of the cTnI concentration, transthoracic echocardiography and surface electrocardiogram represent common first-line, non-invasive diagnostic procedures when suspecting MI in human [1,2,4] and veterinary medicine[a] [5-9]. During

MI, humans [1,2,4] and dogs[a] [5,6,8,9] often show similar echocardiographic abnormalities, including transient or permanent changes in ventricular function (e.g., hypokinesia, akinesia, dyskinesia) and/or structure (e.g., wall thickening, heterogeneous myocardial echogenicity). In contrast, the current list of electrocardiographic changes associated with MI appears to be quite different in the two species.

Traditionally, veterinary cardiologists have focused predominantly on abnormalities of ventricular depolarization rather than those of repolarization; indeed, to date, the latter abnormalities and their clinical role have been accurately investigated in only a few small animal studies[b] [10-13]. Consequently, although data exist on the occurrence of atrial and ventricular arrhythmias in canine MI[a] [5-7], little is known about the development and clinical significance of repolarization changes in this condition. Unlike veterinary medicine, repolarization abnormalities represent a central issue in human arrhythmology [14,15]. To date, several repolarization anomalies have been described in patients with MI, especially in the context of myocardial infarction [4,14-16]. Among the most intriguing anomalies is the transient development of deep or giant negative T waves (NTWs), a rare electrocardiographic pattern characterized by the acute development of prominent NTWs in the context of MI, followed by T-wave normalization after MI resolution [16-18]. In humans, recognition of such a pattern has significant clinical implications. In contrast to persistent repolarization abnormalities, which often indicate irreversible myocardial damage (e.g., ST-segment deviation, persistent NTWs) [19-21], the development of transient NTWs appears to be a predictor of a viable myocardium resulting from early revascularization and/or myocardial edema resolution [17,20-25].

To the best of our knowledge, there are no reports in the veterinary literature describing the aforementioned repolarization abnormality in dogs with a naturally acquired MI. Therefore, the aim of this study was to describe the electrocardiographic features of

spontaneous development of deep and giant NTWs in canine MI, and the associated clinical, echocardiographic, and laboratory findings.

Animals, Materials and Methods

Medical records of dogs diagnosed with MI that underwent diagnostic evaluation at the Department of Veterinary Medical Sciences of the University of Bologna between January 2014 and March 2021 were retrospectively reviewed by one author (GR). For the purpose of this study, dogs were considered affected by MI if they fulfilled all of the following criteria: 1) conclusive diagnosis of ≥1 ongoing cardiovascular and/or non-cardiovascular disease(s) known to be able to induce MI in this species [3]; 2) concomitant demonstration of cTnI elevation over the upper hospital limit (<0.7 ng/mL); and 3) concomitant documentation of ≥1 echocardiographic change(s) among a) diffuse left ventricular (LV) systolic dysfunction (i.e., fractional shortening <25% and ejection fraction <40% [26]), b) LV segmental akinesia (i.e., a segment of the ventricular wall that show no contractile function during systole [27]) or dyskinesia (i.e., a segment of the ventricular wall that exhibits a paradoxical outward movement during systole [27]), c) LV diffuse/segmental wall thickening (i.e., thickness of the LV free wall and/or interventricular septum over the upper body weight-dependent prediction intervals [28]), and d) LV heterogeneous echogenicity due to the presence of ≥1 linear/patch-like hyperechoic area(s) [8,9,29,30]. Based on follow-up data, dogs were diagnosed with acute MI if normalization of cTnI, as well as the disappearance of ventricular wall thickening/motion abnormalities, were documented concurrently with the resolution of the underlying cardiovascular/non-cardiovascular trigger(s) of MI [1-4]. Since changes of myocardial echogenicity can persist after MI resolution [9,29], the permanence of LV hyperechoic areas in dogs with otherwise normalized echocardiography and cTnI did not represent an exclusion criterion for the

115 diagnosis of acute MI. In contrast, dogs showing cTnI values persistently above the upper
116 hospital limit and an irreversibility of the aforesaid echocardiographic changes were
117 diagnosed with chronic MI [1-4].

118 Regarding electrocardiography, recordings were obtained in dogs manually
119 restrained on their right sides; all animals were conscious with no chemical restraint. The
120 conventional electrocardiographic parameters (i.e., heart rate; amplitude and duration of
121 the P wave; PQ interval duration; amplitude and duration of the QRS complex; ST-
122 segment elevation or depression; and QT duration) were manually measured in lead II
123 according to the standard technique, and were judged to be normal/abnormal according to
124 canine reference intervals [31,32]. In addition to the QT-interval duration, duration of the
125 QT interval corrected for the heart rate (QTc) was measured according to the logarithmic
126 formula (QTc = log600 x QT/logRR) [31-33]. For the purposes of this study, particular
127 attention was given to T-wave features, namely amplitude, polarity, and morphology.
128 Concerning T-wave amplitude, it was measured in lead II from the isoelectric line to the
129 peak of the wave and was considered normal between <±0.05 and 1 mV [31]. The ratio
130 between the R- and T-wave amplitudes was also measured in lead II and was considered
131 normal if the T-wave amplitude was approximately ≤1/4 of R-wave amplitude [32]).
132 Concerning T-wave polarity, it was classified as positive and negative. Due to the lack of
133 available canine criteria for the classification of the degree of T-wave negativity, we
134 adapted human cut-offs in our canine population [16]. Specifically, in dogs from this study,
135 NTWs were defined as deep or giant if their amplitude in lead II was ≥-0.5 mV or ≥-1.0 mV,
136 respectively [16]. In comparison between R and T waves in the same lead, T-wave polarity
137 was further defined as concordant or discordant if it was identical or opposite to that of the
138 R wave, respectively [31]. Concerning morphology, T waves were defined as symmetrical
139 or asymmetrical if their initial and terminal branches had similar or clearly different slope,

respectively [31]. As T waves recorded from healthy dogs typically show a gradual upstroke in the initial portion and a more rapid downstroke in the terminal portion [31], possible evidence of asymmetry due to an initial branch that was more steep than the terminal one was considered abnormal. Additional possible morphological peculiarities that were looked for included biphasic (i.e., if T waves showed two peaks that moved in opposite directions) and dome-and-dart T waves (i.e., if the ST segment and the first portion of the T wave formed a convex upward curve, followed by the terminal portion of the T wave, which formed a well-defined second positive peak separated from the first by a low-amplitude negative deflection) [31,32,34].

All cTnI measurements were performed with the same machine[c]. Similarly, all transthoracic echocardiographic and electrocardiographic examinations were performed using the same instruments[d,e] and standardized techniques [35,36].

Data collected from the medical database of dogs with transient deep and giant NTWs included: signalment; ongoing cardiovascular and/or non-cardiovascular disease(s); cTnI concentration, as well as echocardiographic and electrocardiographic abnormalities at the time of MI diagnosis; electrolyte abnormalities at the time of deep/giant NTWs identification; time from MI diagnosis to possible cTnI and echocardiographic normalization; time from MI diagnosis to the demonstration of deep/giant NTWs disappearance; electrolyte abnormalities at the time of the demonstration of deep/giant NTWs disappearance; and survival data.

Data were tested for normality graphically and with the Shapiro-Wilk test[f,g]. Since data were not normally distributed, they were presented as the median and range (minimum to maximum).

Results

During the study period, 139 dogs fulfilled the diagnostic criteria of MI, of which 32/139 (23%) were diagnosed with acute MI. Among dogs with MI, only 6/139 (4.3%) dogs had a diagnosis of transient deep/giant NTWs. All dogs with this electrocardiographic pattern had an acute MI. These six dogs included: two mixed breed dogs, one Beagle, one Cocker spaniel, one English Setter, and one Lagotto Romagnolo. Three of these dogs were female, and three were castrated male. Age ranged from 6 to 13 years (median: 9.5 years). Body weight ranged from 15.3 to 37.4 kg (median: 17.2 kg). Myocardial injury was due to snake envenomation in three dogs, sepsis in two dogs (associated with septic arthritis [n=1] and liver abscesses [n=1]), and systemic inflammatory response syndrome in a dog with pheochromocytoma complicated by inferior vena cava thrombosis. Four dogs (three with giant NTWs and one with deep NTWs) had a concomitant cardiac disease, namely myxomatous mitral valve degeneration (in all cases, American College of Veterinary Internal Medicine stage B1). At the time of MI diagnosis, the cTnI concentration ranged from 1.8 to 180 ng/mL (median: 21.8 ng/mL; upper hospital limit: <0.7 ng/mL).

In addition to changes related to myxomatous mitral valve degeneration (i.e., irregular thickening of mitral valve leaflets and mitral regurgitation), echocardiography revealed diffuse LV systolic dysfunction associated with diffuse LV wall thickening and LV heterogeneous echogenicity in two dogs, diffuse LV wall thickening associated with LV heterogeneous echogenicity in other two dogs, diffuse LV systolic dysfunction in another dog, and diffuse LV wall thickening in the remaining dog. No other echocardiographic abnormalities were documented (Video 1).

Electrocardiograms revealed a sinus rhythm with giant NTWs (amplitude: from -1 to -1.8 mV [median: -1.4 mV]) in five dogs, and a sinus rhythm with deep NTWs (amplitude: -0.55 mV) in the remaining dog. In dogs with giant NTWs, T-wave amplitude was 71% [64-

260%] of R-wave amplitude. In the dog with deep NTWs, T-wave amplitude was 122% of R-wave amplitude. In all dogs, T waves were discordant with R-wave polarity. In four of the five dogs with giant NTWs, T waves had a symmetrical morphology. In contrast, the remaining dog with giant NTWs and the only dog with deep NTWs showed asymmetrical T waves with an initial branch less steep than the terminal one. Neither biphasic nor dome-and-dart T waves were identified. In all dogs with giant NTWs, the QT intervals were prolonged (290 ms [270-340 ms]; upper reference limit: 240 ms [31,32]); the relative QTc ranged between 285 and 322 ms (median: 290 ms). In contrast, the dog with deep NTWs had a normal QT-duration (200 ms; relative QTc: 203 ms). In three dogs with giant NTWs, ventricular premature complexes were also documented. Ventricular ectopies were isolated in one dog, and organized in couplets, triplets, and runs of accelerated idioventricular rhythm and ventricular tachycardia in the remaining two dogs. Additionally, the dog with deep NTWs showed phases of isorhythmic atrioventricular dissociation with synchronization type 1. No additional cardiac rhythm disturbances were observed (Fig. 1A). At the time of identification of deep/giant NTWs, two dogs with giant NTWs had mild electrolyte changes (one dog had mild hypokalemia [serum potassium concentration: 3.6 mEq/L; hospital reference limits: 3.8-5 mEq/L] and one dog had mild hypocalcemia [total serum calcium concentration: 8.9 mg/dL; hospital reference limits: 9.3-11 mg/dL]). No other electrolyte abnormalities were documented in the remaining study population.

All dogs were hospitalized with continuous electrocardiographic monitoring and received proper medical therapies according to the underlying systemic disease. No cardiovascular drugs were prescribed apart from lidocaine[h], which was administrated in two dogs to treat ventricular tachycardia (intravenous bolus [2 mg/kg over 20-30 sec], followed by a constant rate infusion [50-80 µg/kg/min over 6-8 h]). In all cases, resolution of the systemic trigger of MI was achieved. The time from MI diagnosis to demonstration of

cTnI normalization ranged from 4 to 12 days (median: 6.5 days). In all cases, echocardiographic improvement and the disappearance of deep/giant NTWs were demonstrated on the same day of the identification of cTnI normalization (cTnI value: 0.18 ng/mL [0.02-0.29 ng/mL]). At that time, LV morphological and functional parameters were completely normalized in four dogs; in the remaining two dogs (both from the group of dogs with giant NTWs), LV ventricular echogenicity remained persistently heterogeneous, despite otherwise normalized LV echocardiographic parameters (Video 2). Concomitant electrocardiographic analysis demonstrated a sinus rhythm with positive T waves (amplitude: 0.25 mV [0.2-0.5 mV]; T-wave amplitude was 21.5% [10-28%] of R-wave amplitude). Moreover, in all dogs, T waves were concordant with the R-wave polarity, they had an asymmetrical morphology due to an initial branch that was less steep than the terminal one, and the duration of QT intervals was normal (210 ms [190-240 ms]; relative QTc, 215 ms [192-232 ms]). Concerning cardiac rhythm abnormalities identified at the time of arrival, isorhythmic atrioventricular dissociation was still intermittently identifiable in one dog, while ventricular premature complexes were no longer present (Fig. 1B). At the time of the demonstration of deep/giant NTWs disappearance, all dogs had normal serum electrolyte levels.

All dogs were discharged from the hospital. Five dogs were still alive at the time of manuscript writing (8 months [6-24 months] after MI diagnosis). The remaining dog (a subject from the group of dogs with giant NTWs) died 2 months after MI diagnosis due to postoperative complications unrelated to previous MI (i.e., after unilateral adrenalectomy for pheochromocytoma).

Discussion

To the Author's knowledge, this study represents the first report of transient deep/giant NTWs in dogs with naturally acquired MI. The main findings of our retrospective analysis were that (1) deep/giant NTWs were identified exclusively in dogs with acute MI, regardless of the underlying etiology of myocardial damage; (2) changes in T-wave polarity seemed to occur in parallel with the evolution of myocardial damage, as T-wave negativization was documented after the onset of MI and T-wave normalization was synchronous with MI resolution; and (3) deep/giant NTWs were always discordant with the R-wave polarity, often showed a symmetrical morphology, and were frequently associated with long QT intervals.

Interestingly, our results were overall in agreement with human literature. In humans, transient T-wave inversion may also develop during several different conditions, either cardiac [16-20,37] or extra-cardiac [16,18,37-41]. Moreover, as seen in dogs from this report, human transient deep/giant NTWs typically manifest rapidly after the onset of MI (in many patients, ≤100 hours of the onset of related symptoms [17]). The temporal link between MI and T-wave inversion is complex and likely multifactorial. In humans, variables associated with both the myocardial state (e.g., extent and severity of underlying coronary artery disease and timing of functional recovery) and treatment strategy (i.e., timing and type) have been hypothesized to play a role in the timing of transient T-wave negativization [21]. Lastly, similar to our study population, inverted T waves often have an opposite polarity compared to that of R waves, and are typically symmetrical and almost systematically associated with prolonged QT intervals in humans [16-18,37,42].

Knowledge of principles underlying ventricular repolarization is essential to understand the physiology of T-wave genesis on the surface electrocardiogram and the pathophysiology of its inversion. The T wave is formed at the end (phase 3) of the ventricular repolarization and represents the electrical forces resulting from the recovery of

activated ventricular muscle fibers to their resting states [14,15,31]. Ventricular repolarization begins with phase 1 of the monophasic action potential, which corresponds to the J wave on the surface electrocardiogram, and lasts until the end of phase 3. During phases 1 and 2, the epicardial and endocardial cells show similar membrane potential values, which corresponds to the isoelectric ST segment on the surface electrocardiogram, while the phase 3 is characterized by nonhomogeneous variations in the individual action potentials of the different ventricular layers [14,15,31]. Such heterogeneity, which may be found between the apex and the base and transmurally, is mainly due to differences in ion channels density (especially, Ito, IKr and IKs) and action potential duration between epicardial, endocardial, and mid-myocardial cells (M cells) [14,15,31]. Due to this electrophysiological substrate, ventricular repolarization physiologically moves from the epicardium to the endocardium, as well as from the apex to the base, and repolarization velocity is slower in the sub-epicardial regions and faster in the sub-endocardial regions [14,15,31]. Such temporal and spatial patterns of repolarization determine the normal T-wave configuration.

Usually, human and canine T-wave polarity is concordant with that of the R waves, and their morphology is asymmetrical due to the ascending portion (the one associated with the sub-epicardial repolarization) having a more gradual slope than the descending branch [14,15,31,32]. However, a certain variability has been documented both in human and veterinary medicine. For example, the human T waves may be inverted until the age 12 to 14 and then become positive after the age 16 years (namely, juvenile T wave); moreover, T-wave inversion in lead V1 appears to be more common in healthy females than males [43,44]. For this reason, in human medicine, clinicians are encouraged to interpret the T-wave features in the context of the individual patient presentation, with the aim of properly discerning normal variants from abnormal patterns. The interpretation of T-

wave configuration may be challenging even in canine medicine, since both biphasic and mildly NTWs have been documented in healthy dogs [31,32]. Given the above, in both species, T-wave negativity should not be systematically interpreted as a pathological sign, especially when this is observed in healthy subjects and only in one lead, NTWs have a normal morphology, and their amplitude remains stably within the reference ranges on serial recordings (in dogs, <-0.05 mV) [31,32,43,44]. Nevertheless, in humans and dogs, the development of deep (≥-0.5 mV) or giant (≥-1.0 mV) NTWs should raise concern, especially when this pattern is observed in all leads from subjects with cardiac/extracardiac diseases that are able to cause MI, and it is concomitant with a prolonged QT interval and increased cTnI [16,17]. Several conditions can alter the substrate of ventricular repolarization and, consequently, the T-wave configuration. In human coronary artery diseases, subendocardial ischemia can lead to a shorter action potential duration and earlier repolarization prior to the subepicardial area, thus inverting the T-wave polarity [18]. The same may occur in patients with other cardiac and extra-cardiac illnesses associated with excessive sympathetic activation, since significant vasoconstriction of the intramural coronary arteries due to high catecholamine levels may predispose them to subendocardial ischemia [18,45]. Moreover, the possible development of myocardial edema may transitorily invert the physiologic apico-basal gradient of ventricular repolarization, further contributing to transient T-wave negativization [25,42,45]. Myocardial ischemia and edema may also induce concurrent prolongation of the QT interval [25,42,45,46], which is the electrocardiographic representation of the duration of ventricular depolarization and subsequent repolarization [14,15,31,32]. In the present study, we diagnosed transient deep/giant NTWs in dogs with MI due to snake envenomation, sepsis, and systemic inflammatory response syndrome associated with pheochromocytoma. Since these conditions can lead to both ischemic MI and myocardial edema [3,16,47,48], it could be hypothesized that human and canine transient deep/giant

NTWs share a similar pathophysiology. Four of these dogs were also affected by myxomatous mitral valve degeneration, although the cardiac disease was considered not severe enough to precipitate the T-wave changes reported here (i.e., in all cases, American College of Veterinary Internal Medicine stage B1).

Concerning the clinical significance of transient negativization of T waves in the context of MI, growing evidence indicates this repolarization abnormality as a favorable sign rather than an ominous one in humans. Indeed, the spontaneous normalization of NTWs has been interpreted by many authors as a predictor of recovery of regional dysfunction in patients affected by MI without permanent cardiomyocyte damage [17,20-25]. In contrast, persistently inverted T waves have been associated with irreversible transmural necrosis, progressive left ventricular enlargement, and a decline of global left ventricular function over time [19-21]. Whether the same is true in dogs with MI remains to be established, although the overall favorable clinical, electrocardiographic, and echocardiographic outcome of subjects from this report may suggest a similar role for canine transient deep/giant T-wave negativization.

When evaluating the relationship between MI and repolarization abnormalities and their clinical impact, extracardiac factors influencing ventricular repolarization, including heart rate and electrolyte fluctuations, should be considered [11-13,15,31-33,38,41,49]. Since the QT is known to be strongly dependent on the R-R interval, both QT and QTc were measured in dogs in the present study for a better assessment of repolarization duration [15,31-33], as done in other studies with a similar aim and/or design [11-13,16,42]. Regarding the potential effect of electrolytes disorders on the repolarization phase, one dog had mild hypokalemia and another mild hypocalcemia at the time of identification of deep/giant NTWs, while no electrolyte changes were identified at the time of T-wave normalization. Therefore, the influence of electrolyte fluctuations on T-wave

configuration was likely unremarkable. This strengthened the hypothesis of a true pathophysiological link between the different phases of MI and the dynamic T-wave changes.

Results of the present study should be read in the context of certain limitations. First, the retrospective design of our analysis precluded the standardization of timing of diagnostic procedures and therapeutic interventions. Second, the number of dogs was small due to the rarity of the studied electrocardiographic pattern; therefore, further studies enrolling a larger number of animals are required to confirm and expand on our findings. Indeed, the limited study population prevented further analysis on possible correlations, such as that between the degree of cTnI elevation and the amplitude of transient NTWs. Third, no dog underwent invasive diagnostic procedures to gain further information on the nature and extent of myocardial compromise (e.g., cardiac magnetic resonance, endomyocardial biopsy). Lastly, our designation of transient NTWs as deep and giant was arbitrarily adapted from human literature given the lack of pertinent canine criteria. However, the fulfillment of the human cut-offs (≥-0.5 mV and ≥-1.0 mV, respectively [16]) and the remarkable disproportion between the amplitude of NTWs and that of positive R waves during MI, in our opinion, made the aforementioned designation acceptable in this report.

Conclusions

In conclusion, herein we reported six dogs with transient deep/giant NTWs, an electrocardiographic pattern previously not described during canine MI. Clinicians should be aware of the existence, features, and clinical significance of this electrocardiographic entity in dogs with MI and consider it in the list of repolarization abnormalities in this species.

Conflict of interest

None of the authors have a conflict of interest.

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None.

Footnotes

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[c] Immulite 2000 troponin I test, Siemens, Erlangen, Germany

[d] iU22 ultrasound system, Philips Medical Systems S.p.A., Monza, Italy

[e] Cube ECG, Cardioline S.p.A., Caverano, Italy

[f] Microsoft Excel, version 2016, Microsoft Corporation, Redmond, Washington (USA)

[g] R, version 3.5.2, R Foundation for Statistical Computing, Vienna, Austria

384 [h] Lidocaina 2% 20 mg/ml, Ecuphar Italia S.r.l., Milano, Italy

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Figure legends

Figure 1: Example of reversible electrocardiographic changes recorded from a dog with transient giant negative T waves. A. Six-lead electrocardiogram recorded at the time of diagnosis of myocardial injury. A sinus rhythm associated with giant negative T waves is evident (amplitude: -1.3 mV). Note the disproportion between the amplitude of T waves and that of R waves (in lead II, T-wave amplitude is 260% of R-wave amplitude). Also notice that T-wave polarity is discordant with R-wave polarity, T waves have an almost symmetrical morphology, and the QT interval is prolonged (270 ms). B. Six-lead electrocardiogram recorded at the time of resolution of the myocardial injury. A sinus rhythm associated with normal T waves is evident (amplitude: 0.2 mV). At this time, the ratio between the T- and R-wave amplitudes is within the expected value (in lead II, T-wave amplitude is 15% of R-wave amplitude), and T-wave polarity is concordant with R-wave polarity. Moreover, T waves have an asymmetrical morphology (note that the initial branch is less steep than the terminal branch) and the QT-interval duration is normal (190 ms). Paper speed = 50 mm/s; amplitude = 10 mm/mV.

Videos

Video	Title	Description
1	Transthoracic echocardiographic video clip obtained from a right parasternal long axis four-chamber view at the time of diagnosis of	Note the diffuse left ventricular wall thickening, which is particularly severe at the level of the left ventricular free wall and papillary

	myocardial injury from the dog of Figure 1.	muscle, and the heterogeneous echogenicity. Also notice the disproportion between the T- and R-wave amplitudes.
2	Transthoracic echocardiographic video clip obtained from a right parasternal long axis four-chamber view at the time of resolution of myocardial injury from the dog of Video 1.	Note the normalization of the left ventricular wall thickness, which is particularly evident at the level of the left ventricular free wall and papillary muscle, and the more homogenous myocardial echogenicity. Also notice the normalization of the electrocardiographic pattern.

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