



ALMA MATER STUDIORUM  
UNIVERSITÀ DI BOLOGNA

ARCHIVIO ISTITUZIONALE  
DELLA RICERCA

## Alma Mater Studiorum Università di Bologna Archivio istituzionale della ricerca

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

This is the final peer-reviewed author's accepted manuscript (postprint) of the following publication:

*Published Version:*

Romito, G., Cipone, M. (2021). Transient deep and giant negative T waves in dogs with myocardial injury. JOURNAL OF VETERINARY CARDIOLOGY, 36, 131-140 [10.1016/j.jvc.2021.05.009].

*Availability:*

This version is available at: <https://hdl.handle.net/11585/860777> since: 2022-02-18

*Published:*

DOI: <http://doi.org/10.1016/j.jvc.2021.05.009>

*Terms of use:*

Some rights reserved. The terms and conditions for the reuse of this version of the manuscript are specified in the publishing policy. For all terms of use and more information see the publisher's website.

This item was downloaded from IRIS Università di Bologna (<https://cris.unibo.it/>).  
When citing, please refer to the published version.

(Article begins on next page)

45 **Abbreviation table**

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

46

47 **Introduction**

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

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

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

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

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

92

### 93 **Animals, Materials and Methods**

94 Medical records of dogs diagnosed with MI that underwent diagnostic evaluation at  
95 the Department of Veterinary Medical Sciences of the University of Bologna between  
96 January 2014 and March 2021 were retrospectively reviewed by one author (GR). For the  
97 purpose of this study, dogs were considered affected by MI if they fulfilled all of the  
98 following criteria: 1) conclusive diagnosis of  $\geq 1$  ongoing cardiovascular and/or non-  
99 cardiovascular disease(s) known to be able to induce MI in this species [3]; 2) concomitant  
100 demonstration of cTnI elevation over the upper hospital limit ( $< 0.7$  ng/mL); and 3)  
101 concomitant documentation of  $\geq 1$  echocardiographic change(s) among a) diffuse left  
102 ventricular (LV) systolic dysfunction (i.e., fractional shortening  $< 25\%$  and ejection fraction  
103  $< 40\%$  [26]), b) LV segmental akinesia (i.e., a segment of the ventricular wall that show no  
104 contractile function during systole [27]) or dyskinesia (i.e., a segment of the ventricular wall  
105 that exhibits a paradoxical outward movement during systole [27]), c) LV diffuse/segmental  
106 wall thickening (i.e., thickness of the LV free wall and/or interventricular septum over the  
107 upper body weight-dependent prediction intervals [28]), and d) LV heterogeneous  
108 echogenicity due to the presence of  $\geq 1$  linear/patch-like hyperechoic area(s) [8,9,29,30].  
109 Based on follow-up data, dogs were diagnosed with acute MI if normalization of cTnI, as  
110 well as the disappearance of ventricular wall thickening/motion abnormalities, were  
111 documented concurrently with the resolution of the underlying cardiovascular/non-  
112 cardiovascular trigger(s) of MI [1-4]. Since changes of myocardial echogenicity can persist  
113 after MI resolution [9,29], the permanence of LV hyperechoic areas in dogs with otherwise  
114 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 ( $QTc = \log 600 \times QT / \log RR$ ) [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  $<\pm 0.05$  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  $\leq 1/4$  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  $\geq -0.5$  mV or  $\geq -1.0$  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,

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

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

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

160 Data were tested for normality graphically and with the Shapiro-Wilk test<sup>f,g</sup>. Since  
161 data were not normally distributed, they were presented as the median and range  
162 (minimum to maximum).

163

164 **Results**

165 During the study period, 139 dogs fulfilled the diagnostic criteria of MI, of which  
166 32/139 (23%) were diagnosed with acute MI. Among dogs with MI, only 6/139 (4.3%) dogs  
167 had a diagnosis of transient deep/giant NTWs. All dogs with this electrocardiographic  
168 pattern had an acute MI. These six dogs included: two mixed breed dogs, one Beagle, one  
169 Cocker spaniel, one English Setter, and one Lagotto Romagnolo. Three of these dogs  
170 were female, and three were castrated male. Age ranged from 6 to 13 years (median: 9.5  
171 years). Body weight ranged from 15.3 to 37.4 kg (median: 17.2 kg). Myocardial injury was  
172 due to snake envenomation in three dogs, sepsis in two dogs (associated with septic  
173 arthritis [n=1] and liver abscesses [n=1]), and systemic inflammatory response syndrome  
174 in a dog with pheochromocytoma complicated by inferior vena cava thrombosis. Four dogs  
175 (three with giant NTWs and one with deep NTWs) had a concomitant cardiac disease,  
176 namely myxomatous mitral valve degeneration (in all cases, American College of  
177 Veterinary Internal Medicine stage B1). At the time of MI diagnosis, the cTnI concentration  
178 ranged from 1.8 to 180 ng/mL (median: 21.8 ng/mL; upper hospital limit: <0.7 ng/mL).

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

186 Electrocardiograms revealed a sinus rhythm with giant NTWs (amplitude: from -1 to  
187 -1.8 mV [median: -1.4 mV]) in five dogs, and a sinus rhythm with deep NTWs (amplitude: -  
188 0.55 mV) in the remaining dog. In dogs with giant NTWs, T-wave amplitude was 71% [64-

189 260%] of R-wave amplitude. In the dog with deep NTWs, T-wave amplitude was 122% of  
190 R-wave amplitude. In all dogs, T waves were discordant with R-wave polarity. In four of the  
191 five dogs with giant NTWs, T waves had a symmetrical morphology. In contrast, the  
192 remaining dog with giant NTWs and the only dog with deep NTWs showed asymmetrical T  
193 waves with an initial branch less steep than the terminal one. Neither biphasic nor dome-  
194 and-dart T waves were identified. In all dogs with giant NTWs, the QT intervals were  
195 prolonged (290 ms [270-340 ms]; upper reference limit: 240 ms [31,32]); the relative QTc  
196 ranged between 285 and 322 ms (median: 290 ms). In contrast, the dog with deep NTWs  
197 had a normal QT-duration (200 ms; relative QTc: 203 ms). In three dogs with giant NTWs,  
198 ventricular premature complexes were also documented. Ventricular ectopies were  
199 isolated in one dog, and organized in couplets, triplets, and runs of accelerated  
200 idioventricular rhythm and ventricular tachycardia in the remaining two dogs. Additionally,  
201 the dog with deep NTWs showed phases of isorhythmic atrioventricular dissociation with  
202 synchronization type 1. No additional cardiac rhythm disturbances were observed (Fig.  
203 1A). At the time of identification of deep/giant NTWs, two dogs with giant NTWs had mild  
204 electrolyte changes (one dog had mild hypokalemia [serum potassium concentration: 3.6  
205 mEq/L; hospital reference limits: 3.8-5 mEq/L] and one dog had mild hypocalcemia [total  
206 serum calcium concentration: 8.9 mg/dL; hospital reference limits: 9.3-11 mg/dL]). No  
207 other electrolyte abnormalities were documented in the remaining study population.

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

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

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

236

## 237 **Discussion**

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

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

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

263 activated ventricular muscle fibers to their resting states [14,15,31]. Ventricular  
264 repolarization begins with phase 1 of the monophasic action potential, which corresponds  
265 to the J wave on the surface electrocardiogram, and lasts until the end of phase 3. During  
266 phases 1 and 2, the epicardial and endocardial cells show similar membrane potential  
267 values, which corresponds to the isoelectric ST segment on the surface electrocardiogram,  
268 while the phase 3 is characterized by nonhomogeneous variations in the individual action  
269 potentials of the different ventricular layers [14,15,31]. Such heterogeneity, which may be  
270 found between the apex and the base and transmurally, is mainly due to differences in ion  
271 channels density (especially, Ito, IKr and IKs) and action potential duration between  
272 epicardial, endocardial, and mid-myocardial cells (M cells) [14,15,31]. Due to this  
273 electrophysiological substrate, ventricular repolarization physiologically moves from the  
274 epicardium to the endocardium, as well as from the apex to the base, and repolarization  
275 velocity is slower in the sub-epicardial regions and faster in the sub-endocardial regions  
276 [14,15,31]. Such temporal and spatial patterns of repolarization determine the normal T-  
277 wave configuration.

278         Usually, human and canine T-wave polarity is concordant with that of the R waves,  
279 and their morphology is asymmetrical due to the ascending portion (the one associated  
280 with the sub-epicardial repolarization) having a more gradual slope than the descending  
281 branch [14,15,31,32]. However, a certain variability has been documented both in human  
282 and veterinary medicine. For example, the human T waves may be inverted until the age  
283 12 to 14 and then become positive after the age 16 years (namely, juvenile T wave);  
284 moreover, T-wave inversion in lead V1 appears to be more common in healthy females  
285 than males [43,44]. For this reason, in human medicine, clinicians are encouraged to  
286 interpret the T-wave features in the context of the individual patient presentation, with the  
287 aim of properly discerning normal variants from abnormal patterns. The interpretation of T-

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

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

318         Concerning the clinical significance of transient negativization of T waves in the  
319 context of MI, growing evidence indicates this repolarization abnormality as a favorable  
320 sign rather than an ominous one in humans. Indeed, the spontaneous normalization of  
321 NTWs has been interpreted by many authors as a predictor of recovery of regional  
322 dysfunction in patients affected by MI without permanent cardiomyocyte damage [17,20-  
323 25]. In contrast, persistently inverted T waves have been associated with irreversible  
324 transmural necrosis, progressive left ventricular enlargement, and a decline of global left  
325 ventricular function over time [19-21]. Whether the same is true in dogs with MI remains to  
326 be established, although the overall favorable clinical, electrocardiographic, and  
327 echocardiographic outcome of subjects from this report may suggest a similar role for  
328 canine transient deep/giant T-wave negativization.

329         When evaluating the relationship between MI and repolarization abnormalities and  
330 their clinical impact, extracardiac factors influencing ventricular repolarization, including  
331 heart rate and electrolyte fluctuations, should be considered [11-13,15,31-33,38,41,49].  
332 Since the QT is known to be strongly dependent on the R-R interval, both QT and QTc  
333 were measured in dogs in the present study for a better assessment of repolarization  
334 duration [15,31-33], as done in other studies with a similar aim and/or design [11-  
335 13,16,42]. Regarding the potential effect of electrolytes disorders on the repolarization  
336 phase, one dog had mild hypokalemia and another mild hypocalcemia at the time of  
337 identification of deep/giant NTWs, while no electrolyte changes were identified at the time  
338 of T-wave normalization. Therefore, the influence of electrolyte fluctuations on T-wave

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

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

357

## 358 **Conclusions**

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

364

365 **Conflict of interest**

366 None of the authors have a conflict of interest.

367

368 **Acknowledgements**

369 None.

370

371 **Footnotes**

372 <sup>a</sup> Lekane M, Connolly D, Smets P, Borgeat K, Casamian-Sorrosal D, Boswood A, Luis  
373 Fuentes V, Gommeren K, Merveille AC. Clinical, ECG and echocardiographic findings in a  
374 canine case series of presumptive myocardial infarction. J Vet Intern Med 2020;34:403-4.

375 <sup>b</sup> Borgeat K, Vischer AS, Hannabuss J, Casamian-Sorrosal D, Oliveira P, Lopez-Alvarez J,  
376 Kavanah J, Wray J, Luis Fuentes V, Connolly DJ. T wave inversion in precordial ECG leads  
377 as a marker of arrhythmogenic right ventricular cardiomyopathy in boxer dogs. J Vet Intern  
378 Med 2017;31:208-9

379 <sup>c</sup> Immulite 2000 troponin I test, Siemens, Erlangen, Germany

380 <sup>d</sup> iU22 ultrasound system, Philips Medical Systems S.p.A., Monza, Italy

381 <sup>e</sup> Cube ECG, Cardioline S.p.A., Caverano, Italy

382 <sup>f</sup> Microsoft Excel, version 2016, Microsoft Corporation, Redmond, Washington (USA)

383 <sup>g</sup> R, version 3.5.2, R Foundation for Statistical Computing, Vienna, Austria

384 <sup>h</sup> Lidocaina 2% 20 mg/ml, Ecuphar Italia S.r.l., Milano, Italy

385

386 **References**

- 387 [1] Chapman AR, Adamson PD, Mills NL. Assessment and classification of patients with  
388 myocardial injury and infarction in clinical practice. *Heart* 2017;103:10-8.
- 389 [2] Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, White HD,  
390 Executive Group on behalf of the Joint European Society of Cardiology (ESC)/American  
391 College of Cardiology (ACC)/American Heart Association (AHA)/World Heart Federation  
392 (WHF) Task Force for the Universal Definition of Myocardial Infarction. Fourth Universal  
393 Definition of Myocardial Infarction (2018). *J Am Coll Cardiol* 2018;72:2231-64.
- 394 [3] Langhorn R, Willesen JL. Cardiac troponins in dogs and cats. *J Vet Intern Med*  
395 2016;30:36-50.
- 396 [4] Stillman AE, Oudkerk M, Bluemke D, Bremerich J, Esteves FP, Garcia EV, Gutberlet M,  
397 Hundley WG, Jerosch-Herold M, Kuijpers D, Kwong RK, Nagel E, Lerakis S, Oshinski J,  
398 Paul JF, Underwood R, Wintersperger BJ, Rees MR, North American Society of  
399 Cardiovascular Imaging; European Society of Cardiac Radiology. Assessment of acute  
400 myocardial infarction: current status and recommendations from the North American  
401 society for Cardiovascular Imaging and the European Society of Cardiac Radiology. *Int J*  
402 *Cardiovasc Imaging* 2011;27:7-24.
- 403 [5] Driehuys S, Van Winkle TJ, Sammarco CD, Drobatz KJ. Myocardial infarction in dogs  
404 and cats: 37 cases (1985-1994). *J Am Vet Med Assoc* 1998;213:1444-8.
- 405 [6] Falk T, Jönsson L. Ischaemic heart disease in the dog: a review of 65 cases. *J Small*  
406 *Anim Pract* 2000;41:97-103.
- 407 [7] Kidd L, Stepien RL, Amrheiw DP. Clinical findings and coronary artery disease in dogs  
408 and cats with acute and subacute myocardial necrosis: 28 cases *J Am Anim Hosp Assoc*  
409 2000;36:199-208.

- 410 [8] Schneider SM, Coleman AE, Guo LJ, Tou S, Keene BW, Kornegay JN. Suspected  
411 acute myocardial infarction in a dystrophin-deficient dog. *Neuromuscul Disord*  
412 2016;26:361-6.
- 413 [9] Magagnoli I, Romito G, Troia R, Murgia E, Giunti M. Reversible myocardial dysfunction  
414 in a dog after resuscitation from cardiopulmonary arrest. *J Vet Cardiol* 2020;34:1-7.
- 415 [10] Ware WA, Reina-Doreste Y, Stern JA, Meurs KM. Sudden death associated with QT  
416 interval prolongation and KCNQ1 gene mutation in a family of English Springer Spaniels. *J*  
417 *Vet Intern Med* 2015;29:561-8.
- 418 [11] Romito G, Guglielmini C, Mazzarella MO, Cipone M, Diana A, Contiero B, Baron  
419 Toaldo M. Diagnostic and prognostic utility of surface electrocardiography in cats with left  
420 ventricular hypertrophy. *J Vet Cardiol* 2018;20:364-75.
- 421 [12] Brüler BC, Jojima FS, Dittrich G, Giannico AT, Sousa MG. QT instability, an indicator  
422 of augmented arrhythmogenesis, increases with the progression of myxomatous mitral  
423 valve disease in dogs. *J Vet Cardiol* 2018;20:254-66.
- 424 [13] Vila BCP, Camacho AA, Sousa MG. T-wave peak-end interval and ratio of T-wave  
425 peak-end and QT intervals: novel arrhythmogenic and survival markers for dogs with  
426 myxomatous mitral valve disease. *J Vet Cardiol* 2021;35:25-41.
- 427 [14] Hlaing T, DiMino T, Kowey PR, Yan GX. ECG repolarization waves: their genesis and  
428 clinical implications. *Ann Noninvasive Electrocardiol* 2005;10:211-23.
- 429 [15] Conrath CE, Opthof T. Ventricular repolarization: an overview of (patho)physiology,  
430 sympathetic effects and genetic aspects. *Prog Biophys Mol Biol* 2006;92:269-307.

- 431 [16] Said SA, Bloo R, de Nooijer R, Slootweg A. Cardiac and non-cardiac causes of T-  
432 wave inversion in the precordial leads in adult subjects: a Dutch case series and review of  
433 the literature. *World J Cardiol* 2015;7:86-100.
- 434 [17] Agetsuma H, Hirai M, Hirayama H, Suzuki A, Takanaka C, Yabe S, Inagaki H, Takatsu  
435 F, Hayashi H, Saito H. Transient giant negative T wave in acute anterior myocardial  
436 infarction predicts R wave recovery and preservation of left ventricular function. *Heart*  
437 1996;75:229-34.
- 438 [18] Mansour AM, Abdullah O, Allaham H, Danila C, Balla S. Giant negative T waves and  
439 QT prolongation in non-cardiogenic pulmonary edema: a case report and review of  
440 literature. *Cureus* 2018;10:e3423.
- 441 [19] Maeda S, Imai T, Kuboki K, Chida K, Watanabe C, Ohkawa S. Pathologic implications  
442 of restored positive T waves and persistent negative T waves after Q wave myocardial  
443 infarction. *J Am Coll Cardiol* 1996;28:1514-8.
- 444 [20] Bosimini E, Giannuzzi P, Temporelli PL, Gentile F, Lucci D, Maggioni AP, Tavazzi L,  
445 Badano L, Stoian I, Piazza R, Heyman I, Levantesi G, Cervesato E, Geraci E, Nicolosi GL.  
446 Electrocardiographic evolutionary changes and left ventricular remodeling after acute  
447 myocardial infarction: results of the GISSI-3 Echo substudy. *J Am Coll Cardiol*  
448 2000;35:127-35.
- 449 [21] Pierard LA, Lancellotti P. Determinants of persistent negative T waves and early  
450 versus late T wave normalisation after acute myocardial infarction. *Heart* 2005;91:1008-12.
- 451 [22] Mobilia G, Zanco P, Desideri A, Neri G, Alitto F, Suzzi G, Chierichetti F, Celegon L,  
452 Ferlin G, Buchberger R. T wave normalization in infarct-related ECG leads during exercise  
453 testing for detection of residual viability: comparison with PET. *J Am Coll Cardiol*  
454 1998;32:75-82.

- 455 [23] Tamura A, Nagase K, Mikuriya Y, Nasu M. Significance of spontaneous normalization  
456 of negative T waves in infarct-related leads during healing of anterior wall acute  
457 myocardial infarction. *Am J Cardiol* 1999;84:1431-44.
- 458 [24] Watanabe S, Kawamura Y, Watanabe Y, Tanaka K, Tanaka K, Takei Y, Ejiri N,  
459 Shimada K. Viability of Q-wave infarcted myocardium with restored positive and persistent  
460 negative T waves after optimal revascularization compared with dobutamine stress  
461 echocardiography. *Am J Cardiol* 2000;85:31-6.
- 462 [25] Buttà C, Zappia L, Laterra G, Roberto M. Diagnostic and prognostic role of  
463 electrocardiogram in acute myocarditis: A comprehensive review. *Ann Noninvasive  
464 Electrocardiol* 2020;25:e12726.
- 465 [26] Boon JA. Dilated cardiomyopathy. In: Boon JA, editor. *Veterinary Echocardiography*,  
466 2<sup>nd</sup> ed. Iowa, USA: Wiley-Blackwell; 2011, p. 381-95.
- 467 [27] Sever M, Ribarič S, Kordaš M. Simulation of left ventricular function during dyskinetic  
468 or akinetic aneurysm. *Bosn J Basic Med Sci* 2012;12:224-30.
- 469 [28] Esser LC, Borkovec M, Bauer A, Häggström J, Wess G. Left ventricular M-mode  
470 prediction intervals in 7651 dogs: Population-wide and selected breed-specific values. *J  
471 Vet Intern Med* 2020;34:2242-52.
- 472 [29] Bhandari AK, Nanda NC. Two-dimensional echocardiographic recognition of abnormal  
473 changes in the myocardium. *Ultrasound Med Biol* 1982;8:663-71.
- 474 [30] Testa F, Romito G. Left ventricular outflow tract presystolic wave in a dog. *J Small  
475 Anim Pract* 2021;62:403.
- 476 [31] Santilli RA, Moïse NS, Pariaut R, Perego M. Formation and interpretation of the  
477 electrocardiographic waves. In: Santilli RA, Moïse NS, Pariaut R, Perego M, editors.

478 Electrocardiography of the dog and cat – diagnosis of arrhythmia, 2<sup>nd</sup> ed. Milano: Edra;  
479 2018, p. 52-89.

480 [32] Willis R. Electrocardiography. In: Willis R, Oliveira P, Mavropoulou A, editors. Guide to  
481 canine and feline electrocardiography, 1st ed. Oxford: John Wiley & Sons; 2018, p. 35-56.

482 [33] Matsunaga T, Mitsui T, Harada T, Inokuma M, Murano H, Shibutani Y. QT corrected  
483 for heart rate and relation between QT and RR intervals in beagle dogs. J Pharmacol  
484 Toxicol Methods 1997;38:201-9.

485 [34] Romito G, Côté E, Domenech O. ECG of the month. Sinus tachycardia due to  
486 albuterol-induced hypokalemia. J Am Vet Med Assoc 2013;243:1108-10.

487 [35] Thomas WP, Gaber CE, Jacobs GJ, Kaplan PM, Lombard CW, Moise NS, Moses BL.  
488 Recommendations for standards in transthoracic two-dimensional echocardiography in the  
489 dog and cat. Echocardiography Committee of the Specialty of Cardiology, American  
490 College of Veterinary Internal Medicine. J Vet Intern Med 1993;7:247-52.

491 [36] Ferasin L, Amodio A, Murray JK. Validation of 2 techniques for electrocardiographic  
492 recording in dogs and cats. J Vet Intern Med 2006;20:873-6.

493 [37] Hayden GE, Brady WJ, Perron AD, Somers MP, Mattu A. Electrocardiographic T-  
494 wave inversion: differential diagnosis in the chest pain patient. Am J Emerg Med  
495 2002;20:252-62.

496 [38] Chorin E, Rosso R, Viskin S. Electrocardiographic manifestations of calcium  
497 abnormalities. Ann Noninvasive Electrocardiol 2016;21:7-9.

498 [39] Popescu C, Leuştean A, Orfanu AE, Carp CG, Aramă V. Neutropenia and T-Wave  
499 inversion as toxin-mediated complications of a streptococcal infection. J Crit Care Med  
500 (Targu Mures) 2017;3:166-71.

- 501 [40] Romero J, Alviz I, Parides M, Diaz JC, Briceno D, Gabr M, Gamero M, Patel K,  
502 Braunstein ED, Purkayastha S, Polanco D, Valencia CR, Della Rocca D, Velasco A, Yang  
503 R, Tarantino N, Zhang XD, Mohanty S, Bello J, Natale A, Jorde UP, Garcia M, Di Biase L.  
504 T-wave inversion as a manifestation of COVID-19 infection: a case series. *J Interv Card*  
505 *Electrophysiol* 2020;59:485-93.
- 506 [41] Wang X, Han D, Li G. Electrocardiographic manifestations in severe hypokalemia. *J*  
507 *Int Med Res* 2020;48:0300060518811058.
- 508 [42] Perazzolo Marra M, Zorzi A, Corbetti F, De Lazzari M, Migliore F, Tona F, Tarantini G,  
509 Iliceto S, Corrado D. Apicobasal gradient of left ventricular myocardial edema underlies  
510 transient T-wave inversion and QT interval prolongation (Wellens' ECG pattern) in Tako-  
511 Tsubo cardiomyopathy. *Heart Rhythm* 2013;10:70-7.
- 512 [43] Hiss RG, Averill KH, Lamb LE. Electrocardiographic findings in 67,375 asymptomatic  
513 subjects. VIII. Nonspecific T wave changes. *Am J Cardiol* 1960;6:178-89.
- 514 [44] Onat T, Onat A, Can G. Negative T wave in chest lead V1: relation to sex and future  
515 cardiovascular risk factors. *Turk Kardiyol Dern Ars* 2008;36:513-8.
- 516 [45] Guerra F, Giannini I, Capucci A. The ECG in the differential diagnosis between  
517 takotsubo cardiomyopathy and acute coronary syndrome. *Expert Rev Cardiovasc Ther*  
518 2017;15:137-44.
- 519 [46] Candil JJ, Luengo CM. QT interval and acute myocardial ischemia: past promises,  
520 new evidences. *Rev Esp Cardiol* 2008;61:561-3.
- 521 [47] Hussain N. Elevated cardiac troponins in setting of systemic inflammatory response  
522 syndrome, sepsis, and septic shock. *ISRN Cardiol* 2013:723435.

523 [48] Kariyanna PT, Jayarangaiah A, Kamran H, Schechter J, Soroka S, Amarnani A, Ray  
524 J, Yacoub M, Post M, Al-Bayati S, McFarlane SI. Myocardial infarction after snakebite  
525 envenomation: a scoping study. *Scifed J Cardiol* 2018;2:21.

526 [49] Tag TL, Day TK. Electrocardiographic assessment of hyperkalemia in dogs and cats.  
527 *J Vet Emerg Crit Care* 2008;18:61-7.

528

## Figure legends

529 **Figure 1:** Example of reversible electrocardiographic changes recorded from a dog with  
530 transient giant negative T waves. A. Six-lead electrocardiogram recorded at the time of  
531 diagnosis of myocardial injury. A sinus rhythm associated with giant negative T waves is  
532 evident (amplitude: -1.3 mV). Note the disproportion between the amplitude of T waves  
533 and that of R waves (in lead II, T-wave amplitude is 260% of R-wave amplitude). Also  
534 notice that T-wave polarity is discordant with R-wave polarity, T waves have an almost  
535 symmetrical morphology, and the QT interval is prolonged (270 ms). B. Six-lead  
536 electrocardiogram recorded at the time of resolution of the myocardial injury. A sinus  
537 rhythm associated with normal T waves is evident (amplitude: 0.2 mV). At this time, the  
538 ratio between the T- and R-wave amplitudes is within the expected value (in lead II, T-  
539 wave amplitude is 15% of R-wave amplitude), and T-wave polarity is concordant with R-  
540 wave polarity. Moreover, T waves have an asymmetrical morphology (note that the initial  
541 branch is less steep than the terminal branch) and the QT-interval duration is normal  
542 (190 ms). Paper speed = 50 mm/s; amplitude = 10 mm/mV.

543

544

## 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.