Usefulness of *Magnesium Sulfate* in Stabilizing Cardiac Repolarization in Heart Failure Secondary to Ischemic Cardiomyopathy*

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Experimental heart failure is associated with cardiac magnesium loss, causing increased beat-to-beat variability in the action potential. Unstable repolarization contributes to sudden death, but no therapy has been shown to reduce repolarization variability safely. We sought to test whether a prolonged infusion of magnesium sulfate ($MgSO_4$; 40 mmol/24 hours) would normalize QT interval variability in patients with compensated heart failure. Fifteen patients (New York Heart Association class II to III; mean age 63 years) were enrolled in a placebo-controlled, double-blind study. Surface electrocardiograms were recorded and digitized at entry and at 48 and 168 hours (drug washout). Repolarization stability was assessed using an automated method measuring each QT interval in a 5-minute epoch. The QT variability index was derived as the ratio of normalized QT-to-normalized heart rate variability. Seven of 15 patients received $MgSO_4$. Mean heart rate and QT did not change in either group. The QT variability index was stable in the placebo group (−0.69 ± 0.15 at entry, −0.71 ± 0.22 at 48 hours, −0.70 ± 0.18 at 168 hours), but decreased significantly in the treated group at 48 hours (−0.95 ± 0.19 to −1.36 ± 0.13, $p < 0.05$ repeated-measures analysis of variance), returning to baseline at 168 hours (−0.84 ± 0.18). Regression analyses showed that administration of $MgSO_4$ resulted in a stronger correlation between the QT and RR interval ($p < 0.01$). Thus, $MgSO_4$ stabilizes cardiac repolarization in patients with compensated heart failure due to ischemic heart disease. Magnesium therapy may be useful in altering the proarrhythmic substrate in heart failure.

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Magnesium is rapidly cleared from the blood, but intracellular magnesium exchanges slowly. We have previously found that increases in tissue levels of magnesium lag behind serum levels, peaking 24 hours after the cessation of a 24-hour magnesium sulfate ($MgSO_4$) infusion in patients with myocardial infarction.[1] Because we wished to normalize intracellular magnesium levels, we elected to give a 24-hour infusion (a bolus dose would be rapidly cleared by the kidneys) and measure QT variability index (QTV index) at 48 hours, the time of peak intracellular magnesium loading. Although altering intracellular free magnesium has a powerful effect on cardiac repolarization,[2] it is not known whether intravenous $MgSO_4$ can reduce repolarization variability in vivo. In this study, 15 patients with compensated heart failure due to ischemic heart disease were blindly randomized to a 24-hour infusion of either 40 mmol of $MgSO_4$ or placebo. We hypothesized that raising cardiac magnesium levels would reduce beat-to-beat QT interval variability (as measured by the QT variability index), and that this effect would dissipate as cardiac magnesium levels returned to baseline. Because we could not measure cardiac magnesium levels in human volunteers, we substituted sublingual epithelial magnesium levels as a surrogate. We have previously found a good correlation between total atrial magnesium and sublingual epithelial magnesium concentrations in 18 patients undergoing bypass surgery.[1] Digitized surface electrocardiograms were obtained before infusion, again at 48 hours, and at 1 week. Repolarization variability was assessed by 2 methods: by measurement of the QTV index, and by comparison of the regressions of QT versus RR intervals before and after $MgSO_4$.

METHODS

Patient population: The study was approved by the institutional review board of the Johns Hopkins Hospital. The volunteers were recruited from the general cardiology clinic. Inclusion criteria were documented

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TABLE 1 Subject Group: Description and Medical Therapy

Age (yrs) & Sex	NYHA	Loop	ACE	Statin	Amiodorone	Beta Blocker	Nitrates	Hypoglycemic	Digoxin
					Placebo				
49 M	2	0	1	1	0	0	1	0	1
52 M	2	1	1	0	0	1	0	Insulin	0
58 M	3	1	1	0	0	1	0	0	1
61 M	3	1	1	0	1	0	0	0	1
64 M	2	0	1	1	0	1	0	Glyburide	0
69 M	2	0	1	0	1	0	1	0	0
73 M	3	1	1	0	0	0	0	0	1
75 M	2	1	1	0	0	1	0	Insulin	0
					Magnesium				
41 M	2	0	1	0	0	1	0	0	0
56 M	2	1	1	1	0	1	0	Glyburide	0
57 M	2	0	1	1	0	1	0	Glyburide	0
68 M	2	1	1	1	0	0	1	0	0
70 M	2	1	1	1	0	0	0	Glyburide	1
72 F	2	1	1	1	0	0	0	0	1
74 M	2	1	1	0	0	1	0	Glyburide	0

ACE = angiotensin-converting enzyme inhibitor; NYHA = New York Heart Association heart failure class.

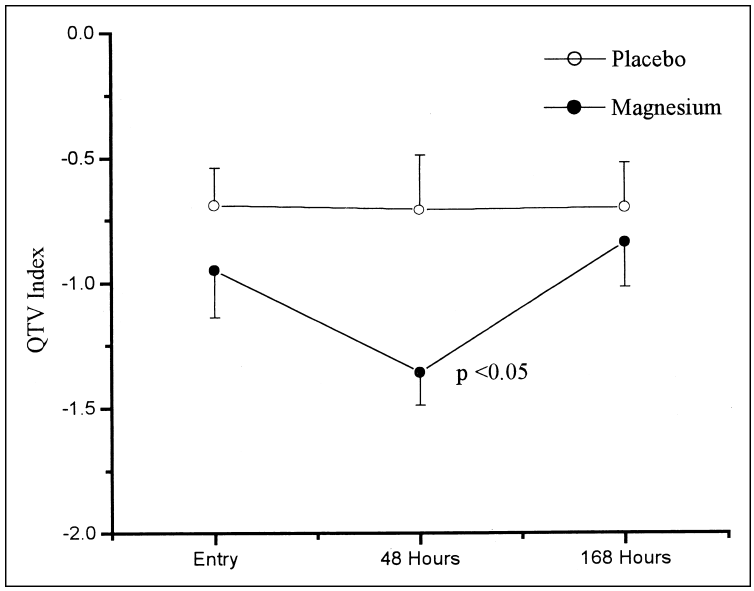

FIGURE 1. Comparison of mean QTV index (± SEM) in placebo *(open circles)* and control *(filled circles)* subjects at entry into the study, 48 hours after entry, and 1 week after entry. A p value <0.05 at 48 hours compared with placebo and entry.

systolic dysfunction and clinical heart failure with New York Heart Association class II or III functional status. Exclusion criteria were uncompensated heart failure, nonischemic etiology of heart failure, systolic blood pressure <100 mm Hg, heart rhythm other than normal sinus rhythm or sinus bradycardia with a heart rate <50 beats/min, serum creatinine of >1.5 mg/dl, concurrent use of magnesium supplements, or an indication for magnesium replacement. All patients gave informed, written consent.

Sixteen patients were recruited into the study. Eight were randomized to placebo (8 men, mean age 63 ± 3 years), and 8 to $MgSO_4$ (7 men, 1 woman, mean age 63 ± 4 years). One patient receiving an active drug was excluded at the end of the study because he was found to have a paroxysmal ectopic atrial tachycardia that was not recognized during recruitment. Patients' medications and New York Heart Association class are summarized in Table 1. All volunteers tolerated the infusion well.

Study protocol: Volunteers were admitted to the Clinical Research Center of the Johns Hopkins Hospital. Surface electrocardiogram, vital signs, sublingual epithelial cells, and serum magnesium and electrolytes were obtained before beginning the infusion. Blinded study drug (40 mmol of $MgSO_4$ or 5% dextrose in water [D_5W]) was infused over 24 hours without a bolus. Twenty-four hours after infusion, the surface electrocardiogram was repeated, a sublingual epithelial specimen was obtained, and serum magnesium and electrolytes were measured, and the patient released. One week later measurements were repeated. No magnesium supplementation was given in the interim to either group.

Measurement of sublingual epithelial magnesium: Tissue magnesium was measured in sublingual epithelial cells scraped from the mucosa adjacent to the frenulum and immediately fixed on a carbon slide with cytology fixative. The slides were examined on a scanning electron microscope (Philips, Einthoven, Holland) and suitable cells identified. Intracellular magnesium content was measured using energy-dispersive x-ray analysis of individual epithelial cells (EXA, Intracellular Diagnostics, Foster City, California). Reported values are the mean of 5 to 10 cells per

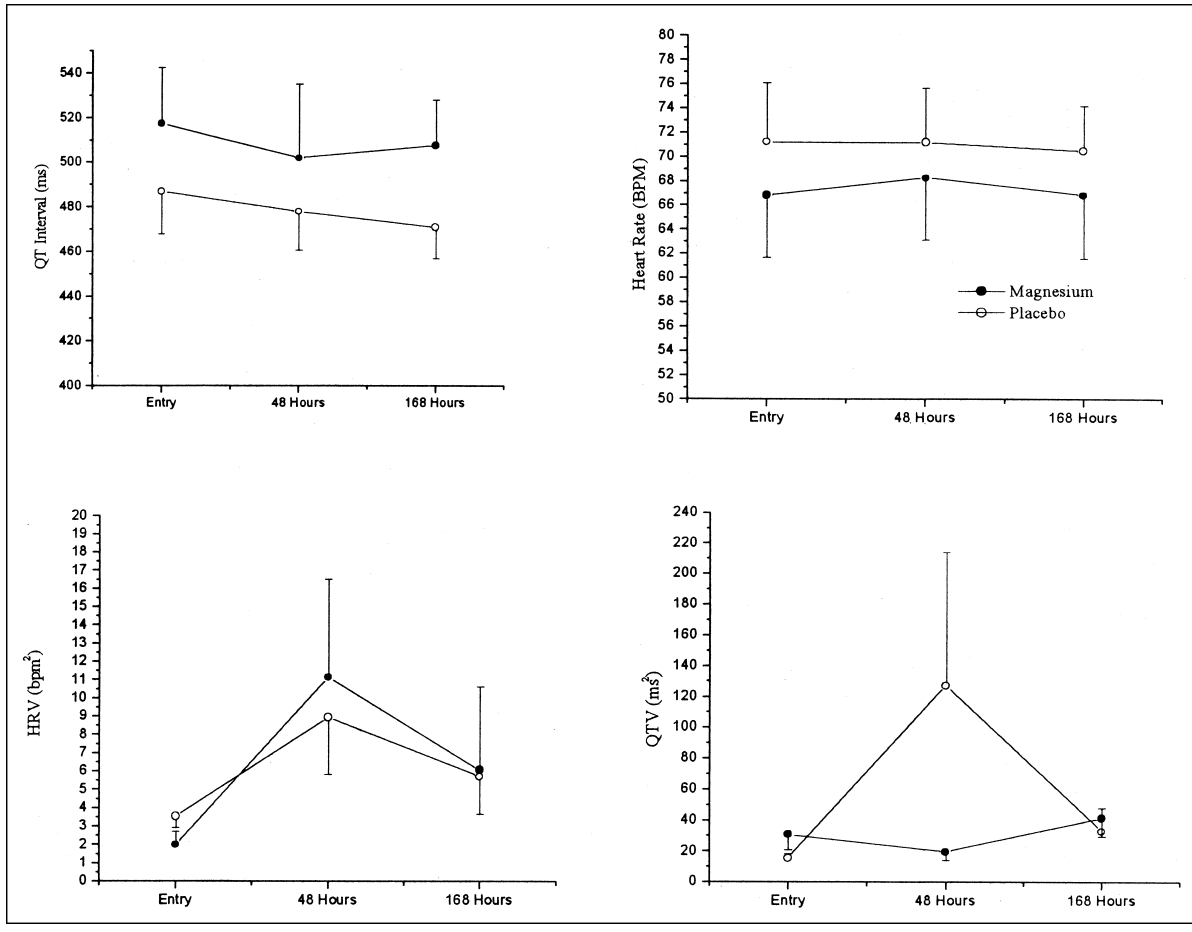

FIGURE 2. Comparison of mean QT, mean heart rate, mean total heart rate power, and mean total QT power (± SEM) in placebo *(open circles)* and control *(filled circles)* subjects at entry into the study, 48 hours after entry, and 1 week after entry (p = not significant for all measures at each time point).

patient; a specimen was rejected if variance exceeded 2%. This method assesses total cellular magnesium and cannot differentiate free magnesium ion from bound species.[1]

Measurement of QTV index: Surface electrocardiograms (leads I and II) were acquired using a high-sampling rate analog-digital converter (1,000 Hz; Biopac, Santa Barbara, California). Five-minute epochs were recorded before drug infusion, 24 hours after drug administration, and at 1 week. Data analyses were performed off-line on a workstation (Sun Microsystems, Inc., Palo Alto, California) after transfer of the DOS file to UNIX (TransferPro, Los Alamos, New Mexico). The analysis samples the electrocardiogram lead with the higher signal-to-noise ratio, usually lead II, using a customized, automated algorithm. After the operator defines a template QT interval by selecting the beginning of the QRS complex and the end of the T wave for 1 beat, the algorithm finds the QT interval of all other beats by determining how much each beat must be stretched or compressed in time so as to best match the template. In this way, changes in QT interval are assessed using the entire T wave instead of just the terminal portion of the T wave. The algorithm is thus robust in the setting of signal noise and allows for detection of subtle beat-to-beat QT variability. QTV index has been found to increase with New York Heart Association class, but is not different in patients with nonischemic versus ischemic cardiomyopathy.[3] All comparisons for each patient were made using the same electrocardiogram lead. Records containing >5% of ventricular premature complexes were rejected. The operator was blinded to the patient's identity and treatment allocation.

Instantaneous heart rate and QT series are derived for each epoch, and from these waveforms the heart rate variability (HRV) and the QT interval variability (QTV) power are derived. The QTV index is calculated from the ratio of normalized QTV and HRV power using the following formula:

$$\text{QTV index} = \frac{\text{Log (QTV total power/mean QT}^2)}{\text{(HRV total power/mean heart rate}^2)}$$

Statistics: The differences in QTV index due to drug status ($MgSO_4$ vs D_5W) were assessed over time (entry 48 hours, 168 hours after infusion) using repeated-measures analysis of variance (ANOVA). Repeated measures ANOVA was also used to compare group differences in mean QT, mean heart rate, QT power, and total heart rate power for each time point.

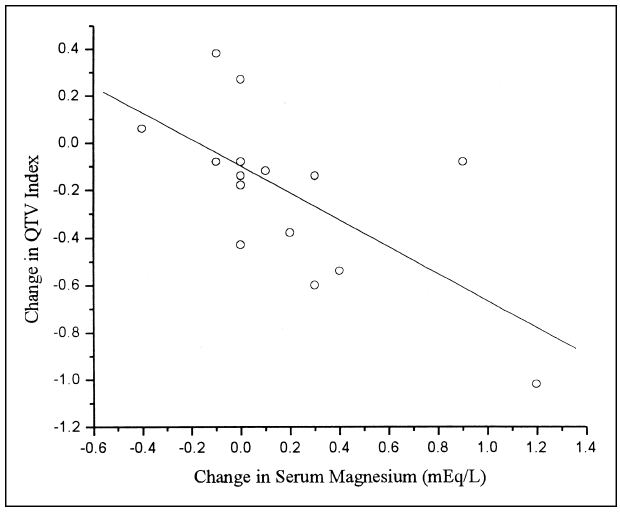

FIGURE 3. Linear regression of change in QTV index versus change in serum magnesium (mEq/L) in 15 patients (8 placebo, 7 magnesium), indicating a significant negative correlation between the change in serum magnesium and change in QTV index. Regression formula y = 0.10 to 0.57x, r = −0.66, p = 0.008.

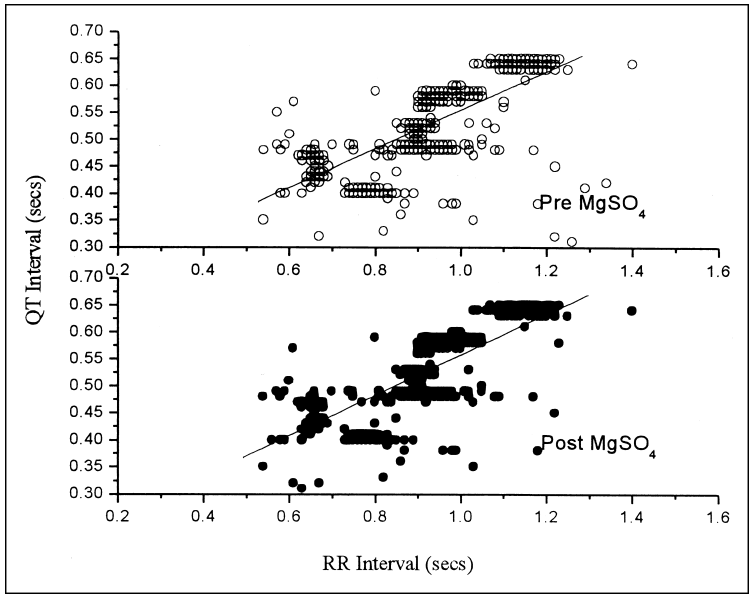

FIGURE 4. Linear regression of QT versus RR intervals for 200 beats in 7 subjects before *(open circles)* and after *(filled circles)* treatment with $MgSO_4$, showing a significant improvement in the correlation between QT and RR by $MgSO_4$, p = 0.01. Regression of QT/RR before magnesium, y = 0.20 +0.36x, r = 0.79, p <0.0001; after magnesium, y = 0.18 +0.38x, r = 0.82, p <0.0001. Comparison of squared residuals showed a trend toward a reduction by magnesium, p = 0.17.

To further evaluate the effect of $MgSO_4$ on the relation between RR and QT intervals, data for 200 QT-RR pairings from each of the 7 treated patients were analyzed using simple linear regression. Once outlying data points (defined as >3 SDs from the mean; n = 42 beats, 1.2%) were replaced with mean heart rate and QT values, residual QT scores were calculated from the regression of QT intervals onto RR intervals (before and after $MgSO_4$). A paired *t* test was then used to compare residual QT. Finally, Fisher's r-to-z transformation was used to standardize the zero-order correlation of QT-RR for each time period. A z test was then used to compare these standardized values. For all analyses, statistical significance was set at a 2-tailed probability level of 0.05 and results are expressed as mean ± SE.

RESULTS

Serum and sublingual magnesium levels: Serum magnesium did not change in the placebo group but remained significantly elevated in the treated group at 48 hours (1.79 ± 0.08 to 1.73 ± 0.05 mEq/L placebo group; 1.70 ± 0.03 to 2.17 ± 0.14 mEq/L treated group, p <0.03). Serum magnesium returned to baseline levels in both groups at 168 hours (1.73 ± 0.1 mEq/L placebo group, 1.64 ± 0.04 mEq/L treated group). Due to technical difficulties, paired sublingual specimens were available in only 5 of the placebo and 4 of the treated persons. The sublingual magnesium level increased significantly in the treated patients (31 ± 1.5 to 36 ± 1 mEq/L, p <0.01) but not in the placebo patients (32 ± 0.7 to 33 ± 0.8 mEq/L).

Effect of drug infusion on QTV index: The QTV index remained stable in the placebo group during the study (−0.69 ± 0.15 at entry, −0.71 ± 0.22 at 48 hours, −0.70 ± 0.18 at 168 hours), but decreased significantly in the treated group at 48 hours (−0.95 ± 0.19 to −1.36 ± 0.13, p <0.05 repeated-measures ANOVA compared with placebo and baseline), returning to baseline at 168 hours (−0.84 ± 0.18, Figure 1). The QTV index values at baseline were similar, but on average less abnormal than previously reported in heart failure patients. Berger et al[3] found a mean QTV index of −0.43 ± 0.08 in a group of 83 heart failure patients compared with −1.29 ± 0.07 in 60 controls. The patients in our protocol would have fallen within the 75% confidence interval for this reported group. The mean QT, mean heart rate, total heart rate power, and total QT power were not different between the 2 groups at any time point (see Figure 2). While the change in tissue magnesium did not correlate significantly with the change in QTV index (r = −0.41, p = 0.28), the change in serum magnesium correlated inversely with change in QTV index (see Figure 3, r = −0.66, p = 0.008).

Effect of drug infusion on the QT-RR interval relation: Figure 4 illustrates the linear regression of QT intervals onto RR intervals for each of the 7 treated subjects, both before (r = 0.79) and 48 hours after (r = 0.82) $MgSO_4$ infusion. Comparison of these values after Fisher's r-to-z transformation revealed that the relation between QT-RR was significantly stronger with $MgSO_4$ infusion (z = 2.25, p = 0.01). Residual

TABLE 2 Drug Effect on QTV Index

	Yes (m)	Mean QTV Index	No (m)	Mean QTV Index	p Value
Digoxin	5	−0.56	10	−1.14	<0.05
Sulfonylureas	5	−0.73	10	−1.02	0.32
β blockers	7	−1.10	8	−0.77	0.15
Loop diuretics	10	−0.89	5	−0.96	0.82

QT, defined as the squared difference between observed and predicted QT intervals, were compared using a paired *t* test. Although there was a reduction in residual QT variability after $MgSO_4$ infusion, this finding was not significant ($p = 0.12$).

Effect of nonstudy medications on initial QTV index: The outpatient regimens of the study subjects were individualized by their referring physicians. Certain medications affect magnesium clearance, and if the QTV index is partially a function of a patient's magnesium balance, then drugs that increase magnesium excretion (i.e., loop diuretics, digoxin) should increase the initial QTV index. Similarly, drugs that reduce magnesium clearance (i.e., angiotensin-converting enzyme inhibitors, β blockers, potassium-sparing diuretics) should reduce the increase QTV index. All but 1 patient was taking an angiotensin-converting enzyme inhibitor, preventing a meaningful comparison. There was a significant effect of the drug on initial QTV index with digoxin only; however, β blockers tended to decrease QTV index (see Table 2).

DISCUSSION

Major findings: In this study, a 24-hour infusion of $MgSO_4$ significantly reduced the QTV index in subjects with compensated heart failure when compared with placebo. Interestingly, this occurred without a significant effect on mean heart rate, mean QT duration, total heart rate variability, or total QT variability. Due to the inverse relation between heart rate and QT, one would expect that an increase in heart rate variability would cause an increase in QT variability. Although there was a trend toward increased heart rate variability in the magnesium-treated group also (perhaps due to 48 hours of bedrest), this was associated with a decrease in QT variability and therefore a significant reduction in the QTV index, which is the log ratio between these measures. Further analysis provided by linear regression demonstrates that $MgSO_4$ significantly improved the correlation between the QT and RR intervals, and also reduced the variance in the QT interval in excess of variance in the RR interval. This effect is consistent with an improvement in action potential restitution.

The QT interval varies on a beat-to-beat basis in normal persons, and this variation is largely (but not entirely) driven by changes in heart rate. Patients with symptomatic heart failure, however, manifest significant QT variability despite having significantly less total heart rate variability.[4] QT and heart rate variability are therefore partially dissociated in heart failure, resulting in an increase in the QTV index.[3] This logarithmic ratio correlates positively with heart failure class. Atiga et al[5] recently showed that the QTV index identifies sudden death survivors more accurately than electrophysiology, echocardiography, signal-averaged electrocardiography, heart rate variability, QT dispersion, or pacing-induced T-wave alternans.[5] It is unclear why sudden death would be associated with an increase in the QTV index. Recent work using an arterially perfused canine ventricle has correlated changes in the QT interval with changes in the transmural dispersion of repolarization.[6] Temporal variations in the QT interval therefore reflect instability in transmural repolarization that may lead to afterdepolarizations and/or functional reentry.

Several groups have found that intravenous $MgSO_4$ infusions rapidly suppress recurrent torsades de pointes,[7] as well as quench ventricular ectopy in heart failure patients.[8] Kaseda et al[9] found that superfusion of canine Purkinje fibers with 2 to 7 mmol of magnesium chloride suppressed triggered activity and reduced early afterdepolarizations induced by action potential prolonging agents within 5 minutes without an effect on the time to 90% repolarization action potential.[9] In vitro data suggest that because magnesium ions cross the sarcolemma slowly in the absence of hormonal stimulation, they presumably would not raise intracellular levels immediately.[10] Because we believed that raising intracellular magnesium levels was crucial to restoring repolarization control in heart failure, we intentionally measured the QTV index 24 hours after completing the infusion based on previous work showing that intracellular levels continue to rise during this period. Tissue magnesium levels obtained in a subset of study patients confirm our ability to raise intracellular concentrations with our protocol. Serum magnesium levels were also significantly elevated at 48 hours, so it is unclear whether the effects of $MgSO_4$ in this study are attributable to changes in intracellular or extracellular magnesium concentrations. Furthermore, changes in the QTV index correlated inversely with changes in serum magnesium (but not with sublingual magnesium), supporting a significant electrophysiologic effect for extracellular magnesium

Study limitation: Although we sought to study the effects on repolarization of raising magnesium levels rather than serum magnesium levels in tissue, both concentrations were significantly raised by our treatment. We were therefore not able to distinguish between the intracellular and extracellular effects of $MgSO_4$ supplementation. Failure to gather QTV index data immediately after the infusion significantly degraded our ability to dissociate the acute and subacute electrophysiologic consequences of $MgSO_4$ therapy.

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