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Tissue Magnesium Levels and the Arrhythmic Substrate in Humans

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Magnesium and Arrhythmias. ***Introduction:*** **Magnesium deficiency has been implicated in the pathogenesis of sudden death, but the investigation of arrhythmic mechanisms has been hindered by difficulties in measuring cellular tissue magnesium stores.**

Methods and Results: **To see if magnesium deficiency is associated with a propensity toward triggered arrhythmias, we measured tissue magnesium levels and QT interval dispersion (as an index of repolarization dispersion) in 40 patients with arrhythmic complaints. Magnesium was measured in sublingual epithelium using X-ray dispersive analysis. QT interval dispersion was assessed on 12-lead surface ECGs in all patients, and programmed stimulation was performed in 28. The sublingual epithelial magnesium level ($[Mg]_i$), but the not the serum level, correlated inversely with QT interval dispersion in 40 patients ($r = 0.58$, $P < 0.005$); in 12 patients undergoing repeat testing on therapy, the change in magnesium also correlated inversely with the change in QT dispersion ($r = 0.61$, $P < 0.05$). Patients with left ventricular ejection fractions > 40% had significantly higher tissue magnesium and lower QT dispersion (34.5 ± 0.5 mEq/L, 81 ± 8 msec) than those with left ventricular ejection fractions < 40% (32.7 ± 0.5 mEq/L, $P < 0.01$, and 114 ± 9 msec, $P < 0.05$). There was no difference in either $[Mg]_i$ or QT dispersion in the 16 patients with inducible monomorphic ventricular tachycardia versus the 12 noninducible patients.**

Conclusion: **Reduced tissue magnesium stores may represent a significant risk factor for arrhythmias associated with abnormal repolarization, particularly in patients with poor left ventricular systolic function, but may not represent a risk for excitable gap arrhythmias associated with a fixed anatomic substrate (e.g., monomorphic ventricular tachycardia).** *(J Cardiovasc Electrophysiol, Vol. 8, pp. 980-986, September 1997)*

magnesium, reentry, heart failure, QT interval

Introduction

Magnesium deficiency has been implicated in arrhythmogenesis by a number of lines of evidence. Low levels of total cellular magnesium have been found in the hearts of patients who died suddenly,[1] and epidemiologic data have linked reduced dietary intake to excess rates of sudden cardiac death.[2] Low serum magnesium levels have been

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associated with prolongation of the QT interval,[3] and intravenous $MgSO_4$ is the therapy of choice for torsades de pointes, a polymorphic ventricular tachycardia (VT) in the setting of delayed ventricular repolarization and "triggered" activity.[4] Magnesium therapy has been found effective in other arrhythmias may be "triggered" in origin, such as multifocal atrial tachycardia[5] and digoxin-toxicity associated arrhythmias.[6]

One cannot conclude that because intravenous magnesium suppresses triggered activity, magnesium deficiency causes triggered activity. Indeed, serum magnesium levels are usually normal in patients experiencing torsades de pointes. Serum magnesium levels, however, do not correlate with tissue levels, and significant cardiac depletion often coexists with normal blood concentrations in patients with heart disease. In this study, we apply a new assay of tissue magnesium (which correlates well with atrial levels[7]) to patients with arrhythmic complaints. We hypothesize that depressed tissue magnesium is associated with increased QT interval dispersion (dQT), an index of heterogeneous cardiac repolarization.

Increased dQT identifies patients at risk for torsades de pointes in the setting of type 1a antiarrhythmics[8] and patients with dilated cardiomyopathy at risk for sudden death,[9] two populations that do not typically manifest anatomic reentry at electrophysiologic study (EPS).[10] Therefore, dQT may be a clinically useful tool for detecting the presence of heterogeneous cardiac repolarization. Little is known about the mechanisms causing an increase in dQT. If sublingual epithelial $[Mg]_i$ correlates inversely with dQT, then magnesium deficiency may contribute to heterogeneous repolarization. Magnesium deficiency may therefore represent a modifiable risk factor for drug-induced proarrhythmia or sudden death in patients with heart failure.

Methods

Patient Population

Forty consecutive patients referred to the Johns Hopkins Arrhythmia service for evaluation of sustained VT (9), syncope (8), cardiac arrest due to ventricular fibrillation/VT (6), nonsustained VT (5), and palpitations/presyncope (12) were entered into the study. Patients gave informed, written consent, and the protocol was approved by the Institutional Review Board of the Johns Hopkins Hospital. The mean patient age was 60 ± 3 years; 28 were male and 18 had known coronary artery disease (previous documented myocardial infarction or at least one vessel stenosis > 70% at angiography), and 21 had left ventricular ejection fractions < 40% (Table 1).

Protocol

Patients were excluded from the study if they were receiving magnesium or had an indication for magnesium therapy. After informed consent was obtained, a complete history and physical examination was performed on each patient by one of the investigators. Left ventricular systolic function was assessed by echocardiogram, gated nuclear scan, or angiogram. Serum electrolytes (including magnesium) and 12-lead ECGs were obtained at entry into the study and after five half-lives following initiation of any antiarrhythmic drug. Invasive EPS was performed at the discretion of the attending electrophysiologist; palpitations/presyncope were evaluated noninvasively. Finally, sublingual epithelial cell scrapings were performed to measure tissue magnesium levels at entry and prior to repeat EPS. ECGs were obtained simultaneously with tissue magnesium levels immediately prior to EPS, while serum electrolytes were obtained within 12 hours of the ECG.

Measurement of dQT

ECGs were interpreted by a single blinded observer. dQT was defined as the difference between the longest and shortest QT interval measured on standard 12-lead ECGs at 25 mm/sec (Marquette Electronics, Milwaukee, WI, USA). The T wave terminus was considered the return to isoelectric baseline or the intersection of the projected downslope of the T wave with the baseline. U waves were not included in the QT interval. QT intervals were also rate corrected using Bazett's formula ($QT/\sqrt{RR}$ interval), and the QTc dispersion (dQTc) was calculated as the difference between the maximum and minimum QTc on the same 12-lead ECG.

Measurement of Tissue Magnesium

Tissue magnesium concentration ($[Mg]_i$) 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)

TABLE 1
Patient Data

Pt. No.	Age (years)	CAD	EF < 40%	Sex	Presenting Symptom	Inducible Monomorphic VT	$[Mg]_i$ (mEq/L)	Serum Mg (mEq/L)	Serum K (mEq/L)	dQT (msec)
1	75	Y	N	F	Cardiac arrest	Y	34.9	2.2	4	60
2	74	ND	Y	F	Cardiac arrest	Y	33.8	ND	4.3	40
3	30	N	Y	M	VT	Y	29.8	1.6	3.1	160
4	72	Y	Y	M	Syncope	Y	32.9	1.8	4.3	80
5	55	Y	Y	M	Cardiac arrest	Y	34.0	1.9	3.8	120
6	73	Y	Y	M	VT	Y	34.8	1.8	4	80
7	39	N	N	M	VT	Y	32.3	1.5	4.2	120
8	59	Y	ND	M	VT	Y	34.8	1.3	4.2	60
9	72	Y	Y	M	Syncope	Y	36.3	2.2	4.4	144
10	71	Y	Y	F	Syncope	Y	29.3	ND	ND	160
11	44	N	N	M	NSVT	Y	25.9	1.9	4.2	140
12	78	N	Y	M	VT	Y	34.7	2.2	4.4	100
13	66	N	N	F	Syncope	Y	36.7	1.8	4.5	80
14	63	Y	Y	M	VT	Y	32.1	2.1	5.3	60
15	78	Y	Y	M	VT	Y	31.5	1.7	4.2	180
16	45	Y	Y	M	VT	Y	34.3	1.8	4.2	100
17	79	Y	N	F	Cardiac arrest	N	34.9	1.9	5	80
18	55	N	N	M	NSVT	N	36.4	1.8	4.6	40
19	71	N	Y	M	NSVT	N	28.5	1.5	4.2	140
20	70	N	Y	M	NSVT	N	31.8	1.8	4.6	116
21	70	N	Y	M	Syncope	N	32.0	ND	ND	80
22	59	Y	Y	M	Syncope	N	30.8	1.9	4.2	120
23	40	N	ND	M	NSVT	N	34.6	1.4	5.3	60
24	20	N	N	F	Cardiac arrest	N	35.8	1.8	4.4	60
25	59	N	N	M	Cardiac arrest	N	33.8	ND	ND	100
26	59	Y	Y	F	Syncope	N	33.8	1.6	3.7	60
27	52	Y	N	M	Syncope	N	31.8	1.7	4.1	140
28	77	Y	Y	F	VT	N	36.5	1.7	4.4	160
29	63	N	Y	F	Presyncope	ND	31.3	ND	ND	100
30	74	Y	N	M	Presyncope	ND	38.1	ND	ND	52
31	71	N	Y	M	Presyncope	ND	34.1	ND	ND	84
32	42	ND	N	M	Presyncope	ND	35.7	1.5	3.3	60
33	71	Y	Y	M	Presyncope	ND	30.9	ND	ND	180
34	61	N	N	M	Presyncope	ND	35.5	ND	ND	40
35	54	Y	Y	M	Presyncope	ND	33.3	ND	ND	120
36	38	N	N	F	Presyncope	ND	32.9	1.9	5	120
37	34	N	N	M	Palpitations	ND	34.8	ND	ND	80
38	32	N	N	M	Palpitations	ND	34.3	ND	ND	80
39	32	N	N	F	Palpitations	ND	34.3	ND	ND	80
40	44	N	N	F	Palpitations	ND	35.4	ND	ND	40

CAD = coronary artery disease; Cardiac arrest = cardiac arrest due to VT/ventricular fibrillation; dQT = QT interval dispersion; EF = left ventricular ejection fraction; EPS= electrophysiologic study; ND = not done; NSVT = nonsustained VT; VT = ventricular tachycardia.

and suitable cells identified. Intracellular magnesium content was measured using energy dispersive X-ray analysis of individual epithelial cells (EXA [Intracellular Diagnostics, Foster City, CA, USA]). Reported values are the mean of 5 to 10 cells per patient; a specimen was rejected if variance exceeded 2%. This method assesses total cellular magnesium and cannot differentiate free (Mg^{2+}) from bound species.[7]

Electrophysiologic Programmed Stimulation

EPS was performed at two right ventricular locations using up to three basic cycle lengths and triple extrastimuli with a closest coupling interval of 200 msec or ventricular effective refractory period. Inducible VT was defined as a monomorphic ventricular rhythm faster than 100 beats/min lasting > 30 seconds or requiring cardioversion due to hemodynamic instability. In 11 patients, a repeat study was performed after five half-lives of a drug or 10 g of amiodarone was given.

Statistics

Results are given as mean ± SE. Group differences were compared using unpaired *t*-tests (Statview [Brainpower Inc., Calabasas, CA, USA]), and

linear regression was used to establish correlation between parameters (Deltagraph [Proximity Technologies, Inc., Monery, CA, USA]). $P < 0.05$ were considered significant.

Results

Relationship Between $[Mg]_i$, QT Interval, and QT Dispersion

There was a significant inverse correlation between $[Mg]_i$ and both the dQT and the dQTc (Figs. 1 and 2; $r = 0.58$ and 0.55 respectively, $P < 0.005$ for each). The inverse correlation between $[Mg]_i$ and the mean QT interval, however, was less strong ($r = 0.41$, $P < 0.05$, data not shown). No correlation existed between serum magnesium ($r = 0.03$) or serum potassium ($r = 0.22$) and the dQT (data not shown). In patients who underwent repeat EPS, there was a significant inverse correlation between change in the $[Mg]_i$ and a change in the dQT (Fig. 3; $r = 0.61$, $P < 0.05$). Interestingly, there was a significant difference in both $[Mg]_i$ and dQT between patients with left ventricular ejection fractions > 40% (34.5 ± 0.5 mEq/L, 81 ± 8 msec) and those with < 40% (32.7 ± 0.5 mEq/L, $P < 0.01$; 114 ± 9 msec, $P < 0.05$). Four patients with left ventricular ejection fractions < 40% were taking diuretics, but there was no difference between their $[Mg]_i$ and that of the remainder of the group with reduced left ventricular systolic function (32.7 ± 1 mEq/L vs 32.7 ± 0.5 mEq/L for nondiuretic users, $P = 0.96$).

Relationship Between Sublingual Magnesium, QT Dispersion, and the Results of EPS

Of the 28 patients who underwent EPS, 16 had inducible monomorphic VT (Table 1). There was no difference in sublingual epithelial magnesium in the inducible (33.2 ± 0.7 mEq/L) versus the noninducible patients (33.4 ± 0.7 mEq/L, P = NS). Similarly, there was no significant difference in dQT between the two groups (113 ± 12.5 msec with inducible monomorphic VT vs 97.8 ± 12.1 msec noninducible).

Twelve patients (of the original 16 found to have inducible monomorphic VT) underwent repeat EPS (5 on sotalol, 3 on quinidine, 2 on amiodarone, 1 on procainamide, and 1 after defibrillator implantation and atenolol therapy). As a group, the mean sublingual epithelial magnesium level increased significantly at the second EPS (33.1 ± 1 mEq/L at first study vs 34.2 ± 1 mEq/L at follow-up, $P < 0.05$), yet nine were still inducible. Magnesium was not administered to any patient. In the repeat EPS patients, there was no significant difference either in the sublingual epithelial $[Mg]_i$ or in the dQT of those with inducible monomorphic VT (34.5 ± 0.8 mEq/L, 92 ± 22 msec) versus noninducible groups (33.2 ± 3 mEq/L, 93 ± 24 msec).

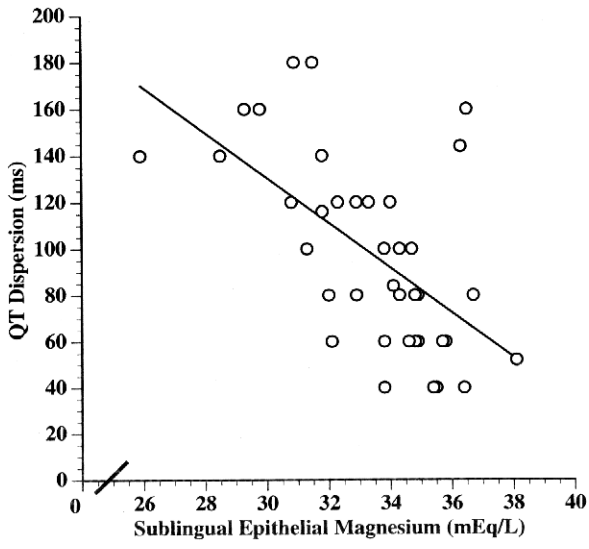

Figure 1. *Linear regression of the QT interval dispersion (y-axis) as a function of the sublingual epithelial magnesium level (x-axis). r = 0.58, P < 0.005.*

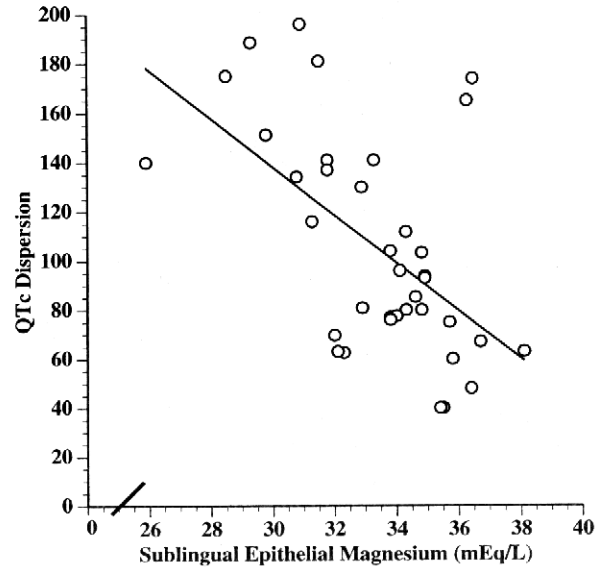

Figure 2. *Linear regression of the rate-corrected QT interval dispersion (y-axis) as a function of the sublingual epithelial magnesium level (x-axis). r = 0.55, P < 0.005.*

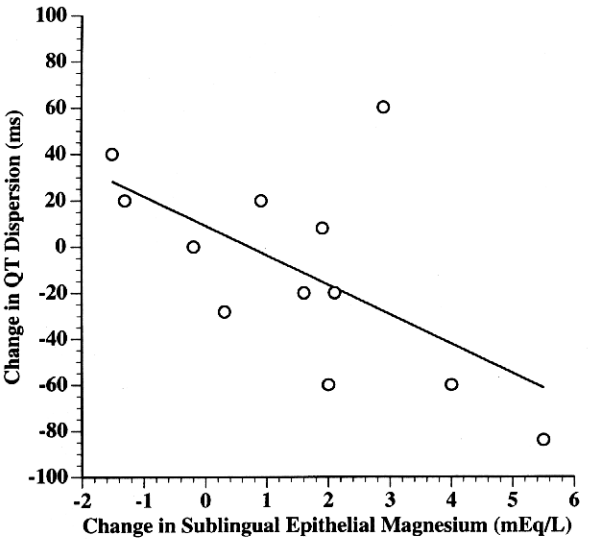

Figure 3. *Linear regression of the change in QT dispersion (y-axis) as a function of the change in the sublingual epithelial magnesium level (x-axis). r = 0.61, P < 0.05.*

Discussion

Intracellular Magnesium and Abnormal Repolarization

Delayed repolarization due to drug therapy, congenital ion channel abnormalities, or heart failure are all associated with an increase in "triggered" arrhythmias. Action potential prolongation promotes secondary depolarizations and heterogeneous recovery, which may support propagation of depolarizing wavefronts. Unlike monomorphic VT, these arrhythmias are typically not inducible in the electrophysiology laboratory, and little is known about the factors promoting heterogeneities in repolarization. Magnesium deficiency may represent a modifiable risk factor for unstable repolarization.

The present study supports a possible association between tissue magnesium levels and QT dispersion, an index of unstable repolarization that has been found to predict sudden death in patients with heart failure. These data are correlative and do not prove that the increased QT dispersion is caused by a reduction in cardiac magnesium, since no attempt to directly alter $[Mg]_i$ was made.

The effect of cardiac magnesium deficiency on ventricular repolarization is poorly characterized. Magnesium movement across the sarcolemma is very slow in the absence of hormonal stimulation, making it difficult to manipulate intracellular [Mg] in intact cellular preparations. Most work has therefore focused on the effects of altering extracellular magnesium. Roden and Iansmith[11] found little effect on the action potential duration of guinea pig myocytes despite superfusion with magnesium-free buffer. Recently, Zhang et al.[12] found that reducing extracellular magnesium from 3 to 0.5 mmol caused a 20% shortening in the time to 90% repolarization. These data would predict a shortening of the QT interval at lower serum magnesium levels, which is not supported by clinical observations of alcoholics and patients with long-standing nutritional deficits. The present study found no association between serum magnesium and mean QT, suggesting that extracellular magnesium has only a weak effect on repolarization.

Some existing data link low intracellular free magnesium with delayed repolarization. Agus et al.[13] found that internal dialysis of guinea pig myocytes with nominal magnesium buffer caused a prolongation in the action potential, perhaps by augmenting I_{Ca}. Other currents associated with repolarization are modulated by free cardiac magnesium, including the delayed rectifier, the inward rectifier, and cAMP-sensitive chloride current.[14] The ryanodine receptor is also sensitive to changes in free magnesium in the physiologic range,[15] but the net effect of a reduction in cardiac magnesium is impossible to predict. Given that magnesium modulates currents that are mutually antagonistic, one might speculate that magnesium acts as a "regulator" of repolarization. Based on published studies, one could argue that a reduction in cytosolic magnesium should result in a relative increase in the calcium current, prolonging the action potential in one beat. The consequent increase in cytosolic calcium might inhibit I_{Ca} and augment calcium-sensitive repolarizing currents, resulting in a shorter action potential on the next beat. Since the delayed rectifier current is also antagonized by magnesium, voltage-gated potassium currents would be increased, further hastening repolarization. Cytosolic calcium might then fall, triggering an increase in the calcium current in the next beat, resetting the cycle. The plateau phase is a time of high membrane resistance; small fluctuations in current amplitude have significant effects on action potential duration.[10] We have previously demonstrated an increase in action potential variability in rat cardiac myocytes from magnesium-deprived animals; variability was significantly suppressed after normalization of intracellular free magnesium.[16] Kaseda et al.[17] found that increasing extracellular magnesium to supraphysiologic concentrations suppresses triggered activity, but intracellular levels were not measured in their study.

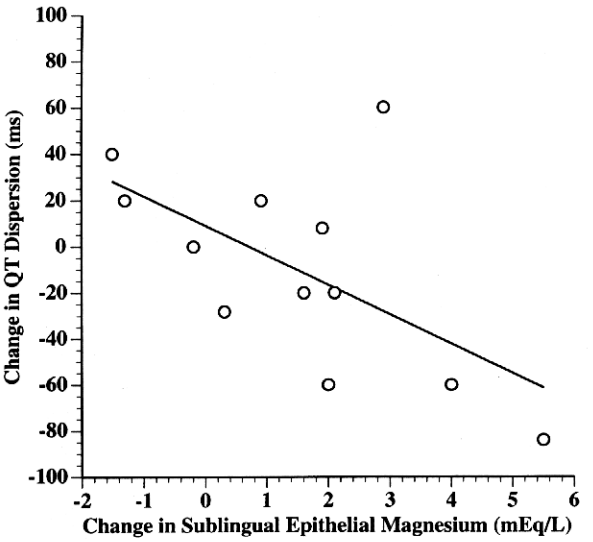

Figure 3. *Linear regression of the change in QT dispersion (y-axis) as a function of the change in the sublingual epithelial magnesium level (x-axis). r = 0.61, P < 0.05.*

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The finding in the present study that sublingual epithelial $[Mg]_i$ correlates better with dQT than with mean QT supports the notion that magnesium plays a greater role in controlling dispersion of repolarization than in determining its absolute duration. Although further study is needed, this observation suggests that increasing cardiac magnesium may shorten prolonged action potentials while prolonging short action potentials. Magnesium antagonizes both depolarizing and repolarizing currents, so an increase in the intracellular concentration may not result in a uniform shortening of repolarization.

Tissue Magnesium Deficiency and Heart Failure

Sublingual magnesium levels were significantly lower in patients with reduced left ventricular ejection fractions. Previous data from autopsy[1] and intraoperative biopsy[18] have found a significant reduction in total cardiac magnesium in patients with heart failure. Neurohumoral stimulation may be responsible, as cardiac magnesium efflux appears to be triggered by β_2-adrenergic stimulation and to be blocked by propranolol.[19] In this study, a significant increase in $[Mg]_i$ was seen in the 12 patients undergoing repeat EPS, the majority of whom were receiving agents that depress β-adrenergic receptor-mediated sympathetic activity.

The arrhythmogenic significance of cardiac magnesium depletion in heart failure is unknown, although small studies demonstrate a significant reduction in ectopy and nonsustained VT in response to intravenous or oral magnesium replacement.[20,21] Patients with dilated cardiomyopathy are at increased risk for sudden death, and conventional methods of risk stratification are ineffective. Unstable repolarization has been demonstrated in these patients and may represent an important mechanism of tachyarrhythmia.[10] Further studies investigating the time course of magnesium loss and development of abnormal repolarization in heart failure are needed.

Magnesium and Monomorphic VT

Induciblity of monomorphic VT at EPS is highly reproducible, particularly in patients with a history of a prior myocardial infarction, and suggests the presence of an anatomic substrate for reentry. It appears from this small study that the existence of this substrate does not require a reduced tissue magnesium level. Furthermore, a rise in tissue magnesium does not seem to prevent reentry. While magnesium levels rose in 9 of 12 patients who underwent repeat EPS, only two of these were noninducible at follow-up study. Since monomorphic VT occurs in the setting of a reentrant circuit with an excitable gap resulting from the presence of a zone of slow conduction, the lack of correlation between magnesium levels and VT inducibility suggests that the existence of an excitable gap is unaffected by tissue magnesium concentrations.

Monomorphic VT and dQT

Although not designed to assess the utility of dQT for predicting the inducibility of monomorphic VT, this study suggests that there is considerable overlap of dQT between patients with and without inducible monomorphic VT. A recent report of 35 patients with coronary artery disease and nonsustained VT found that no patient with a dQT < 90 msec had inducible monomorphic VT[22]; however, this finding was based on only six patients with inducible monomorphic VT. In the present study, 7 of 16 patients with inducible monomorphic VT had dQT < 90 msec, five of whom had significant coronary artery disease. A large prospective study is needed, but in our hands, at least, dQT does not appear to be a useful predictor of inducibility.

Limitations of the Study

The major weakness of this study is that it is observational; no attempt to alter QT dispersion through the administration of magnesium was made. Interventional studies are needed to prove a cause-and-effect relationship between magnesium deficiency and abnormal repolarization.

All measurements of QT interval dispersion were made by a single, blinded observer to increase consistency, yet significant intraobserver variability appears unavoidable with this technique. Furthermore, QT interval dispersion may not represent a good measure of regional repolarization heterogeneity or be the best predictor of an arrhythmogenic substrate. A larger study of the effect of magnesium supplementation on sudden death is desirable. Finally, the assay of sublingual epithelial magnesium offers a measure of tissue stores that correlates well with cardiac levels, but ideally cardiac tissue would have been available.

Conclusion

This study suggests that low tissue magnesium levels are associated with an increase in QT dispersion and, therefore, represent a risk factor for heterogeneous repolarization and the development of

triggered arrhythmias. Our findings do not support a significant role for magnesium deficiency in reentrant arrhythmias dependent on an excitable gap.

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