Torsades de pointes during complete atrioventricular block: Genetic factors and electrocardiogram correlates

Rajesh N Subbiah BSc(Med) MBBS PhD¹, Michael H Gollob MD², Lorne J Gula MSc MD¹, Robert W Davies BSc², Peter Leong-Sit MD¹, Allan C Skanes MD¹, Raymond Yee MD¹, George J Klein MD¹, Andrew D Krahn MD¹

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INTRODUCTION: Atrioventricular (AV) block is infrequently associated with QT prolongation and torsades de pointes (TdP). It was hypothesized that patients with AV block-mediated QT-related arrhythmia may have latent congenital long QT syndrome or a vulnerable genetic polymorphism.

METHODS: Eleven patients with complete AV block and TdP were prospectively identified. Patients underwent assessment, resting electrocardiography and telemetry at baseline, during AV block and pre-TdP. Genetic testing of *KCNH2*, *KCNQ1*, *KCNE1*, *KCNE2* and *SCN5A* was performed. Thirty-three patients with AV block without TdP were included for comparison.

RESULTS: Genetic variants were identified in 36% of patients with AV block and TdP. Patients with AV block who developed TdP had significantly longer mean ($\pm$ SD) corrected QT intervals (440 ± 93 ms versus 376 ± 40 ms, $P=0.048$) and T_{peak} to T_{end} (T_p-T_e) intervals (147 ± 25 ms versus 94 ± 25 ms, $P=0.0001$) than patients with AV block alone. In patients with a genetic variant, there was a significant increase in T_p-T_e intervals at baseline, in AV block and pre-TdP compared with those who were genotype negative. A personal or family history of syncope or sudden death was more likely observed in patients with a genetic variant.

CONCLUSIONS: TdP in the setting of AV block may be a marker of an underlying genetic predisposition to reduced repolarization reserve. The T_p-T_e interval at baseline, in AV block and pre-TdP may predict a genetic mutation or polymorphism compromising repolarization reserve. Patients with TdP in the setting of AV block represent a phenotypic manifestation of latent congenital long QT syndrome.

Key Words: AV block; Bradycardia; Genetics; QT interval; Torsades de pointes

Ventricular arrhythmias have been reported in the setting of complete atrioventricular (AV) block since 1918 (1). In 1966, Dessertenne (2) described such an arrhythmia as torsades de pointes (TdP), a polymorphic ventricular tachycardia preceded by QT interval prolongation, now known to be caused by congenital or acquired long QT syndrome (LQTS) (3).

Bradyarrhythmias caused by high-grade AV block are common. It is, however, infrequent that bradyarrhythmias are associated with QT interval prolongation and TdP phenomena (4-6). In patients with bradycardia-induced TdP, a number of electrocardiogram (ECG) parameters during bradycardia correlate with increased risk of TdP, including the QT interval (4-6), T wave morphology and T_{peak} to T_{end} (T_p-T_e) (6). Although ECG parameters can be reasonable predictors of TdP in bradyarrhythmias (4-6), there are limited data on cellular or genetic mechanisms of bradycardia-induced TdP (7,8).

We hypothesized that patients with bradycardia-mediated QT arrhythmia may have latent congenital LQTS or a vulnerable genetic

Les torsades de pointe pendant un bloc auriculoventriculaire complet : les facteurs génétiques et les corrélats à l'électrocardiogramme

INTRODUCTION : Dans des cas peu fréquents, le bloc auriculoventriculaire (AV) s'associe à la prolongation de l'intervalle Q-T et à des torsades de pointe (TdP). Les auteurs ont postulé que les patients ayant une arythmie liée à l'intervalle Q-T causée par un bloc AV peuvent avoir un syndrome du Q-T long congénital latent ou un polymorphisme génétique vulnérable.

MÉTHODOLOGIE : Les chercheurs ont repéré prospectivement 11 patients ayant un bloc AV complet et des TdP. Les patients ont subi une évaluation, un électrocardiogramme au repos et une télémétrie au départ, pendant le bloc AV et avant les TdP, de même que des tests génétiques des *KCNH2*, *KCNQ1*, *KCNE1*, *KCNE2* et *SCN5A*. Trente-trois patients ayant un bloc AV sans TdP ont été inclus dans l'étude pour des besoins de comparaison.

RÉSULTATS : Les chercheurs ont repéré des variantes génétiques chez 36 % des patients ayant un bloc AV et des TdP. Les patients ayant un bloc AV qui ont développé des TdP avaient des intervalles Q-T moyens ($\pm$ ÉT) corrigés (440 ± 93 ms par rapport à 376 ± 40 ms, $P=0,048$) et des intervalles T_{pointe} à T_{fin} (T_p-T_f) (147 ± 25 ms par rapport à 94 ± 25 ms, $P=0,0001$) plus longs que les patients ayant seulement un bloc AV. Chez les patients présentant une variante génétique, on constatait une augmentation significative des intervalles T_p-T_f au départ, pendant le bloc AV et avant les TdP que chez ceux qui étaient négatifs au génotype. Des antécédents personnels ou familiaux de syncope ou de mort subite étaient plus probables chez les patients présentant une variante génétique.

CONCLUSIONS : Les TdP en présence d'un bloc AV peuvent être un marqueur de prédisposition génétique sous-jacente à une réserve de repolarisation réduite. L'intervalle T_p-T_f au départ, pendant le bloc AV et avant les TdP peut être prédicteur d'une mutation génétique ou d'un polymorphisme qui compromet la réserve de repolarisation. Les patients ayant des TdP en présence d'un bloc AV présentent la manifestation phénotypique d'un syndrome Q-T long congénital latent.

polymorphism. In the setting of AV block, reduced repolarization reserve may be 'unmasked' in patients, manifesting as QT interval prolongation and TdP. Such an occult form of LQTS has previously been reported among patients with undiagnosed congenital LQTS who develop marked QT interval prolongation and TdP when exposed to QT-prolonging drugs (9,10). Moreover, the development of TdP in the setting of AV block may identify ion channel mutations that have a propensity to cause TdP and sudden cardiac death.

METHODS

Patients

A total of 11 patients referred to the Arrhythmia Service at London Health Sciences Centre in London, Ontario, with complete AV block and TdP were prospectively identified. TdP was defined as 10 or more beats of polymorphic ventricular tachycardia (rate of more than 150 beats/min) preceded by QT interval prolongation (corrected QT [QTc] interval of greater than 440 ms [men] or 460 ms [women]).

¹Arrhythmia Service, Division of Cardiology, University of Western Ontario, London; ²Ottawa Heart Institute, University of Ottawa, Ottawa, Ontario
Correspondence: Dr Andrew D Krahn, London Health Sciences Centre, University Campus, 339 Windermere Road, London, Ontario N6A 5A5.

Telephone 519-663-3746, fax 519-663-3782, e-mail akrahn@uwo.ca
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TABLE 1
Genotypes of patients with complete atrioventricular (AV) block and torsades de pointes (TdP)

AV block + TdP	Gene	Ion channel	Mutation
Patient 1*	SCN5A	I_{Na}	Exon 4 – Glu161Lys
Patient 2	SCN5A	I_{Na}	Exon 12 – His558Arg
Patient 3	KCNH2	I_{Kr}	Exon 14 – Pro1075Leu
Patient 4†	KCNH2	I_{Kr}	Exon 11 – Lys897Thr

*Recurrent TdP after device implantation requiring a rate increase from 60 beats/min to 80 beats/min; †Recurrent episodes of TdP requiring electrical cardioversion, not responsive to isoproterenol, with continued episodes of TdP despite pacing at 80 beats/min, requiring bisoprolol. I_{Kr} Rapid delayed rectifier K^+ current; I_{Na} Inward Na^+ current

Inclusion criteria were TdP in the setting of complete AV block, without a history of TdP, or known congenital or acquired LQTS. Patients with bradycardia or AV block and TdP in the setting of acute myocardial infarction, or exposure to known QT-prolonging drugs were excluded. Patients underwent clinical assessment including history, physical examination, drug review and ECG analysis. ECGs before AV block were examined for comparison of baseline characteristics. Blood analysis was performed to rule out electrolyte or metabolic abnormalities. All patients received a permanent pacemaker or implantable cardioverter defibrillator, with follow-up in the Arrhythmia Service at London Health Sciences Centre.

ECG acquisition

All ECGs recorded during hospitalization and clinic visits were reviewed. ECGs were obtained using standard gain (10 mV/mm) and paper speed (25 mm/s, GE Marquette MUSE system, GE Healthcare, USA). A 1:3 case control model was chosen; controls were patients with complete AV block but without TdP. ECGs were analyzed for rate, rhythm, QRS duration, QT and QTc intervals, T_p - T_e interval, T wave morphology and RR interval at three time points – at baseline, during complete AV block and immediately preceding TdP. The QT interval was defined as the onset of QRS to the point of return of the T wave to the isoelectric line using the maximum slope technique. The QT interval was measured in all leads where the terminal segment of the T wave was clearly demarcated (11), with the longest interval in any lead used as the representative QT interval. The RR interval was calculated from the preceding two consecutive R waves. The QT interval was then corrected (QTc) for rate using Bazett's formula (12): QTc interval = QT/square root of RR interval in seconds. The T_p - T_e was the interval from the apex of the T wave to the end of the QT interval.

Genetic testing

Written informed consent was obtained before genetic testing. Blood for DNA analysis was sent to the Ottawa Heart Institute (Ottawa, Ontario). Genetic testing of *KCNH2*, *KCNQ1*, *KCNE1*, *KCNE2* and *SCN5A* was performed. Genomic DNA isolated from blood lymphocytes was screened using temperature-gradient capillary electrophoresis and/or direct DNA sequencing. In temperature-gradient capillary electrophoresis analysis (SpectruMedix, USA), polymerase chain reaction-amplified DNA samples were separated by capillary electrophoresis under two temperature gradient conditions (50°C to 58°C and 55°C to 63°C). Samples containing mutations were identified on the basis of altered electrophoretic patterns of heteroduplexes caused by their different melting equilibria and electrophoretic mobilities. Samples containing heteroduplexes then underwent direct DNA sequencing.

Statistics

Univariate analyses were conducted by using the two-tailed Student's *t* test for continuous variables and the χ^2 test for categorical variables. Statistical analysis was performed using SAS software version 9.1 (SAS Institute, USA). $P < 0.05$ was considered significant. All results are expressed as mean $\pm$ SD.

TABLE 2
Electrocardiogram parameters of patients with a genetic mutation or polymorphism

Parameter, ms	Patient 1	Patient 2	Patient 3	Patient 4
QTc at baseline	429	430	439	436
QTc in complete AV block	516	439	446	527
QTc pre-TdP	665	531	581	613
T_p - T_e baseline	100	120	80	100
T_p - T_e in complete AV block	170	160	170	200
T_p - T_e pre-TdP	180	200	200	220

AV Atrioventricular; QTc Corrected QT interval; TdP Torsades de pointes; T_p - T_e T_{peak} to T_{end} interval

Figure 1 Representative electrocardiograms (ECGs) from patient 1 with a Glu161Lys mutation involving SCN5A. Although this mutation has previously been associated with a Brugada-type ECG and conduction abnormalities, this patient clearly developed dramatic bradycardia-related QT prolongation and polymorphic ventricular tachycardia, with a relatively normal-appearing reference ECG before the development of complete atrioventricular block

RESULTS

Genetic screening in patients with complete AV block and TdP identified DNA variants in four of 11 patients (36%). The *SCN5A* Glu161Lys mutation has been reported to cause disease (13). The *KCNH2* Pro1075Leu mutation, recently reported to cause LQTS (14), is in a region of the gene known to be a 'hot spot' for disease-causing mutations. Two additional sequence variations were identified as genetic polymorphisms (Table 1).

Individual ECG characteristics of the four patients with genetic mutations or polymorphisms are listed in Table 2. The ECGs of patient 1 are shown in Figure 1. At baseline, all four patients had normal QTc intervals. In the setting of complete AV block, patient 1 and patient 4 had significantly prolonged QTc intervals. All four patients had marked QTc interval prolongation pre-TdP. Similarly, the T_p - T_e interval increased from baseline, in complete AV block and pre-TdP (Table 2). Of note, there were no differences in PR interval, QRS duration or ST-T segments at baseline.

Patients were divided into three groups (Tables 3 and 4). Group 1 included patients with complete AV block and TdP who had a genetic mutation or polymorphism. Group 2 included patients with complete AV block and TdP in whom a genetic abnormality was not identified. Group 3 included patients with complete AV block but no TdP. When patients with and without TdP were compared (groups 1 and 2 compared with group 3), those with complete AV block who developed TdP had significantly longer QTc intervals (440 ± 93 ms versus 376 ± 40 ms, $P = 0.048$; Table 4). This difference was almost entirely explained by the dramatic difference in the T_p - T_e intervals, which were significantly longer in patients with complete AV block and TdP (groups 1 and 2) compared with those without TdP (group 3)

TABLE 3
Electrocardiogram and clinical characteristics of patients with complete atrioventricular (AV) block and torsades de pointes (TdP)

Characteristic	Group 1 (n=4)	Group 2 (n=7)	P
Age, years, mean $\pm$ SD	74 $\pm$ 14	70 $\pm$ 10	0.66
Women	3 (75)	6 (86)	0.66
Cardiomyopathy with ejection fraction <40%	0	2 (29)	0.24
History of atrial fibrillation	0	3 (43)	0.13
Family history of SCD	2 (50)	0	0.039
Family history of syncope	4 (100)	2 (29)	0.022
History of syncope (>12 months before presentation in complete AV block)	2 (50)	0	0.039
Recurrent TdP despite treatment	2 (50)	0	0.039
T wave abnormalities	1 (25)	2 (29)	0.90
QTc baseline, ms, mean $\pm$ SD	434 $\pm$ 5	413 $\pm$ 25	0.067
QTc in complete AV block, ms, mean $\pm$ SD	482 $\pm$ 46	416 $\pm$ 108	0.29
QTc pre-TdP, ms, mean $\pm$ SD	597 $\pm$ 56	564 $\pm$ 78	0.48
T_p-T_e baseline, ms, mean $\pm$ SD	100 $\pm$ 9	71 $\pm$ 4	0.016
T_p-T_e in complete AV block, ms, mean $\pm$ SD	175 $\pm$ 17	131 $\pm$ 9	0.0072
T_p-T_e pre-TdP, ms, mean $\pm$ SD	200 $\pm$ 16	141 $\pm$ 22	0.0013
RR interval pre-TdP, ms, mean $\pm$ SD	1.2 $\pm$ 0.3	1.2 $\pm$ 0.2	0.70

Data presented as n (%) unless otherwise indicated. Group 1 represents patients with complete AV block and TdP who are mutation positive. Group 2 represents patients with complete AV block and TdP who are mutation negative. QTc Corrected QT interval; SCD Sudden cardiac death; T_p-T_e T_{peak} to T_{end} interval

TABLE 4
Electrocardiogram and clinical characteristics of patients with complete atrioventricular (AV) block and torsades de pointes (TdP) compared with complete AV block controls

Characteristic	Complete AV block		P
	With TdP (n=11)	No TdP (n=33)	
Women, n (%)	9 (82)	18 (55)	0.11
QTc in complete AV block, ms, mean $\pm$ SD	440 $\pm$ 93	376 $\pm$ 40	0.048*
T_p-T_e in complete AV block, ms, mean $\pm$ SD	147 $\pm$ 25	94 $\pm$ 25	<0.0001*

* $P<0.05$. QTc Corrected QT interval; T_p-T_e T_{peak} to T_{end} interval

(147 $\pm$ 25 ms versus 94 $\pm$ 25 ms, $P=0.0001$, Table 4). Chart and serum electrolyte review did not identify specific triggers for complete AV block or TdP.

Comparing groups 1 and 2, there was a striking difference in T_p-T_e intervals at baseline, in complete AV block and pre-TdP but no differences in QTc intervals at baseline, in complete AV block or pre-TdP (Figure 2 and Table 3).

Recurrent TdP in AV block was more likely in patients with an underlying genetic mutation or polymorphism ($P=0.039$; Table 3). Two patients had recurrent TdP; both had an underlying genetic mutation or polymorphism. Patient 1 had recurrent TdP after pacemaker implantation with initial programming at a lower rate of 60 beats/min (Table 1). The pacemaker was reprogrammed to a pacing rate of 80 beats/min and no further TdP occurred. Patient 4 had multiple episodes of TdP at presentation that required electrical cardioversion. After device implantation, the patient continued to have high ventricular rate episodes with documented TdP, despite a minimum pacing rate of 80 beats/min. Bisoprolol 10 mg orally daily was started and the patient remained free of symptoms in follow-up for eight months.

Clinical history provided important correlates. Patients with a family history of sudden cardiac death ($P=0.039$) or syncope ($P=0.022$), and

Figure 2 T_{peak} to T_{end} (T_p-T_e) intervals for patients at baseline, in complete atrioventricular (AV) block and pre-torsades de pointes (TdP). There was a clear difference among patients who had a genetic mutation or polymorphism identified (closed squares) compared with those who did not have a genetic mutation or polymorphism (open circles) at baseline, in complete AV block and pre-TdP

those with a personal history of syncope ($P=0.039$) were more likely to have an underlying genetic mutation or polymorphism than genotype-negative patients with complete AV block and TdP (Table 3).

DISCUSSION

The findings of the current study suggest that bradycardia alters the repolarization milieu and may unmask a propensity to life-threatening tachyarrhythmias based on genetic and clinical factors. The results of the present study demonstrated the feasibility of genetic screening of patients with TdP in the context of high-grade AV block.

Mechanism of TdP in complete AV block

Mechanistically, it has been reported that during bradyarrhythmias, downregulation of the repolarizing currents – rapid and slow delayed rectifier K^+ currents (I_{Kr} and I_{Ks} , respectively) – results in QT interval prolongation and TdP (15-18). These findings were based on canine and rabbit models of chronic complete AV block that showed reduction in I_{Kr} and I_{Ks} , and altered L-type Ca^{2+} current, with other currents (inward Na^+ current, transient outward K^+ current and inward rectifier K^+ current) remaining normal (15,16,18). The antiarrhythmic drugs, dofetilide and azimilide, produced similar electrophysiological and proarrhythmic effects on canine hearts (19). Thus, evidence suggests that over four or more weeks, downregulation of repolarizing currents in the setting of chronic complete AV block may reduce repolarization reserve. In addition, AV block was associated with the development of biventricular hypertrophy in the canine model, which may have played a contributory role (17,20).

In humans with high-grade AV block and TdP, the clinical course is far more rapid from admission for bradycardia to the onset of TdP (6). Also, patients can continue to have recurrence of TdP after implantation of a pacemaker, if the lower rate of the device is programmed in the 'nominal' range at 60 beats/min (6). If the observed QT interval prolongation and TdP were purely due to bradycardia-mediated downregulation of I_{Kr} and I_{Ks} , one would expect pacing at a rate of 60 beats/min to prevent recurrence of TdP. Taken together, these observations suggest that there are other factors present that may influence repolarization reserve in patients with bradycardia-mediated TdP.

Genetic mutations and polymorphisms may influence repolarization reserve

There is mounting evidence that acquired LQTS is a manifestation of reduced repolarization reserve, which is unmasked by physiological or pharmacological stressors (8-10). Bradycardia-induced TdP may be further proof of this phenomenon. Chevalier et al (8) recently described a series of patients with pacemakers who had preimplant QT intervals of greater than 600 ms and complete AV block. These patients underwent genetic screening for mutations in ion channels known to cause congenital LQTS. Five of 29 patients had mutations in *KCNH2* (8). The study only included patients with profound QT interval prolongation and only identified one patient with TdP, who also had hypokalemia. The T_p - T_e interval was not measured and no ECGs before the development of AV block were obtained (8). Our study provided novel data on baseline (before the development of AV block), during AV block and pre-TdP ECG parameters, as well as probable genetic correlates of TdP in complete AV block.

Although genetic abnormalities found in the general population at a frequency of greater than 1% are classified as polymorphisms, physiological or pharmacological stress may unmask repolarization vulnerabilities. For instance, the *KCNQ1* G643S polymorphism predisposes to marked QT interval prolongation with class IA antiarrhythmic drugs (21), and the *SCN5A* S1102Y polymorphism increases the likelihood of drug-induced QT interval prolongation and TdP (22,23). It is, therefore, conceivable that the presence of a genetic polymorphism in the setting of AV block may predispose to QT interval prolongation and TdP. Further genetic correlation studies are required to explore this hypothesis.

Predictors of TdP, and an underlying genetic mutation or polymorphism in AV block

Our study demonstrated that 36% of patients with complete AV block and TdP had an underlying genetic mutation or polymorphism. Moreover, we identified the QTc interval and, in particular, the T_p - T_e interval as significant predictors of TdP in AV block. We also determined that the T_p - T_e interval was more likely to be prolonged in patients with a genetic mutation or polymorphism at baseline, in AV block and pre-TdP (Figure 1 and Table 3). The present study was the first to specifically include ECG parameters at baseline, before the development of AV block. The T_p - T_e is an ECG correlate of the transmural dispersion of repolarization (24,25). This measure reflects the heterogeneity of repolarization, an intrinsic property of the cells that populate the endocardium, midmyocardium and epicardium. Prolongation of the transmural dispersion of repolarization may predispose to TdP (24,25). In our study, the T_p - T_e interval appears to identify a subgroup of patients with an underlying genetic mutation or polymorphism, and subsequent propensity to TdP in the setting of AV block. A larger study will be required to explore this further.

The Glu161Lys mutation involving *SCN5A*, identified in patient 1, has been associated with a Brugada-type ECG and conduction abnormalities (13). In our patient, the phenotype appears to be more consistent with LQTS and conduction disease. *SCN5A* has been shown to have considerable phenotypic variability, with reports of both Brugada and LQT3 phenotypes with a single genotype (26-31). The underlying electrophysiological explanation for this may involve differential effects on the fast and slow components of sodium channel inactivation (31). Further cellular expression studies are necessary to provide insight into the underlying mechanism; nonetheless, it is a known disease-causing mutation. Moreover, extensive analysis of our patient with the Glu161Lys mutation, including all previous ECGs and drug challenge with class IA antiarrhythmic agents, did not reveal evidence of Brugada syndrome, which suggests that this is the first report of Glu161Lys mutation associated with LQTS.

Patient 3 had a Pro1075Leu mutation involving *KCNH2*, identified on genetic screening. This mutation was recently reported to cause LQTS (14). The mutation is located at the C-terminus of *KCNH2*, which is believed to be a mutation 'hot spot' because there are reports of mutations involving nearby residues also causing congenital LQTS (9,32). Patient 3 had a normal QTc interval at baseline

with marked QT interval prolongation pre-TdP (439 ms versus 581 ms, Table 2). Complete AV block appears to have unmasked a genetic predisposition to reduced repolarization reserve. Characterization of the Pro1075Leu mutation at a cellular level may provide further insight into the mechanism of the observed phenotype.

Two of our patients had known genetic polymorphisms. Both patients had clinical characteristics and ECG features similar to patients with a clear-cut disease-causing mutation. In addition, both patient 1 and patient 4 had recurrent episodes of TdP. The *KCNH2* Lys897Thr polymorphism in patient 4 has a population frequency of 6% to 30% (33). When expressed in human embryonic kidney-293 cells, Lys897Thr channels have reduced current density caused by reduced channel expression (34). When patients with the *KCNH2* Lys897Thr polymorphism underwent stress testing, their QTc intervals were longer than those of controls (34). Similar observations were made in a study of Finnish women with the *KCNH2* Lys897Thr polymorphism (35). Taken together, these data suggest that the *KCNH2* Lys897Thr polymorphism reduces repolarization reserve, which may be 'unmasked' in the setting of physiological stress.

The *SCN5A* H588R polymorphism in patient 2 has an estimated population frequency of 15% to 30% (36). The *SCN5A* H588R polymorphism has been shown to significantly modify the phenotype of some mutations and, as such, is known as an internal disease gene modifier (37,38). At slower heart rates caused by complete AV block, this polymorphism may modulate the $I_{Na,1.5}$ current. So far, QT interval prolongation and TdP have not been associated with this polymorphism. However, in the absence of electrophysiological data, the manifestation of QT interval prolongation and TdP in patient 2 may not be explained by the presence of this polymorphism alone.

History of syncope and likelihood of an underlying genetic mutation or polymorphism

A personal or family history of syncope or a family history of sudden cardiac death was more likely in patients with a genetic mutation or polymorphism (Table 3). This emphasizes the importance of a thorough clinical history in patients presenting with TdP and complete AV block. Without symptom-rhythm correlates, it is difficult to be certain about the etiology of the syncope and whether the genetic mutation or polymorphism could be causally implicated. Regardless of etiology, however, a family history of syncope should alert the clinician to consider an underlying genetic mutation or polymorphism in patients with AV block and TdP.

Clinical implications

In principle, there may be no real distinction between congenital and acquired LQTS. A genetic repolarization complement is present in any given individual, influenced by autonomic tone including heart rate, electrolytes, QT-prolonging drugs, ischemia and a range of other factors, which we simplistically measure with a surface QT interval. Further assessment of other repolarization genes, as well as measures of gene expression and gene-gene interaction will undoubtedly provide further insight into the concept of repolarization reserve.

The present study is novel because ECG correlates were provided at baseline as well as in AV block and pre-TdP. In addition, patients with AV block and TdP, rather than just profound QT interval prolongation, were included in the analysis (8). The current study suggests that AV block is another QT 'stressor' in a genetically susceptible population. In this context, genetic assessment of the proband, as well as clinical and genetic assessment of first-degree relatives, should be considered. Moreover, patients who are found to have a mutation or vulnerable polymorphism should be treated with the same precautions as patients with congenital LQTS, and genetic screening should be offered to their families. Further studies are needed to assess implications to patient care. However, there is little doubt that some patients have a genetic predisposition to arrhythmia. We anticipate that genetic screening will become more accessible and be used to guide therapy in susceptible individuals. There are major implications pertaining to the future use of

potentially proarrhythmic drugs, family screening for arrhythmia risk and tailoring treatment to genotype.

Limitations

The present study prospectively evaluated a modest number of patients with complete AV block and TdP for underlying genetic mutations or polymorphisms. A larger sample of patients to establish the range of causative mutations and polymorphisms is needed. Genetic screening was targeted specifically at the known ion channel genes involved in LQTS. Regulatory proteins, effects of gene expression and the involvement of other ion channels may have had a contributory role. We did not perform cellular expression studies on the identified genetic mutations or polymorphisms. However, all except the Pro1075Leu mutation were previously characterized at a cellular level. The 33 patients whose ECGs were used for comparison did not undergo genetic testing because the general population frequency is known for the described genetic mutations.

CONCLUSION

TdP in the setting of AV block may be a marker of an underlying genetic predisposition to reduced repolarization reserve. A personal or family history of syncope or sudden death, as well as the T_p-T_e interval at baseline, in AV block and pre-TdP may predict a genetic mutation or polymorphism compromising repolarization reserve. Patients with TdP in the setting of AV block, previously considered an 'acquired' form of LQTS, may represent a phenotypic manifestation of a genetic vulnerability.

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REFERENCES

- Wilson FN, Robinson CC. Two cases of complete heart block showing unusual features. *Arch Intern Med* 1918;21:166-75.
- Dessertenne F. La tachycardia ventriculaire a deux foyers opposes variable. *Arch Mal Coeur Vaiss* 1966;59:263-72.
- Vincent GM. The long-QT syndrome – bedside to bench to bedside. *N Engl J Med* 2003;348:1837-8.
- Kurita T, Ohe T, Marui N, et al. Bradycardia-induced abnormal QT prolongation in patients with complete atrioventricular block with torsades de pointes. *Am J Cardiol* 1992;69:628-33.
- Strasberg B, Kusnec K, Erdman S, et al. Polymorphous ventricular tachycardia and atrioventricular block. *Pacing Clin Electrophysiol* 1986;9:522-6.
- Topilski I, Rogowski O, Rosso R, et al. The morphology of the QT interval predicts torsade de pointes during acquired bradyarrhythmias. *J Am Coll Cardiol* 2007;49:320-8.
- Yoshida H, Horie M, Otani H, Kawashima T, Onishi Y, Sasayama S. Bradycardia-induced long QT syndrome caused by a de novo missense mutation in the S2-S3 inner loop of HERG. *Am J Med Genet* 2001;98:348-52.
- Chevalier P, Bellocq C, Millat G, et al. Torsades de pointes complicating atrioventricular block: Evidence for a genetic predisposition. *Heart Rhythm* 2007;4:170-4.
- Napolitano C, Schwartz PJ, Brown AM, et al. Evidence for a cardiac ion channel mutation underlying drug-induced QT prolongation and life-threatening arrhythmias. *J Cardiovasc Electrophysiol* 2000;11:691-6.
- Yang P, Kanki H, Drolet B, et al. Allelic variants in long-QT disease genes in patients with drug-associated torsades de pointes. *Circulation* 2002;105:1943-8.
- McLaughlin NB, Campbell RW, Murray A. Comparison of automatic QT measurement techniques in the normal 12 lead electrocardiogram. *Br Heart J* 1995;74:84-9.
- Bazett HC. An analysis of the time relations of electrocardiograms. *Heart* 1920;7:353-67.
- Smits JP, Koopmann TT, Wilders R, et al. A mutation in the human cardiac sodium channel (E161K) contributes to sick sinus syndrome, conduction disease and Brugada syndrome in two families. *J Mol Cell Cardiol* 2005;38:969-81.
- Chung SK, McCormick JM, McCulley CH, et al. Long QT and Brugada syndrome gene mutations in New Zealand. *Heart Rhythm* 2007;4:1306-14.
- Vos MA, de Groot SH, Verduyn SC, et al. Enhanced susceptibility for acquired torsade de pointes arrhythmias in the dog with chronic, complete AV block is related to cardiac hypertrophy and electrical remodeling. *Circulation* 1998;98:1125-35.
- Volders PG, Sipido KR, Vos MA, et al. Downregulation of delayed rectifier K(+) currents in dogs with chronic complete atrioventricular block and acquired torsades de pointes. *Circulation* 1999;100:2455-61.
- Volders PG, Sipido KR, Vos MA, Kulcsar A, Verduyn SC, Wellens HJ. Cellular basis of biventricular hypertrophy and arrhythmogenesis in dogs with chronic complete atrioventricular block and acquired torsade de pointes. *Circulation* 1998;98:1136-47.
- Tsuji Y, Opthof T, Yasui K, et al. Ionic mechanisms of acquired QT prolongation and torsades de pointes in rabbits with chronic complete atrioventricular block. *Circulation* 2002;106:2012-8.
- Van Opstal JM, Leunissen JD, Wellens HJ, Vos MA. Azimilide and dofetilide produce similar electrophysiological and proarrhythmic effects in a canine model of torsade de pointes arrhythmias. *Eur J Pharmacol* 2001;412:67-76.
- Swynghedauw B, Baillard C, Milliez P. The long QT interval is not only inherited but is also linked to cardiac hypertrophy. *J Mol Med* 2003;81:336-45.
- Kubota T, Horie M, Takano M, et al. Evidence for a single nucleotide polymorphism in the KCNQ1 potassium channel that underlies susceptibility to life-threatening arrhythmias. *J Cardiovasc Electrophysiol* 2001;12:1223-9.
- Splawski I, Timothy KW, Tatemura M, et al. Variant of SCN5A sodium channel implicated in risk of cardiac arrhythmia. *Science* 2002;297:1333-6.
- Roden DM, Viswanathan PC. Genetics of acquired long QT syndrome. *J Clin Invest* 2005;115:2025-32.
- Antzelevitch C. Heterogeneity and cardiac arrhythmias: An overview. *Heart Rhythm* 2007;4:964-72.
- Antzelevitch C. The role of spatial dispersion of repolarization in inherited and acquired sudden cardiac death syndromes. *Am J Physiol Heart Circ Physiol* 2007;293:H2024-38.
- Bezzina C, Veldkamp MW, van den Berg MP, et al. A single Na(+) channel mutation causing both long-QT and Brugada syndromes. *Circ Res* 1999;85:1206-13.
- van den Berg MP, Wilde AA, Viersma TJW, et al. Possible bradycardic mode of death and successful pacemaker treatment in a large family with features of long QT syndrome type 3 and Brugada syndrome. *J Cardiovasc Electrophysiol* 2001;12:630-6.
- Grant AO, Carboni MP, Neplioueva V, et al. Long QT syndrome, Brugada syndrome, and conduction system disease are linked to a single sodium channel mutation. *J Clin Invest* 2002;110:1201-9.
- Priori SG, Napolitano C, Schwartz PJ, Bloise R, Crotti L, Ronchetti E. The elusive link between LQTS and Brugada syndrome: The role of flecainide challenge. *Circulation* 2000;102:945-7.
- Remme CA, Verkerk AO, Nuyens D, et al. Overlap syndrome of cardiac sodium channel disease in mice carrying the equivalent mutation of human SCN5A-1795insD. *Circulation* 2006;114:2584-94.
- Veldkamp MW, Viswanathan PC, Bezzina C, Baartscheer A, Wilde AA, Balser JR. Two distinct congenital arrhythmias evoked by a multidysfunctional Na(+) channel. *Circ Res* 2000;86:E91-E97.
- Arnestad M, Crotti L, Rognum TO, et al. Prevalence of long-QT syndrome gene variants in sudden infant death syndrome. *Circulation* 2007;115:361-7.
- Ackerman MJ, Tester DJ, Jones GS, Will ML, Burrow CR, Curran ME. Ethnic differences in cardiac potassium channel variants: Implications for genetic susceptibility to sudden cardiac death and genetic testing for congenital long QT syndrome. *Mayo Clin Proc* 2003;78:1479-87.
- Paavonen KJ, Chapman H, Laitinen PJ, et al. Functional characterization of the common amino acid 897 polymorphism of the cardiac potassium channel KCNH2 (HERG). *Cardiovasc Res* 2003;59:603-11.
- Pietila E, Fodstad H, Niskasaari E, et al. Association between HERG K897T polymorphism and QT interval in middle-aged Finnish women. *J Am Coll Cardiol* 2002;40:511-4.
- Ackerman MJ, Splawski I, Makielski JC, et al. Spectrum and prevalence of cardiac sodium channel variants among black, white, Asian, and Hispanic individuals: Implications for arrhythmogenic susceptibility and Brugada/long QT syndrome genetic testing. *Heart Rhythm* 2004;1:600-7.
- Viswanathan PC, Benson DW, Balser JR. A common SCN5A polymorphism modulates the biophysical effects of an SCN5A mutation. *J Clin Invest* 2003;111:341-6.
- Ye B, Valdivia CR, Ackerman MJ, Makielski JC. A common human SCN5A polymorphism modifies expression of an arrhythmia causing mutation. *Physiol Genomics* 2003;12:187-93.