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Genetic Predisposition and Cellular Basis for Ischemia-induced ST Segment Changes and Arrhythmias

Dan Hu, MD, PhD[1], **Sami Viskin, MD**[2], **Antonio Oliva, MD**[1,3], **Jonathan M. Cordeiro, PhD**[1], **Alejandra Guerchicoff, PhD**[1], **Guido D. Pollevick, PhD**[1], and **Charles Antzelevitch, PhD**[1]

1 *Masonic Medical Research Laboratory, Utica, New York, USA*

2 *Department of Cardiology, Tel-Aviv Sourasky Medical Center, and Sackler School of Medicine, Tel-Aviv University, Israel*

3 *Institute of Forensic Medicine, Catholic University, Rome, Italy*

Abstract

Recent reports have highlighted the importance of a family history of sudden death as a risk for ventricular fibrillation in patients experiencing an acute myocardial infarction (AMI), pointing to the possibility of a genetic predisposition. This report briefly reviews two recent studies designed to examine the hypothesis that there is a genetic predisposition to the development of arrhythmias associated with AMI. Ventricular tachycardia and fibrillation (VT/VF) complicating AMI as well as the arrhythmias associated with Brugada syndrome, a genetic disorder linked to SCN5A mutations, have both been linked to phase 2 reentry. Because of these mechanistic similarities in arrhythmogenesis, we examined the contribution of SCN5A mutations to VT/VF complicating AMI in patients developing VF during AMI. A missense mutation in SCN5A was found in a patient who developed an arrhythmic electrical storm during an evolving MI. All VT/VF episodes were associated with ST segment changes and were initiated by short-coupled extrasystoles. The G400A mutation and a H558R polymorphism were on the same allele and functional expression in TSA201 demonstrated a loss of function of sodium channel activity. These results suggest that a subclinical mutation in SCN5A resulting in a loss of function may predispose to life-threatening arrhythmias during acute ischemia. In another cohort of patients who developed long QT intervals and Torsade de Pointes (TdP) arrhythmias in days 2–11 following an AMI, a genetic screen of all long QT genes was performed. Six of eight patients (75%) in this group displayed the same polymorphism in KCNH2, which encodes the α subunit of the rapidly activating delayed rectifier potassium current, I_{Kr}. The K897T polymorphism was detected in only 3 of 14 patients with uncomplicated myocardial infarction (MI) and has been detected in 33% of the Caucasian population. Expression of this polymorphism has previously been shown to cause a loss of function in HERG current consistent with the long QT phenotype. These observations suggest a genetic predisposition to the development of long QT intervals and TdP in the days following an AMI. These preliminary studies provide support for the hypothesis that there is a genetic predisposition to the type and severity of arrhythmias that develop during and after an acute myocardial infarction and that additional studies are warranted.

Address for editorial correspondence and reprint requests: Charles Antzelevitch, PhD, FACC, FAHA, FHRS, Gordon K. Moe Scholar, Masonic Medical Research Laboratory, 2150 Bleecker Street, Utica, New York, U.S.A. 13501-1787, Phone: (315) 735-2217, FAX: (315) 735-5648, E-mail: ca@mmrl.edu.

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Keywords

Ventricular tachycardia; fibrillation; arrhythmia; ischemia; sudden cardiac death

Nearly 1 million Americans suffer an acute myocardial infarction (AMI) each year. Approximately 20% to 25% experience sudden cardiac death soon after due to the development of ventricular tachycardia and fibrillation (VT/VF).[1] Although identification of patients at risk for primary VF during AMI remains rather poor, recent reports have highlighted the importance of family history, pointing to the possibility of a genetic predisposition.[2] This report briefly reviews two recent studies designed to examine the hypothesis that there is a genetic predisposition to the development of arrhythmias associated with AMI. [3, 4]

Genetic Predisposition to the Development of Arrhythmic Storm During AMI

The SCN5A gene encodes the α-subunit of the human cardiac voltage-gated sodium channel $hNa_v1.5$. The protein product of this gene expresses in the membrane with one or more β-subunits,[5] to initiate the action potential in most cardiac cells. SCN5A mutations have been linked to sudden cardiac death associated with a number of inherited arrhythmic syndromes, including the LQT3 form of the long QT syndrome, conduction disease, atrial standstill and Brugada Syndrome (BS).[6, 7] However, their association with acquired forms of VF is not well defined. Because mechanistic similarities exist between the VT/VF caused by Brugada syndrome and that caused by VT/VF associated with myocardial ischemia (both are linked to phase 2 reentry), we hypothesized that SCN5A mutations similar to those linked to Brugada syndrome, may predispose to the development of VT/VF during AMI.

We recently examined the contribution of SCN5A mutations to arrhythmogenesis in a cohort of patients who developed one or more episodes of VT/VF during acute myocardial infarction (AMI).[3]

Clinical Characteristics

Nineteen patients admitted with AMI who developed ventricular fibrillation (VF) immediately prior to, or shortly after arrival to the intensive care unit, were studied. All patients had obvious ST segment elevation and elevated cardiac enzymes diagnostic of AMI. Nine were admitted with anterior and ten with inferior MI. Eighteen of the 19 were male and the average age was 57 ± 10 years. All patients had preserved left ventricular ejection fraction, reflecting the fact that for all except 1 patient this was the first myocardial infarction. Sixteen of the 19 displayed 1 episode of VF, two had 2 episodes and one patient presented with an arrhythmic storm, displaying 6 episodes of polymorphic VT and VF within the first 12 hours.

The ECG of the patient with the electrical storm revealed marked ST segment deviation preceding all polymorphic VT/VF episodes, which were triggered by a short-coupled extrasystole. He had no history of previous syncope or of familial sudden death. Moreover, he did not display ST segment elevation suggestive of Brugada syndrome at any time prior to the AMI. Finally, provocative tests with flecainide[8] and adenosine,[9] performed to exclude subclinical forms of Brugada syndrome and long QT syndrome, were both negative.

Genetic Analysis

Polymerase chain reaction (PCR)-based sequencing of all exons and exonintron boundaries revealed H558R polymorphism between domain I and domain II in 5 of the 19 patients, and R34C polymorphism in the C-terminal of SCN5A in one patient. These heterozygous polymorphisms are common in the population, appearing with a frequency of 20% and 4%, respectively.[10]

The patient with the arrhythmic storm was the only one in which a SCN5A mutation was uncovered. He had a novel missense mutation, G400A, combined with H558R polymorphism in the same allele of the SCN5A gene.

Because the QT interval was slightly prolonged during the early phase of recovery from myocardial infarction (MI), we screened this patient for 4 of the common long QT genes KCNH2, KCNQ1, KCNE1 and KCNE2.

Functional Expression

The G400A, G400A+H558R mutant and the wild-type (WT) sodium channel were expressed in TSA201 cells to assess the effects of the mutation on sodium channel function. Peak G400A and G400A+H558R current were 70.7% and 88.4% less than WT current at −35mV (P 0.001). G400A current decay was accelerated and steady-state inactivation was shifted −6.39 mV ($V_{1/2}$= −98.9 ± 0.1 mV vs. −92.5 ± 0.1 mV, P 0.001).

Mechanism of MI-associated Arrhythmic Storm

The patient carrying the SCN5A mutation was the only one who developed an arrhythmic storm during AMI in this small series. The fact that this patient developed his first VF only at 70 years of age and only in the setting of AMI supports the thesis that the SCN5A mutation served as a modulating factor in this acquired arrhythmic syndrome. The G400A missense mutation in SCN5A caused a loss of function in sodium channel current due to reduced current density, impaired recovery from inactivation, and shift in the voltage dependence of inactivation to hyperpolarized potentials.

The G400A carrier had a common polymorphism (H558R) on the same allele. H558R has been shown to correct the trafficking defect observed with some mutations such as M1766L[11] and R282H[12] and to mitigate the loss of function produced by T512I.[13] The R558-encoding allele has been shown to yield a sodium channel with reduced function when expressed in the context of the Q1077-containing transcript, which is the minor alternatively spliced transcript, accounting for approximately one third of SCN5A transcripts.[14, 15] Our study was the first to demonstrate an effect of H558R to further accentuate the effect of a loss of function mutation.[3]

The SCN5A mutation was subclinical throughout the patient's life, expressing clinically only in the setting of an AMI. Ischemia is known to lead to a reduction of inward currents such as sodium (I_{Na}) and calcium (I_{Ca}) channel current and an increase of outward currents such as the adenosine triphosphate (ATP)-sensitive potassium channel current ($I_{K\text{-}ATP}$), resulting in a net increase in repolarization forces, especially in the early phases of the action potential. These changes in turn lead to reduced excitability, slowed conduction and thus can facilitate the induction of reentry. The presence of an already compromised sodium channel would be expected to exacerbate this arrhythmogenic substrate.

Experimental studies indicate that a rebalancing of currents active during the early phases of the action potential can give rise to prominent ST segment changes in addition to creating the substrate for the development of reentrant arrhythmias under ischemic conditions as well as in inherited sudden death syndromes such as the Brugada syndrome.[16–19] It has been suggested that the two may be additive or synergistic.[20] Recent clinical studies have provided support for this hypothesis demonstrating a synergism between ST segment elevation and arrhythmogenesis in patients with the Brugada syndrome when an ischemic insult is superimposed.[21]

In the Brugada syndrome, sodium channel blockers are known to unmask the syndrome regardless of genotype and loss-of-function SCN5A mutations have been identified as

causative in 15–20% of cases.[22–24] In the present study, we provide evidence in support of the corollary hypothesis that SCN5A mutations can exacerbate arrhythmogenesis in the setting of AMI. Our findings suggest a genetic predisposition for acquired (i.e., ischemia related) VF in 1 out of 19 patients with AMI complicated by VF. A similar percentage of genetic anomalies predisposing to ventricular arrhythmias have been reported for other forms of "acquired arrhythmic syndromes", such as drug-induced long QT syndrome.[25]

The absence of QRS widening during AMI and immediately preceding VF episodes in the patient with the arrhythmic storm, favor a Brugada-like mechanism. In this mechanistic framework, the reduced sodium channel current would leave the transient outward current (I_{to}) unopposed, resulting in an outward shift in current, which allows phase 1 to proceed to more negative potentials. All-or-none repolarization leading to loss of the action potential dome generally occurs when phase 1 reaches potentials of approximately −30 mV. Reduced peak I_{Na} can selectively hasten epicardial repolarization, thus creating both the substrate and trigger for reentry, accounting for the arrhythmic storm and observed ischemia-related change in ECG. Of note, VT/VF episodes in our arrhythmic storm patient were all precipitated by closely coupled extrasystoles (<390 msec), consistent with a phase 2 reentrant mechanism.

Earlier studies have shown that despite similar changes in resting membrane potential, ischemia induces a greater depression of the action potentials of ventricular epicardial versus endocardial tissues.[26, 27] Studies performed in isolated canine ventricular epicardial and endocardial tissues have demonstrated that intrinsic cellular electrophysiological differences form the basis for the differential sensitivity to ischemic conditions.[16, 17, 28–30] The presence of a prominent transient outward current (I_{to})-mediated spike and dome morphology (notch) in epicardium[31] was shown to be, in large part, responsible for the differential response. In isolated endocardial and epicardial preparations, superfusion with a simulated "ischemic" Tyrode's solution induces an all-or-none repolarization at the end of phase 1 leading to loss of the epicardial action potential dome and marked abbreviation of the action potential.[16]

The presence of a large epicardial I_{to} is essential for all-or-none repolarization. It is for this reason that, loss of the epicardial action potential dome observed under ischemic conditions and conditions mimicking "components" of ischemia (pinacidil-induced $I_{K(ATP)}$ activation),[28] elevated extracellular calcium combined with rapid pacing,[29] occurs preferentially in right ventricular (RV) epicardial tissues, where I_{to} is most prominent.[32]

The effect of coronary occlusion to give rise to a differential loss of the action potential dome in epicardium, resulting in the development of ST segment changes and arrhythmogenesis has recently been demonstrated in isolated coronary-perfused ventricular wedge preparations.[33, 34] Heterogeneous loss of the action potential dome during ischemia has been shown to give rise to transmural dispersion of repolarization as well as phase 2 reentry, thus precipitating reentry in the form of VT/VF.[17, 33, 34]

Our results suggest that a subclinical mutation in SCN5A resulting in a loss of function may predispose to life-threatening arrhythmias during acute ischemia. A more extensive study is clearly needed to test this hypothesis.

Genetic Predisposition to Post-MI prolongation of QT Interval and TdP Arrhythmias

The early post-myocardial infraction (MI) period (days 2–11) is associated with a slight QT prolongation in most patients.[35] In some, this electrical remodeling leads to a prominent prolongation of the QT interval and the development of Torsade de Pointes (TdP).[35] We have recently endeavored to test the hypothesis that there is a genetic predisposition to post-MI

associated TdP. As a test of the hypothesis, we screened long QT genes, including *SCN5A, KCNQ1, KCNH2, KCNE1*, and *KCNE2*, in a cohort of patients presenting with prolonged QT intervals and TdP in days 2–11 following an MI.

Preliminary evidence in support of the hypothesis derives from a recent genetic analysis of these genes in 8 patients who developed long QT intervals and TdP in days 2 to 11 after MI.[4] The affected patients were selected from among 434 consecutive admissions for acute MI. None had active ischemia or other known causes of QT prolongation at the time of TdP occurrence. The 8 affected patients were compared with 14 consecutive patients with uncomplicated MI who served as controls. QTc prolonged by day 2 in both groups, but more so in patients with TdP (from 470 ± 46 to 492 ± 57 ms [$p < 0.05$] and from 445 ± 58 to 558 ± 84 ms, respectively [$p < 0.01$]).[35] In 6 of the 8 (75%) patients who developed TdP after MI, we detected a K897T single nucleotide polymorphism (SNP) in KCNH2. K897T was detected in only 3 or the 14 (21.3%) uncomplicated controls of the same ethnic background.

The K897T polymorphism has been shown to cause a loss of function in heterologous expression systems and to contribute to the development of other forms of acquired long QT syndrome.[36] The incidence of K897T in the general population is approximately 33%.[37] These findings provide support for the hypothesis that there is a genetic predisposition to post-MI associated TdP. We hope to expand this study population so as to increase the power of the study in the months ahead.

Conclusion

These preliminary studies provide support for the hypothesis that there is a genetic predisposition to the type and severity of arrhythmias that develop during and after an acute myocardial infarction and that additional studies are warranted.

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