Cardiac Metabolic State and Brugada Syndrome

A Link Revealed

Mohamed Chahine

Brugada syndrome (BrS) is an inherited cardiac disorder with variable ECG features characteristic of right bundle branch block (RBBB) and ST segment elevation in the right precordial leads (V1-V3) at rest, which was first described by the Brugada brothers as a clinical entity with a genetic background.1

In Southeast Asia, BrS causes a high risk of sudden unexplained nocturnal death syndrome (SUNDS) in young adults.2,3

In genetically determined forms of BrS, a number of mutations in the SCN5A gene located on chromosome 3p21-23 have been implicated in BrS and account for 20% to 30% of BrS in genotyped families.4 More recently, mutations in other genes such as those coding for glycerol-3-phosphate dehydrogenase 1-like (GPD1-L),5 the α-subunit of the Ca1.2 L-type calcium channel (CACNA1C), the β2 calcium channel regulatory subunit (CACNB2),6,7 and the hERG potassium channel (KCNH2)8 have been shown to be associated with BrS clinical phenotypes.

Mutations in the SCN5A gene are associated with loss-of-function caused by trafficking defects, truncated sodium channel proteins, or changes in the biophysical properties of sodium channels. Loss-of-function mutations of the Ca1.2 L-type calcium channel and its regulatory subunit, which are encoded by CACNA1C and CACNB2, respectively (A39V- and G490R/CACNA1C and S481L/CACNB2), have been reported to be associated with a BrS phenotype combined with shorter QT intervals. Two gain-of-function mutations in the KCNH2 (hERG) of the cardiac potassium channel (G873S and N985S) have been reported in patients with BrS syndrome.

Glycerol-3-phosphate dehydrogenase (GPD) catalyzes the reduction of dihydroxyacetone phosphate to glycerol-3-phosphate. GPD uses nicotinamide adenine dinucleotide (NADH) as a cofactor for this reaction and may play a role in energy production. GPD is involved in glycerol phosphate metabolism and is expressed abundantly in cardiac myocytes. Mutations in GPD1-L have been found in patients with BrS and in sudden infant death syndrome. It is surprising that Dutch and Japanese BrS cohort studies did not identify potential mutations in the GPD1-L gene.9,10 Because BrS is widespread in Southeast Asia, studies using cohorts of Southeast Asian patients are warranted to determine whether GPD1-L mutations are a risk factor in this population.

Subsequent gene analysis studies of the same family revealed the presence of a novel missense mutation A280V in GPD1-L that cosegregates with the BrS phenotype.5 Cotransfection of GPD1-L/A280V with the Na1.5 sodium channel produces a 50% reduction in sodium currents with no effect on gating and the kinetics of sodium currents. This study showed that GPD1-L does not associate with Na1.5, which excludes any direct effect of GPD1-L on sodium channels. It has been shown that the expression of GPD1-L in rabbit hearts is similar in males and females, suggesting that the cellular mechanism by which mutant GPD1-L triggers arrhythmias is related to the hypothesis that a less depolarizing sodium current causes early repolarization in the right ventricular epicardium where the transient outward K+ current (Ito) is large. This leads to a voltage gradient from the endocardium to the epicardium, ST elevation on the surface ECG, and a propensity to develop arrhythmias caused by phase 2 re-entry.12

Van Norstrand et al reported three additional GPD1-L mutations in autopsy-negative sudden infant death syndrome cases (E83K, I124V, and R273C).13 The coexpression of GPD1-L mutations with Na1.5 in HEK293 cells results in a significantly reduced sodium current. This suggested that the loss-of-function of sodium currents can result in a sudden death-predisposing clinical phenotype such as BrS and sick sinus syndrome.

These studies indicated that GPD1-L can potentially alter cellular NAD+/NADH levels and operate as a bridge between the metabolic state of the heart and the observed reduction in sodium currents.5 Indeed, Liu et al report on the mechanism by which GPD1-L reduces sodium currents in this issue of Circulation Research.14 They showed that GPD1-L regulates sodium channels through the redox state of NAD+/NADH.
They also showed that A280V mutation in GPD1-L, which was discovered in a patient with BrS, increases the intracellular concentration of NADH ([NADH]i) more than 2-fold in a HEK293 cell expression system. In another set of experiments, the authors found that increasing the [NADH]i results in a rapid reduction in sodium current amplitude. Whereas there is no effect on sodium current kinetics, the gating properties of the channel are moderately affected. These findings have been confirmed in a study using rat neonatal cardiomyocytes which are less sensitive, however, than the transfected HEK293 cells to the higher NADH concentration. The reduction in the sodium current is not related to a transcriptional or trafficking alteration of Na,1.5 sodium channels. Because NADH and NAD+ are a redox couple, Liu et al tested the hypothesis that NAD+ may antagonize the NADH effect. When NADH is applied in a patch pipette, the reduction in the sodium current caused by NAD+ is blocked. This effect is reminiscent of the effect of protein kinase (PK)C on sodium channels. Chelerythrine, a PKC inhibitor, also inhibits the effect of NADH. Interestingly, superoxide dismutase inhibits the reduction in the sodium current observed with NADH. It remains to be determined how NADH interferes with PKC. Is it through diacylglycerol (DAG) and activation of protein kinase C (DAG-PKC)-mediated signaling pathways? A recent study showed that excess NADH can also increase de novo synthesis of DAG. The link between reactive oxygen species and PKC must also be elucidated because PKC can phosphorylate and therefore directly regulate sodium channels. Lastly, which PKC isoform is involved? Is it the same isoform that is involved in the late sodium channels.

In the same vein, PKA activation is known to increase cardiac sodium currents. Using PKAI6–22, a specific PKA inhibitor, Liu et al show that NAD+ prevents the antagonizing effect of NADH, most likely by activating PKA.

Liu et al confirm their finding using SCN5A α-subunit transgenic mice in which 50% of the sodium channels have been knocked out. In this mouse model, programmed electric stimulation results in ventricular tachycardia. The authors showed that after a 20-minute perfusion with NAD+, programmed electric stimulation fails to induce ventricular tachycardia and that the effect is reversible. When the NAD+ is removed, programmed electric stimulation–induced ventricular tachycardia is again observed. This suggests NAD+ has a potential antiarrhythmic effect in this mouse model. Also, given the fact that NAD+ is membrane impermeable and no NAD+ transporter has been identified, the effects of NAD+ perfusion of hearts are probably not directly related to changes in cytoplasmic NAD+. Also, because this mouse model does not harbor a GPD1-L mutation and appears to have normal NADH/NAD+ levels, these findings suggest that this strategy could be used to treat BrS patients with reduced sodium currents that are not necessarily related to GPD1-L. However, there are several questions that need to be addressed first:

1. What is the effect of NADH levels on mediating the effect on other GPD1-L mutations that cause BrS and sudden infant death syndrome?
2. What is the long-term effect of NAD+? This question will have to be answered before proposing its use as a strategy to treat patients with BrS who have GPD1-L mutations.
3. What is the effect of SCN5A mutations in BrS patients with BrS that result in reduced sodium channel expression?

### Sources of Funding
M.C. is supported by grants from the Heart and Stroke Foundation of Quebec and the Canadian Institutes of Health Research (grant MT-13181) and is a J.C. Edwards Foundation Senior Investigator.

### Disclosures
None.

### References


**Key Words:** Brugada syndrome ■ Na,1.5 ■ SCN5A ■ cardiac arrhythmias ■ NADH
Cardiac Metabolic State and Brugada Syndrome: A Link Revealed
Mohamed Chahine

doi: 10.1161/CIRCRESAHA.109.208405

_Circulation Research_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2009 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/105/8/721

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation Research_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation Research_ is online at:
http://circres.ahajournals.org//subscriptions/