Increased Sensitivity to Local Anesthetic Drugs
Bedside to Bench

Harry A. Fozzard

This issue of Circulation Research contains the surprising report of a middle-aged African American with Brugada syndrome associated with 2 widely separated missense mutations in the Na channel gene and with dramatically increased lidocaine sensitivity. Following a seizure in the emergency room, the patient developed an episode of monomorphic ventricular tachycardia terminated by electric shock. After IV lidocaine was started, the patient quickly developed the ECG characteristics of Brugada phenomenon. Although local anesthetics (LAs) with slow off rates typically induce such ECG changes, this has not been reported for lidocaine. After identifying the 2 mutations in the Na channel α subunit gene of this individual, Barajas-Martinez et al exposed the mutated channel to lidocaine and found markedly increased sensitivity to block.

The finding of 2 unrelated mutations in the same Na channel gene is unusual. Ackerman et al reported that 1 of these mutations, L1308F, is a rare polymorphism (seen once in 319) in an African-American population but not in white, Asian, or Hispanic populations. Barajas-Martinez et al indicated that they have seen this polymorphism in 1% of their white population. No previous studies of lidocaine sensitivity have been reported for this polymorphism, but it now seems possible that individuals with the L1308F polymorphism are at risk of local anesthetic toxicity. This question deserves follow-up.

Why should we care much about rare syndromes such as Brugada when they are a mere drop in the bucket of total cardiac arrhythmic death? They are a window into mechanisms of lethal arrhythmia and their study can lead to preventive or corrective therapy. Although these monogenetic diseases are rare, the conditions can be reproduced in the laboratory, an invaluable tool that is very difficult to achieve. After the CAST trial. This has led to a flourishing of alternative methods, most dramatically in the use of implanted defibrillators or of ablative catheter procedures. For particularly high risk groups, these approaches have been lifesaving. However, as we consider expanding them into the overwhelming majority of those at risk, we find that they are only partially effective and/or associated with serious medical and economic side effects. Without disparate the achievements of the device-intervention approach for the appropriate population, we can recognize their limitations for management of the larger population at risk for lethal arrhythmia. It remains crucial that we develop effective and safe drugs. Such development requires that we understand how drugs affect their targets, typically ion channels or their modifiers. For this effort, we should not restrict the possible drug targets excessively, while recognizing that ion channels represent the final pathway for antiarrhythmic action.

Drugs do not intrinsically have good or bad effects; the good or harm depends on their actions and the desired therapeutic goal. A recent example of this is as follows. Drugs that prolong repolarization are harmful for those with intrinsic normal repolarization (acquired long QT syndrome) but potentially therapeutic for those with abbreviated repolarization (short QT syndrome). The therapeutic goal requires that we match the pathological process with the drug action. Consequently, understanding their mechanisms of action is crucial. Modern ion channel biophysical methods now make that goal achievable.

The finding that the 2 mutations found by Barajas-Martinez et al increase lidocaine sensitivity raises the question of how LA drugs act. With some exceptions, the LA drugs access their binding site from inside. We know a great deal about their binding site; it is in the inner pore of the channel, a few angstroms below the selectivity filter. For use-dependent block, the key residue is Phe1759 of DIV-S6. The opinions expressed in this editorial are not necessarily those of the editors or of the American Heart Association. From the Cardiac Electrophysiology Laboratory, Department of Medicine, The University of Chicago, Ill. Correspondence to Dr Harry A. Fozzard, PO Box 574, Dana, NC 28724. E-mail hafozzar@uchicago.edu (Circ Res. 2008;103:325-327.) © 2008 American Heart Association, Inc. Circulation Research is available at http://circres.ahajournals.org DOI: 10.1161/CIRCRESAHA.108.182055

325
resting conformation of the pore, either because Phe1759 does not face the pore in that state or because it is sterically blocked. With conformational changes in the S6 segments on channel opening, and particularly on binding of the inactivation particle, the site is fully available and high affinity binding occurs. It is these conformational changes that lead to the important use dependence of LA action.

Most mutations in the binding site reduce LA affinity. Several nearby residues on DIV-S6 and DIII-S6, when mutated to Ala, do enhance resting LA block but not use-dependent block.\textsuperscript{14,15} However, the mutations reported by Barajas-Martinez et al\textsuperscript{1} to increase affinity are far from this binding site. How can these mutations affect LA block? The key to answering this question is recognizing the difference between binding and block. Drug binding initiates a series of allosteric conformational changes that alter channel gating. In addition, local drug concentrations in the pore are affected by the access/egress path(s) for the drug. Although the main path for LA drug access to its binding site is from the inside, the cardiac isoform normally has an accessory outside path for entry and exit of charged LA drugs, resulting in less accumulation of block between depolarizations and less use-dependent block.\textsuperscript{14,15} These isoform differences probably explain the most of the difference in LA block between the cardiac channel and nerve and skeletal isoforms.

Gating currents reflect the movement of the positively charged S4 helices in response to changes in the membrane electric field.\textsuperscript{16} It has long been known that Na channel gating currents are reduced by LA drugs.\textsuperscript{17} These effects have been recently confirmed for the cardiac channel by Sheets and Hanck,\textsuperscript{18} and they further showed that lidocaine immobilized the DIII-S4 in its outward position, delayed recovery of DIV-S4, and shifted its voltage dependence. Prepositioning of these S4 segments to their more external locations by outside biotin–N-methanethiosulfonate interaction with Cys mutants caused a markedly increased lidocaine affinity for resting block.\textsuperscript{19} This result argues that DIII-S4 and lidocaine high-affinity binding reciprocally influence each other. It is plausible to think that the L1308F polymorphism in DIII-S4 also results in a resting position of S4 different from normal, favoring exposure of the high affinity LA site and interfering with normal recovery of DIII-S4. Mutations in the S4 of the Shaker K channel have been shown to alter the rates of conformational changes during the final steps into and out of pore opening.\textsuperscript{20} Such an idea can be tested by measuring gating currents in the L1308F mutant.

The increase in lidocaine affinity by V232I in DI-S4 is less understandable. However, Chanda et al\textsuperscript{21} have found striking effects of a mutation in DI-S4 of Nav1.4 on the movement of DIV-S4, which is linked to inactivation. We can make a suggestion as to the mechanism, by inference of the K channel, then the domain IV voltage-sensing unit would lie behind the pore unit of domain I. This provides a possible way that destabilization of conformational changes in domain 1 could affect the voltage sensor of domain IV. It has long been puzzling that widely distributed mutations affect channel functions at a distance, but as we learn how these amazing ion channel machines work, the mutational effects are becoming more understandable.

In summary, an astute bedside observation of an individual with Brugada phenomenon has revealed important information about how the Na channel interacts with local anesthetics and points to a polymorphism that may put these individuals at risk for local anesthetic toxicity. Continued clinical and laboratory cooperation, combined with the rapid progress in the molecular physiology of ion channels, promises to enhance our search for effective antiarrhythmic drugs.

**Sources of Funding**
The author is supported by NIH grant HL-065661.

**Disclosures**
None.

**References**


**Key Words:** Brugada syndrome ■ local anesthetics ■ Na channels
Increased Sensitivity to Local Anesthetic Drugs: Bedside to Bench
Harry A. Fozzard

_Circ Res._ 2008;103:325-327
doi: 10.1161/CIRCRESAHA.108.182055

_Circulation Research_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2008 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/103/4/325

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/