Catecholaminergic polymorphic ventricular tachycardia (CPVT) is an inherited arrhythmogenic disease characterized by the development of adrenergically mediated bidirectional and polymorphic ventricular tachycardia in individuals with a normal heart. Although this disease was initially described by Counel in the seventies, it was only after the identification of its genetic substrate that interest about this uncommon clinical condition has extended beyond pediatric cardiology to involve a broader spectrum of clinicians and basic scientists.

CPVT is caused by mutations in 2 genes encoding calsequestrin and the cardiac ryanodine receptor; i.e., 2 proteins strongly implicated in the regulation of intracellular calcium. The currently incomplete understanding of calcium homeostasis in the heart under normal settings as well as in disease states has led to consideration of CPVT as a simplified human and experimental model that may help to clarify intracellular calcium regulation.

Since the clinical description of CPVT, it was noted that the bidirectional VT that is the distinguishing manifestation of the disease resembles the VT observed in patients with digitalis intoxication. For that reason it has been speculated that DAD-mediated triggered activity would be the most likely electrophysiologic mechanism for arrhythmia initiation in CPVT. As of today, a conclusive demonstration of this hypothesis is lacking, and this is why studies like the one presented by Jiang et al in this issue of Circulation Research are of major relevance.

Jiang et al have investigated in vitro the functional characteristics of different point mutations identified in patients with CPVT: their study is not the first of this kind, yet it brings novel insight and provides new arguments that help addressing controversial aspects in the field. In this editorial we will examine the areas of debate in the understanding of CPVT and will discuss the data reported by Jiang et al in the context of the leading speculations that have been elaborated to account for arrhythmogenesis in CPVT.

What Is the Role of FKBP12 in the Pathogenesis of CPVT?

The results presented by Jiang et al address an important unresolved dispute that is present in the literature about the molecular mechanism that links a mutation in RYR2 protein and the development of tachyarrhythmias. In the last few years Wehrens et al have elaborated a converging theory to explain arrhythmogenesis in heart failure and in CPVT. Based on the evidence that arrhythmias in the failing heart are likely to be initiated by triggering rhythms, these authors have proposed that a common final pathway for arrhythmogenesis in CPVT and HF is provided by the reduced affinity of RyR2 for the FKBP12.6 protein. Functional characterization of RyR2 performed by investigators of this group has provided experimental evidence suggesting that RyR2 mutations reduce the affinity of the ryanodine receptor for FKBP12.6 and that the same effect is produced by the disease process occurring in the failing heart. Additional compelling evidence to link FKBP12.6 binding to RyR2 and arrhythmias has come from studies based on a FKBP12.6 knock-out model in which reduced FKBP12.6 binding, assessed by FKBP12.6-RYR2 coimmunoprecipitation, has been linked to the development of adrenergically-mediated polymorphic VTs that resemble those occurring in CPVT patients. In the present study, however, Jiang et al further extend their previous observations and contest the data by Wehrens showing that CPVT mutations of RyR2 do not alter the binding of FKBP12.6 (see also George et al).

This debate is not limited to a theoretical interest, as it has remarkable practical implications: the hypothesis advanced by Wehrens et al had been accompanied by a remarkable effort of these authors to develop a novel pharmacological approach to restore FKBP12.6 binding. These authors tested a novel compound called JTV519 that increases affinity of FKBP12.6 for RyR2, and they demonstrated that in vivo administration of JTV519 is able to restore binding of FKBP12.6 to RyR2 to levels observed in controls and to prevent the development of adrenergically-mediated arrhythmias. These results raised hope of having identified a new pharmacological strategy for the treatment of CPVT: this achievement would represent a major clinical finding. CPVT patients are incompletely protected by therapy with beta blockers, and the implant of an ICD, although life-saving, is certainly associated with reduction of the quality of life in this pediatric population that is more susceptible to device-related complications. The data presented here by Jiang et al raise the concern that, in carriers of mutations of RyR2, the pharmacological approach proposed by Wehrens et al may
not be applicable. To provide a more conclusive answer to the
issue, it is expected that the recently developed knock-in
mouse model17 manifesting arrhythmias identical to those
observed in patients will be a better preclinical setting to test
the hypothesis of Wehrens13 and to assess the role of JTV in
preventing the CPVT arrhythmic phenotype.

**CPVT or ARVC?**

One intriguing aspect of the phenotype linked to \( RYR2 \)
mutations is related to the fact that, whereas most of the
investigators have reported that \( RYR2 \) is the gene for CPVT
(i.e., adrenergically mediated arrhythmias in the normal heart),
one single group has supported the view that \( RYR2 \) is the
gene for right ventricular cardiomyopathy of type 2. Because
right ventricular cardiomyopathy is a disease of adhesion
molecules,18 the identification of one variant of ARVC
caused by mutations in a calcium-controlling protein has raised
substantial interest and scientific debate. Tiso et al19
have proposed that mutations in the amino terminus of the
ryanodine receptor gene cause ARVC2 and that these muta-
tions cause different functional derangements than those
associated with CPVT. Tiso et al20 had in fact suggested that
at least one amino-terminal mutation of \( RYR2 \) reduces the
affinity of the ryanodine receptor for the regulatory protein
FKBP12.6; the same authors reported that CPVT mutations
would instead increase this affinity. The data presented by
Jiang et al6 on the contrary clearly show that, irrespective
of their position on the putative topology of the protein, all
mutations identified in patients with polymorphic and bidi-
rectional VT lead to a similar “gain of function” that
sensitizes the ryanodine receptor to a premature release of
calcium from the intracellular stores. In light of these data it
seems prudent to call for a reappraisal of the diagnosis of
ARVC in patients with \( RYR2 \) mutations and to carefully
consider the hypothesis that the presence of some minor
structural abnormalities of the ventricles may be part of the
phenotype of CPVT that nonetheless remains a condition
clinically and physiologically distinct from ARVC. It should
be noted that a similar debate is surrounding another inherited
arrhythmogenic disease: Brugada Syndrome. The same in-
vestigators, who diagnosed as affected by ARVC2 patients
with \( RYR2 \) mutations, also supported the view that Brugada
Syndrome is a form of right ventricular cardiomyopathy.21
Other investigators, on the contrary, supported the view that
minor structural abnormalities may be present in the heart of
patient with Brugada Syndrome even if they do not meet the
criteria for ARVC.22 This debate is likely to remain a difficult
one to solve, and it will support the need for a reappraisal in
the classification of cardiomyopathy. It will also promote
research to link ion channel dysfunction to the development
of structural abnormalities.

**Do RyR2 Mutations Alter Calcium Handling
at Rest?**

A final controversy that is addressed by Jiang et al6 concerns
the role of \( RYR2 \) mutations in modifying intracellular calcium
control in the absence of adrenergic stimulation. The group
of Chen7 has thus far been the only laboratory reporting
the presence of abnormalities in calcium release from intra-
cellular store in resting conditions (i.e., without caffeine
administration or beta adrenergic stimulation). The issue is
not marginal, as in clinical settings it may have major
relevance to know if abnormalities are constantly present in
the heart of CPVT patients and that they are exacerbated by
adrenergic stimulation, or if the heart of patients affected by
CPVT have normal calcium control at rest which becomes
altered only in response to excitatory stimulation. The fact
that beta-blockers afford only an incomplete protection and
that they seem more effective in slowing ventricular
tachycardia rather than abolishing it would favor the concept
that abnormalities are present already in resting conditions.
Once more the availability of an animal model of CPVT17
may help sort this issue: if the presence of abnormal SOIRC
would be confirmed in vivo, the therapeutic strategy for
CPVT should explore means of preventing SOIRC and
stabilizing RyR2 rather than simply blocking the trigger for
calcium release as currently done with the use of beta
blockers.

**Does Triggered Activity Initiate Arrhythmias
in CPVT?**

The study by Jiang et al6 reinforces the hypothesis that
delayed after-depolarisations (DADs) trigger arrhythmia ini-
tiation in CPVT. The role of triggered activity in vivo is still
debated, and whether DADs originating in the myocardium
may initiate ventricular tachycardia is still unproven. Because
\( RYR2 \) is a very large gene, it has not been possible so far to
transduce adult myocytes with the mutant \( RYR2 \) gene and
assess the consequences of genetic abnormalities present in
CPVT in cardiac cells in vitro. Surrogate experiments, like
the one presented by Jiang et al,6 suggest that mutant \( RYR2 \)
may lead to the development of DADs; however, further
support of this hypothesis in adult myocytes is needed before
the mechanism for arrhythmogenesis in CPVT can be con-
clusively demonstrated.

Another open issue that will have to be addressed in
knock-in animal models of CPVT whenever a role for DADs
is confirmed will be to define whether DADs in vivo
originate in the ventricular myocytes or in the Purkinje fibers.
For several years this debate has remained unsettled, and only
few studies have supported the concept that DADs originat-
ing in the ventricular tissue may propagate the entire heart
and elicit ventricular tachycardia.23,24 If the development of
triggered activity in myocytes isolated from transgenic mod-
els of CPVT will confirm the presence of DADs, it will
become possible to devise mapping studies to identify the site
of origin of the triggered beats and also to explain why the
tachycardia often has its typical bidirectional morphology.17
Such a contribution will extend beyond the pathophysiology
of CPVT and will contribute to shed new light on the role of
triggered activity in the human heart.

**Conclusion**

Although CPVT is an uncommon genetic disorder, it has
become to the study of intracellular calcium control in heart
what the Long QT Syndrome has represented for the under-
standing of the role of voltage-dependent channels in the
study of cardiac excitability. It is thanks to the availability of
clinical models in which severe arrhythmic phenotypes are caused by 1 amino acid replacement that we may gain invaluable and largely unexpected insight in the fine processes controlling the heart rhythm.

Acknowledgments

The data from our laboratory discussed in this article were supported by the following grants: Telethon GP0227Y01 and GP04066, Ricerca Finalizzata 2003/180, FIRB RBNE01XMP4_006, and RBLA035A4X_002, COFIN 2001067817_003.

References


Key Words: sudden death | arrhythmias | genetics
Intracellular Calcium Handling Dysfunction and Arrhythmogenesis: A New Challenge for the Electrophysiologist

Silvia G. Priori and Carlo Napolitano

Circ Res. 2005;97:1077-1079
doi: 10.1161/01.RES.0000194556.41865.e2

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/97/11/1077

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/