N-type Calcium Channel Blockade: A New Approach to Preventing Sudden Cardiac Death?

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Congestive heart failure (CHF) is a major cause of death in the population, and sudden cardiac death is a common terminal event in CHF.\(^1\) CHF patients have elevated resting sympathetic activity, and a simple carbohydrate meal can further raise their sympathetic nerve discharge rates to values characteristic of patients with acute myocardial infarction.\(^2\) Autonomic abnormalities play important roles in sudden cardiac death (SCD) due to ventricular tachyarrhythmias (VTs) resulting from a wide range of cardiac pathologies, including ischemic heart disease, CHF and genetic SCD-syndromes.\(^3\) Classical antiarrhythmic drugs are ineffective in preventing CHF-associated SCD,\(^4\) whereas beta-adrenoceptor antagonists have significant value,\(^1\) emphasizing the importance of the autonomic nervous system in VTs related to CHF.

A wide range of voltage-dependent Ca\(^{2+}\)-channels have been described, including L-type Ca\(^{2+}\)-channels (LTCCs) responsible for cardiac excitation-contraction coupling, T-type Ca\(^{2+}\)-channels (TTCCs) involved in cardiac automaticity, and N-type neuronal Ca\(^{2+}\)-channels (NTCCs).\(^5\) NTCCs, encoded by Cav2.2 (CACNA1B) subunits, are particularly involved in cardiovascular sympathetic regulation.\(^6\)

**Autonomic nervous system intervention in CHF-related SCD**

In this issue of Cardiovascular Research, Yamada et al report the results of a fascinating series of experiments that evaluate the role of NTCCs and their inhibition in a model of CHF-associated SCD.\(^7\) The model involves mice engineered to produce cardiomyocyte-specific overexpression of a dominant-negative (dn) form of neuron-restrictive silencing factor (NRSF), a transcriptional repressor that controls cardiac gene-expression. Cardiac-restricted NRSF-suppression induces a dilated cardiomyopathy with a high incidence of VTs, and sudden premature death presumably
due to arrhythmias. Yamada et al study the effects of a variety of interventions targeting the autonomic nervous system (including genetic NTCC suppression, a drug that inhibits NTCCs (cilnidipine) and beta-adrenoceptor blockade (bisoprolol)) on VTs and mortality.

Interestingly, all of the anti-sympathetic interventions normalized indices of abnormal autonomic function (increased urinary noradrenaline secretion, reduced high- and low-frequency components of heart rate variability), suppressed VTs and reduced mortality. There were some important differences in consequences among the interventions, however. Whereas bisoprolol and cilnidipine had no effect on cardiac function, genetic NTCC-suppression (heterozygous Cav2.2 knockout) normalized left-ventricular dimensions and systolic-function indices, indicating reversal of the dnNRSF-induced cardiomyopathy.

**NTCC-inhibition with cilnidipine as an anti-SCD intervention**

Cilnidipine is a “4th-generation” Ca$_{2+}$-channel blocker. Its Kd for NTCCs is at least an order of magnitude less than that of 9 comparison Ca$_{2+}$-channel blockers, with a higher Kd for LTCC blockade than the other agents, giving it ≥20-fold increased selectivity for NTCCs at a constant test-potential (-80 mV). Studies in well-controlled animal models suggest that the drug decreases sympathetic effects on the heart, with reduced heart rate and contractility. Clinical investigations have provided variable results, some compatible with reduced sympathetic outflow and others not so clear-cut. In the Yamada study, cilnidipine produced dramatic protection against autonomic-tone abnormalities, VTs and death in the dnNRSF mouse CHF-model. If the drug could be shown to have similar effects in human CHF patients, it could be a very valuable component of SCD-prevention in such individuals. At the very least, consideration should be
given to a controlled clinical trial comparing the effects of cilnidipine to those of a more standard dihydropiridine drug like amlodipine on indices of autonomic function and ventricular ectopy in CHF patients. Positive results would motivate a larger-scale study on ventricular arrhythmias and potentially-lethal arrhythmias, perhaps beginning with a trial in high-risk subjects with implanted defibrillators.

Limitations of the study

While the Yamada study is interesting and uses several elegant models, the work has a number of significant limitations. First, there are important discrepancies between the effects of pharmacological autonomic inhibition and genetic NTCC inhibition. Cilnidipine- and bisoprolol-treated mice showed reduced arrhythmias and autonomic abnormalities, but the CHF-phenotype remained unabated; whereas the CACNA1B heterozygous knockout mice demonstrated reversal of autonomic, arrhythmic and hemodynamic abnormalities. The authors note the discrepancy for cilnidipine and suggest that it may be due to adverse effects of the drug’s LTCC blocking action on cardiac function, to insufficient cilnidipine doses or to a lack of central nervous system penetration of cilnidipine. The authors do not comment on the discrepancy between the benefits of genetic NTCC inhibition against CHF and the lack of such benefit with bisoprolol.

Another internal inconsistency relates to the mortality rates of dnNRSF-mice in the various experimental series. Bisoprolol-treated dnNRSF-mice had a mortality-rate of about 20% at 90 days. This was significantly lower than the mortality-rate of the control dnNRSF-group, >60% at 90 days (Figure 3N). However, the mortality of the latter group was unusually high, compared to virtually no mortality at 90 days (13 weeks) in the dnNRSF control group for
the cilnidipine studies (Figure 1E) and about a 25% death-rate for the dnNRSF/CACNA1B+/+
mice in the genetic NTCC-suppression study (Figure 6A). With a more typical control-group
mortality, there would have been no significant difference with bisoprolol-therapy; this
discrepancy requires resolution.

Another concern relates to the functional selectivity of cilnidipine in vivo. The selectivity
reported for NTCCs based on in vitro studies is indeed impressive. However, the Kd values
were obtained in voltage-clamp studies at -80 mV. Ca\textsuperscript{2+}-channel blocking action is critically
dependent on the frequency and voltage profile of action-potential history; therefore, in vivo
blocking effects are poorly predicted by in vitro blocking potencies under controlled conditions.
The in vivo effects of “selective” Ca\textsuperscript{2+}-channel suppressing drugs may thus differ greatly from in
vitro predictions or from the effects of truly specific genetic suppression. For example, quite a
number of studies have shown protective effects of the TTCC-selective blocker mibefradil on
ventricular remodeling post-myocardial infarction; however, TTCC knockout mice show worse
ventricular function impairment and arrhythmogenesis post-myocardial infarction than wild-type
mice.

A final issue that remains to be resolved is the mechanism of death in dnNRSF-mice.
While the deaths appear to be sudden (mice found dead in their cage) and the mice clearly are
prone to VTs, it remains to be clarified whether VTs are truly the cause of their premature death.
Mice are resistant to ventricular fibrillation, and even in humans Holter monitor-recorded SCD is
not infrequently caused by bradyarrhythmias. The authors do provide one example of a fatal VT
in a nitrendipine-treated dnNRSF-mouse (Supplemental Figure 2), but more detailed information
on cardiac rhythms recorded by ambulatory monitoring at the time of death would be of interest.
Conclusions

The study by Yamada et al provides plenty of food for thought. The important role of autonomic neural activity in cardiac arrhythmias, including VTs causing SCD, has long been recognized. The notion of suppressing arrhythmia-risk by interfering with autonomic neural function through the manipulation of neural ion-channels has not, to my knowledge, been proposed before. The ability of cilnidipine to fulfill this role certainly merits further examination. At worst, this will be another potentially-interesting but failed new antiarrhythmic drug approach. At best, it will introduce a new and valuable class of antiarrhythmic drug to a class of agents badly in need of rejuvenation.

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References


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