Letter by Herring and Paterson Regarding Article, “Common NOS1AP Variants Are Associated With a Prolonged QTc Interval in the Rotterdam Study”

To the Editor:

We read with interest the recent study by Aarnoudse et al,1 which provides convincing evidence for an association between 2 common single-nucleotide polymorphisms in the neuronal nitric oxide synthase (nNOS/NOS-1) activator protein gene and prolongation of the heart rate–adjusted QT interval on ECGs from subjects in the Rotterdam study. This study builds on the findings of a recent genome-wide association study showing a similar link.2 These results are both surprising and clinically relevant, as it is not immediately obvious how NOS-I may influence the QT interval and Long-QT syndrome, which is strongly associated with sudden cardiac death. Is it possible that the myocyte alone is not the defective site for NOS-1 and Long-QT syndrome interactions?

In the same issue of Circulation, the review by Samuels3 points out that many cases of sudden cardiac death are precipitated by the autonomic nervous system. Increased sympathetic drive to the heart increases myocardial oxygen demand, reduces coronary perfusion time, and can cause calcium overload in ventricular myocytes, which can be proarrhythmic. Patients with certain forms of Long-QT syndrome and Brugada syndrome are also particularly susceptible to adrenergic-induced arrhythmia. It is interesting, therefore, to note a body of physiological evidence that has convincingly demonstrated a role for nNOS/NOS-1, both in the autonomic control of cardiac function and in cardiac contraction and calcium handling. Defective nNOS-cGMP activity in the sympathetic innervation of the heart leads to increased norepinephrine release and tachycardia,4 while the ability of the vagus nerve to release acetylcholine and counteract these effects is impaired.5 Postsynaptically, defective myocyte nNOS activity leads to increased contractility, prolonged calcium transients, and reduced L-type calcium current inactivation,6 which may be reflected in prolongation of the action potential duration. It is not, perhaps, as surprising as it may first seem, therefore, that defective nNOS/NOS-1 activity may increase corrected QT interval, an ECG surrogate for action potential duration, and also predispose to catecholamine-induced sudden cardiac death through defective cardiac neurotransmission to amplify the dysfunctional electrical phenotype. It remains to be demonstrated experimentally whether the single nucleotide polymorphisms in NOS-1-AP described by Aarnoudse et al can directly alter cardiac norepinephrine release and ventricular action potential duration.

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Disclosures

None.

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References

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