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Genetic susceptibility to atrial fibrillation (AF) in patients with congestive heart failure

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To the Editor:

We read with great interest the article on the genetic susceptibility to atrial fibrillation (AF) in patients with congestive heart failure by Bedi et al[1] in the July 2006 issue of *Heart Rhythm.*

The authors examined the role of *angiotensin-converting enzyme (ACE)* I/D and *endothelial nitric oxide synthase (eNOS)* polymorphisms in predisposing to AF and speculate, in particular, on the role of the *eNOS* 894 G wild-type allele in affecting this predisposition.

We have a comment on the emphasis on the role of the *eNOS* G894T polymorphism in predisposing to AF. In reading carefully the results in both the abstract and the text, we noticed a conflictual finding. In the abstract, a significant association between *eNOS* 894 T/T genotype (odds ratio 3.2) and AF is reported. On the contrary, in the Results section, the same odds ratio is referred to the homozygosity for the *eNOS* 894 G wild-type allele. Thus, the role of the 894 G/G genotype as a predisposing factor to AF is reported in the Results section, whereas the role of the eNOS T rare allele as a predisposing factor to the disease is discussed. These divergent data confuse the reading and the interpretation of results.

Studies in the literature reported that the 894 T rare allele is associated with reduced basal nitric oxide production,[2] even if this functional role still is a matter of debate.[3] In particular, experimental data demonstrated that nitric oxide enhances cardiac vagal activity and participates in the inhibition of sympathetic activity.[4] Moreover, eNOS regulates the L-type calcium channel and modulates myocyte contractility. The L-type calcium channel is essential for normal sinus function, and nitric oxide, by stimulating the formation of cGMP, which affects this channel, might play a role in suppressing arrhythmias through a cGMP-mediated pathway. A decrease in nitric oxide levels, related to the presence of the *eNOS* 894 T variant, might contribute to modulation of AF through an increase in L-type calcium current. Normal availability of nitric oxide, related to the presence of *eNOS* 894 G wild-type allele, could contribute to maintenance of normal sinus function.

Finally, the authors state that their findings are at variance with those from our group.[5] In actuality, the results are completely in agreement with ours, demonstrating no association between the *eNOS* 894 T/T genotype and predisposition to AF.

In consideration of our comment, we do not believe that the conclusions stated by Bedi et al (i.e., that the *eNOS* 894 T/T genotype is significantly associated with AF) can be drawn from this study.

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To The Editor—Response:

We appreciate the letter from Dr. Fatini regarding the detection of an error in our recent publication in *Heart Rhythm.*[1] The error is typographical in nature and is located in the abstract, in which T/T (characterizing homozygous thymine replacement of guanine at position 894 of exonic segment 7 of the eNOS gene2) appears rather than that which we had intended, G/G (characterizing homozygous guanine in this position). In the text of the article, the data presented and the subsequent discussion are consistent in associating the G allele (in particular the G/G genotype), not the T allele, with the presence of atrial fibrillation (AF). As we intimate in the discussion, this finding was counterintuitive based on prior reports (cited), which suggest that the G allele should not be associated with an increased propensity to AF. Although we could have deduced a protective (anti-AF) effect for the T allele from our data, we decided to conclude that although there appears to be a relationship between polymorphism at position 894 and AF, its nature remains obscure.

We are embarrassed by the error and sincerely apologize to the readership for any confusion arising from it.[2]

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