Mechanism of Sinus Bradycardia in Carriers of the A414G Mutation in the *HCN4* Gene

Arie O. Verkerk, Ronald Wilders*

Amsterdam University Medical Centers, location Academic Medical Center, University of Amsterdam
Amsterdam, The Netherlands

Background: Heterozygous carriers of the A414G mutation in the *HCN4* gene, which encodes the HCN4 protein, show moderate to severe sinus bradycardia. Tetramers of HCN4 subunits constitute the ion channels that conduct the cardiac hyperpolarization-activated 'funny current' (I_f), also known as the 'pacemaker current', which plays an important modulating role in the pacemaker activity of sinus node cells.

Aim: We assessed the mechanism by which the A414G mutation in *HCN4* causes sinus bradycardia in the mutation carriers.

Methods: We carried out voltage clamp experiments on wild-type and heterozygous mutant HCN4 channels expressed in Chinese hamster ovary (CHO) cells at physiological temperature, using the amphothericin-perforated patch-clamp technique. We incorporated the experimentally observed mutation-induced changes in I_f into the Fabbri-Severi model of a single human sinus node cell.

Results: The half-maximal activation voltage of the heterozygous mutant HCN4 current was 24 mV more negative than that of the wild-type current ($P<0.05$). The voltage dependence of the (de)activation time constant showed a similar shift, whereas no significant differences were observed in the slope factor of the activation curve, in the fully-activated current density, and in the reversal potential. In the Fabbri-Severi model, the −24 mV shift increased the cycle length from 813 to 1002 ms, corresponding with a 19% decrease in beating rate from 74 to 60 beats/min. Hyperpolarizing atrial load, simulated by incorporating an outward current with a conductance of 0.4–0.8 pS/pF and a reversal potential of −80 mV into the model sinus node cell, resulted in a 23–38% decrease in beating rate, indicating that the bradycardia was even more prominent in the presence of sinus node–atrial interactions.

Conclusion: We conclude that the experimentally identified mutation-induced changes in I_f can explain the clinically observed sinus bradycardia in carriers of the A414G mutation in the *HCN4* gene.