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Autoimmune channelopathies: questions remain

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We read with interest the Review by Lazzerini *et al.* (Autoimmune channelopathies as a novel mechanism in cardiac arrhythmias. *Nat. Rev. Cardiol.* http://dx.doi.org/10.1038/nrcardio.2017.61; 2017)[1]. In their manuscript, Lazzerini *et al.* provide a comprehensive overview of the current understanding of autoimmune-mediated cardiac arrhythmias. However, several aspects need to be clarified. Special focus is given to antibodies targeting cardiac ion channels, and the authors adopt the term "autoimmune cardiac channelopathies" (REF. 1), a designation first introduced by Li *et al.* in 2013 to define this disease entity[2].

In Figures 1 and 3 and their respective legends, Lazzerini *et al.* illustrate and state that autoantibodies against K^+ voltage-gated channel subfamily KQT member 1 (KCNQ1) "enhance the slow component of the delayed rectifier K^+ current (I_{Ks})" (REF. 1). Furthermore, they claim that the anti-KCNQ1 autoantibodies "exerted an agonist-like electrophysiological effect on the KCNQ1 K^+ channel". Our concern is that anti-KCNQ1 autoantibodies *per se* have not been proven to be the mediators of the increase in I_{Ks}. Previous data have shown that patient serum that contains anti-KCNQ1 autoantibodies increases I_{Ks} current density in human embryonic kidney (HEK) 293 cells expressing KCNQ1 and K^+ voltage-gated channel subfamily E member 1 (KCNE1)[2], and that cardiac action potentials are shortened as a result of an increase in I_{Ks} in cardiomyocytes isolated from KCNQ1-immunized rabbits[3]. However, to date, no studies have been performed to establish a direct link between anti-KCNQ1 autoantibodies and an increase in I_{Ks}.

Finally, Lazzerini *et al.* state that "anti-$Na_v1.5$ autoantibodies inhibiting I_{Na} were detected" (REF. 1). This claim constitutes an overstatement of the current literature, most probably arising from a misconception. Although a causative relationship between circulating anti-$Na_v1.5$ autoantibodies and the observed electrophysiological effects is likely, such a relationship has not been demonstrated[4]. From this perspective, we believe that Figures 1 and 2 and their respective legends illustrating anti-$Na_v1.5$ antibody-mediated I_{Na} inhibition are misleading and overemphasize the current state of knowledge in this field.

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Competing interests statement
The authors declare no competing interests.