Killing the primary heart pacemaker

Matteo E. Mangoni*

CNRS UMR 5203, Inserm U661, Université de Montpellier 1 et 2, Institut de Génomique Fonctionnelle, Département de Physiologie, 34396 Montpellier Cedex 5, France

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This editorial refers to ‘Insights into sick sinus syndrome from an inducible mouse model’ by S. Herrmann et al., pp. 38–48, this issue.

The most aggressive reviewer I have ever experienced is my barber. When I first came into his shop, conviviality naturally drove the conversation towards my job. Once asked about my research field I proudly replied: ‘I work on the mechanisms underlying the genesis and regulation of the heartbeat’. He looked surprised that such an important and apparently self-evident physiological function was still enveloped by some kind of uncertainty. ‘I am amazed that we are still paying researchers with public money to work on such an obvious thing’. To demonstrate that we still deserve our salaries, I explained that, while potentially counterintuitive, cardiac pacemaking is a complex function and several aspects of how heart rate is determined at the cellular and tissue level are not completely understood. Herrmann et al.1 will further fuel the current debate on cardiac automaticity (and accessibly my personal debate with the barber).

Heart pacemaker activity is generated in the sino-atrial node (SAN) by a relatively small population of specialized automatic myocytes. Beside the SAN, the atrioventricular node (AVN) and the Purkinje fibres network also contain spontaneously active myocytes. However, since the SAN possesses the highest intrinsic rate of pacing, it determines the heart rate under physiological conditions and constitutes the ‘primary’ cardiac rhythmogenic centre.2

Congenital or acquired SAN dysfunctions are responsible for the so-called ‘sick-sinus syndrome’ (SSS). This disease is characterized by bradycardia, often associated with atrial fibrillation and atrial flutter.3 Dysfunction of atrioventricular conduction can also be observed in SSS patients. Roughly, we can distinguish between three main aetiologies of SSS. Mutations in ion channels involved in pacemaking activity can underlie congenital SSS.4 Medication intake can also induce secondary SSS, probably due to SAN remodelling or intoxication. In the ageing SAN, SSS is due to progressive fibrotic degeneration of SAN tissue accompanied by the loss of pacemaker cells. Irrespective of the underlying causes, SSS accounts for a substantial fraction of electronic pacemaker implantations in Europe and USA. Even if modern pacemaker devices are very efficient, it would be highly desirable to develop alternative (or complementary) therapeutic strategies for SSS. In this respect, several research groups now focus on the creation of ‘biological’ pacemakers based on implantation of pacemaker myocytes derived from stem cells or on gene transfer of ion channels involved in pacemaking.5 During the past few years, animal models of complete AV block have been created for testing biological pacemakers,5 but until now a mouse model of age-related SSS has been lacking.

Herrmann et al.1 used spatial and time-controlled expression of the diphtheria toxin (DTA) to induce selective cell death of SAN and AVN myocytes. Expression of DTA was obtained by crossing two genetically engineered mouse lines, the ROSA-eGFP-DTA and HCN4-KiT-Cre. The ROSA-eGFP-DTA line allows DTA expression upon recombination of a floxed stop site. In HCN4-KiT-Cre (HCN4KIT) mice, the Cre recombinase is knocked inside the mouse hcn4 gene. In a previous manuscript, the authors showed that Cre expression allows specific recombination of floxed genes in SAN and AVN, while sparing gene activity in the atrium, ventricle, and Purkinje fibre network.6 The SAN of double-transgenic DTA/KiT mice show progressive loss of pacemaker myocytes after tamoxifen injection, evidence that is well documented by histological analysis of SAN tissue. Terminally, the SAN of DTA/KiT mice show destruc-
tive fibrosis of the SAN region, absence of myocytes inside the SAN, and no detectable expression of the HCN4 protein (used as a specific marker of pacemaker myocytes).

DTA/KiT mice develop phenotype characteristics comparable with SSS in humans. Electrocardiograms (ECGs) of DTA/KiT mice show progressive bradycardia that reached a heart rate reduction of ~40%. DTA/KiT mice also show a depressed degree of β-adrenergic regulation of heart rate, a phenomenon known as chronotropic incompetence in human SSS subjects. The authors also describe supraventricular arrhythmias typical of tachy–brady syndromes registered in SSS patients. In particular, sinus pauses and atrial fibrillation were consistently observed in DTA/KiT mice. The authors report that AV conduction is severely impaired. Indeed, most DTA/KiT mice progressively developed complete atrioventricular block and dissociated atrial and ventricular rhythms. Intracardiac ECGs are indicative of a supra-Hisian AVN block site and indicate intact inra-ventricular conduction. This last observation is consistent with the absence of significant expression of Cre in Purkinje fibres of HCN4KIT mice.6 In conclusion, DTA/KiT mice appear to be a good model of human SSS. Future experiments to evaluate the performance of biological pacemakers can take advantage of the characteristics of DTA/KiT mice of Herrmann et al.

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* Corresponding author. Tel: +33 04 67 54 24 32. Email: matteo.mangoni@igf.cnrs.fr

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It could be expected that a complete loss of automatic SAN myocytes in DTA/KiT mice would result in abolition of atrial pacemaker activity. Upon SAN failure, automatic myocytes of the AVN or that of the Purkinje fibres can effectively drive the heartbeat. Even if the authors do not specifically analyse AVN pacemaking in DTA/KiT mice, it is likely that DTA expression also induce the loss of AVN pacemaker cells. The observation that SAN destruction only moderately increased mortality indicates that ventricular pacemakers are viable. On the other hand, in spite of an apparently complete loss of SAN myocytes atrial pacemaker activity is still recorded as P-waves in ECGs of DTA/KiT mice. The site of origin of atrial pacemaker activity in DTA/KiT mice is at present unknown. Pacemaker activity of the so-called atrial extension of conduction system could be responsible for atrial automaticity of DTA/KiT mice. However, this tissue expresses a significant amount of HCN4 protein and it may thus be subject to cell death due to DTA expression, which has very high cellular toxicity. The left atrium also contains automatic cells around the pulmonary veins. These cells can trigger atrial arrhythmias, but at present it is not known whether these cell populations can also sustain co-ordinated atrial rhythms in mice. The authors suggest that the recently described paranodal area in human SAN tissue could take over the SAN after induction of DTA expression. At present, it is not known whether such a structure is present in the mouse heart. It is also important to note that the responsiveness of heart rate to pharmacological interventions activating the parasympathetic nervous system is preserved in DTA/KiT mice. Consequently, the still unidentified actor controlling atrial rate would not only be endowed with a relatively high degree of automaticity, but could also allow proper parasympathetic regulation of atrial rate.

In conclusion, Hermann et al. open intriguing perspectives in defining how heart rate can be generated after loss of SAN cells and is a straight example of the complexity of the heartbeat regulation. Now, armed with this new powerful argument to justify my salary, I will face my barber and his usual nasty question: ‘Sir, any progress in pacemaker research this month?’

References