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# Desmosomes and sino-atrial dysfunction

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**This editorial refers to ‘Desmosomal junctions are necessary for adult sinus node function’ by V. Mezzano et al., pp. 274–286.**

Heart automaticity is a fundamental physiological function, yet it remains still incompletely understood, probably because of its intrinsic complexity at both cellular and tissue levels. A population of specialized myocytes called ‘pacemaker’ cells generates cardiac automaticity under physiological conditions.<sup>1</sup> These cells are the predominant cellular component of the sino-atrial node (SAN) and control heart rate in everyday life. Dysfunction in the generation of the SAN impulse leads to bradycardia, which in severe cases brings invalidating symptoms and often requires the implant of an electronic pacemaker. Bradycardia and atrioventricular block are responsible for about half of the total pacemaker implantations worldwide.<sup>2</sup> The SAN is a highly heterogeneous structure.<sup>3</sup> Beside pacemaker cells, other cell types, including atrial myocytes, fibroblasts and melanocytes, populate the SAN. In addition, the population of pacemaker cells *per se* shows heterogeneity, with different cell sizes and morphologies. The atrial myocardium is a relatively big and dense tridimensional structure, exerting a potentially overwhelming electrotonic charge on the SAN. A major issue in SAN physiology is thus to understand how this small and thin pacemaker region can generate and conduct the cardiac impulse to control atrial rate without being electrotonically suppressed by the atria themselves. In the past, structural, electrophysiological and modelling works have been dedicated to the definition of the properties of the SAN in relation to its interactions with the right atrium.<sup>4</sup> While these studies showed some species-specific structural differences in the SAN-atrium tissular organization, there is a general agreement that a relatively reduced degree of electrical coupling between pacemaker cells within the SAN and between the SAN and the atrium is a key factor to allow the pacemaker region to generate and conduct the cardiac impulse. Consequently, the identification and the functional study of the structural proteins involved in the electrical coupling and adhesion between pacemaker cells are of primary importance to understand SAN-atrium impulse conduction and SAN dysfunction. In relation to electrical coupling, SAN cells predominantly express the low conductance connexin (Cx)45 instead of the high conductance atrial Cx43 to ensure a relatively reduced degree of electrical coupling between pacemaker cells.<sup>5</sup> However, beside Cxs, pacemaker cells also express other cell adhesion structures including desmosomes.<sup>6</sup> The functional role of

desmosomes in SAN physiology and impulse generation has not been studied in detail.

In this issue of *Cardiovascular Research*, Mezzano and co-workers<sup>7</sup> describe the effects of conditional cardiac conduction system-specific ablation of the central desmosome protein desmoplakin (DSP) on pacemaker activity. The study also reports the case of a young patient presenting reduced mean heart rate and presenting frequent SAN pauses. This patient carries a heterozygous splice site mutation on the DSP gene (c273 + 5 G > A, IVS2 + 5 G > A), which is predicted to cause abnormal mRNA splicing. To demonstrate the relevance of the DSP protein in SAN function, Mezzano *et al.* employ mice carrying a floxed DSP allele crossed with transgenic mice in which the recombinase Cre-ERT2 construct has been knocked in the gene coding for the predominant isoform of the hyperpolarization-activated ‘funny’ f-(HCN) channel *Hcn4* (*Hcn4*-Cre-ERT2). This transgenic line allows selective expression of Cre recombinase in the SAN and the cardiac conduction system (atrioventricular node and Purkinje fibres).<sup>7</sup> DSP is thus inactivated in SAN cells but is spared in the atria and ventricles. The heart rate of DSP-ablated mice (DSP cskO) is characterized by SAN pauses, a hallmark of mild pacemaker dysfunction. These sporadic but frequent SAN pauses appear to increase the heart rate variability of DSP cskO mice without reducing the average heart rate. This is a marked difference between the heart rate of DSP cskO mice and that of the patient carrying the DSP mutation, who presents with clear bradycardia (30–40 bpm). The increased severity of the human vs. the mouse phenotype may be due to the different heart rate regulation in rodents. Since spontaneously beating SAN-atrial preparations of DSP cskO mice present a similar dispersion in the interbeat interval as *in vivo* hearts, it is unlikely that a dysfunction of the autonomic nervous system underlies the phenotype. However, on the basis of the experiments shown, it cannot be excluded that the input of the autonomic nervous system has changed in DSP cskO mice to compensate for the loss of the cell adhesion protein. Under the activation of the autonomic nervous system and/or under the action of several other intrinsic factors, the leading pacemaker site of the SAN can shift.<sup>3</sup> In humans, pacemaker shift underlies the variability of the P wave morphology. However, in the absence of the autonomic nervous system, pacemaker shift may be considered a sign of SAN dysfunction. Mezzano *et al.* have performed clever experiments of optical mapping of the time course of the membrane voltage during pacemaker activity of isolated SAN-atrial preparations. They report permanent (wandering) pacemaker shift in

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DSP cskO SAN preparations in comparison with wild-type preparations. Beside SAN pauses, the phenomenon of wandering pacemaker may explain in part the increased heart rate variability in knockout mice. An interesting finding by Mezzano *et al.* is that DSP ablation induces strong down-regulation of Cx45 expression and localization at the plasma membrane. It is unclear whether Cx45 down-regulation is due to an altered protein stability or protein targeting to the cell membrane, but given that Cx45 is the major Cx isoform in the SAN it is possible that SAN pauses and wandering pacemaker are induced by an excessive reduction in coupling between SAN pacemaker cells. In addition, the authors cannot exclude that DSP ablation also causes SAN exit block via Cx45 down-regulation, which would still cause SAN pauses.

In conclusion, the work by Mezzano *et al.* constitutes the first direct evidence of the functional impact of desmosomes loss of function on pacemaker activity. It will be interesting to address whether SAN dysfunction is the result of impairment of cell adhesion or Cx45 down-regulation. In addition, while Mezzano *et al.* tested only the f-HCN4 channel as potentially being affected by DSP knockout other membrane ion channels have been shown in the past to play a major role in pacemaking and could be involved in the phenotype. It will also be interesting to study whether desmosomes are involved in SAN ageing and if they can contribute to dysfunction in heart automaticity in the elder.

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