

NaV1.8: a novel contributor to cardiac arrhythmogenesis in heart failure

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This editorial refers to ‘Differential regulation of sodium channels as a novel proarrhythmic mechanism in the human failing heart’ by N. Dybkova et al., pp. 1728–1737.

NaV1.8 is a tetrodotoxin-resistant Na⁺ channel with a slow inactivation kinetics first identified in dorsal root ganglion sensory neurons with unmyelinated C-fibres (pain neurons).^{1,2} A-803467, a Na⁺ channel blocker with >100-fold higher selectivity for NaV1.8 over other neuronal and cardiac channels, was developed as an analgesic drug.³ The selective antinociceptive effect of A-803467 was supported by the localized expression of NaV1.8 in pain neurons. More recently however, genome-wide association studies showed that common variations of SCN10A (NaV1.8 gene) modulated cardiac electrical function, including PR interval and QRS duration.^{4,5} Following these observations, functional NaV1.8 channels were identified both in cardiac nerves⁶ and cardiac myocytes.⁷ Cardiomyocyte NaV1.8 channels are located near gap junctions⁷ and are crucial modulators of electrical conduction. SCN10A variants are associated with cases of Brugada syndrome⁸ and early-onset atrial fibrillation.⁹ Moreover, the slowly-inactivating NaV1.8 appears to contribute to cardiac late Na⁺ current (I_{NaL}). Consistently, A-803467 reduced I_{NaL} and shortened action potentials (APs) in mouse and rabbit cardiomyocytes.¹⁰ Increased I_{NaL} is a central determinant of contractile dysfunction and arrhythmogenesis in human heart failure (HF)¹¹ and cardiac hypertrophy,¹² as confirmed by the beneficial effects of the I_{NaL} -inhibitor ranolazine in diseased human myocardium.^{11,12} According to current literature, increased I_{NaL} in human HF and hypertrophy is caused by post-transcriptional modifications (phosphorylation and oxidation) of cardiac NaV1.5 channel proteins¹² that delay current inactivation. Do changes of cardiac NaV1.8 current contribute to the increase of I_{NaL} in HF and hypertrophy? The work by Dybkova et al.¹³ answers this question. The authors studied fresh left ventricular samples from 25 explanted hearts of patients with terminal HF. The most striking result reported by the authors is the observed two times increase of NaV1.8 protein in HF samples when compared with non-failing donor hearts, caused by a comparable elevation of SCN10A mRNA, suggesting up-regulation at the level of gene expression. The expression of several ion channels changes as a part of the hypertrophic remodelling programme that precedes HF,¹² featuring reduction of potassium channels and increase of funny (I_f) channels (Figure 1). These changes are often linked with altered expression or function of transcriptional modulators such

as miRNAs¹² or histone deacetylases, yet the causes of SCN10A increase in HF remain to be determined. All-in-all, ion current changes in HF determine a marked prolongation of APs, consistently observed in cardiomyocytes from the hearts of HF patients.¹³ The enhanced I_{NaL} , by increasing the amplitude of net depolarizing current during the AP plateau, contribute to prolong repolarization in conjunction with the reduction of delayed-rectifier K⁺ currents. This work shows that increased NaV1.8 current due to transcriptional up-regulation contributed to enhance I_{NaL} and thus to prolong APs in human HF. Indeed, the selective NaV1.8 inhibitors (A-803467 and PF-01247324), used at submicromolar concentrations, reduced the integral of I_{NaL} current (estimating the total inflow of Na⁺) by 50–60% in human HF cardiomyocytes.¹³ Expectedly, the reduced I_{NaL} was responsible for a significant shortening of APs that was more evident at slower stimulation rates, as previously observed with ranolazine.¹² The reduced inflow of Na⁺ following I_{NaL} inhibition is expected to cause a decrease of intracellular Na⁺ concentration that in turn increases the forward activity of the Na⁺/Ca²⁺ exchanger, ultimately determining increased sarcolemmal Ca²⁺ outflow and lower diastolic cytosolic Ca²⁺ concentrations [Ca²⁺]_i.¹² As [Ca²⁺]_i is the main determinant of the open probability of cardiac ryanodine receptors (RyR2) during diastole, the reduction of [Ca²⁺]_i following I_{NaL} inhibition is expected to reduce the rate of diastolic Ca²⁺ sparks and Ca²⁺ waves, ultimately reducing the likelihood of diastolic depolarization (delayed after depolarizations, DADs) and spontaneous premature APs¹² (Figure 1). Though the authors did not measure whether NaV1.8 inhibitors caused a reduction of diastolic intracellular Na⁺ or Ca²⁺, they observed that A-803467 and PF-01247324 reduced Ca²⁺ spark frequency and cellular arrhythmic events in human HF cardiomyocytes.¹³ The authors put a great effort into confirming the selectivity of A-803467 and PF-01247324 by using ventricular cardiomyocytes from a transgenic mouse model completely lacking NaV1.8 channels due to SCN10A gene knockout. While both drugs inhibited I_{NaL} and shortened APs in wild-type, they did not exert any effects in mice lacking NaV1.8. Interestingly, the authors analysed the contribution of NaV1.8 and NaV1.5 to I_{NaL} by using low-dose tetrodotoxin, which inhibits only NaV1.5-mediated I_{NaL} but not the resistant NaV1.8 channel. In the healthy mouse, NaV1.5 accounts for 2/3 of I_{NaL} while NaV1.8 for the remaining one-third.¹³ The relative contribution of NaV1.8 and NaV1.5 to I_{NaL} in human cardiomyocytes remains to be determined. The work by Dybkova et al.¹³ has some limitations that stem from the difficulty of conducting studies in human

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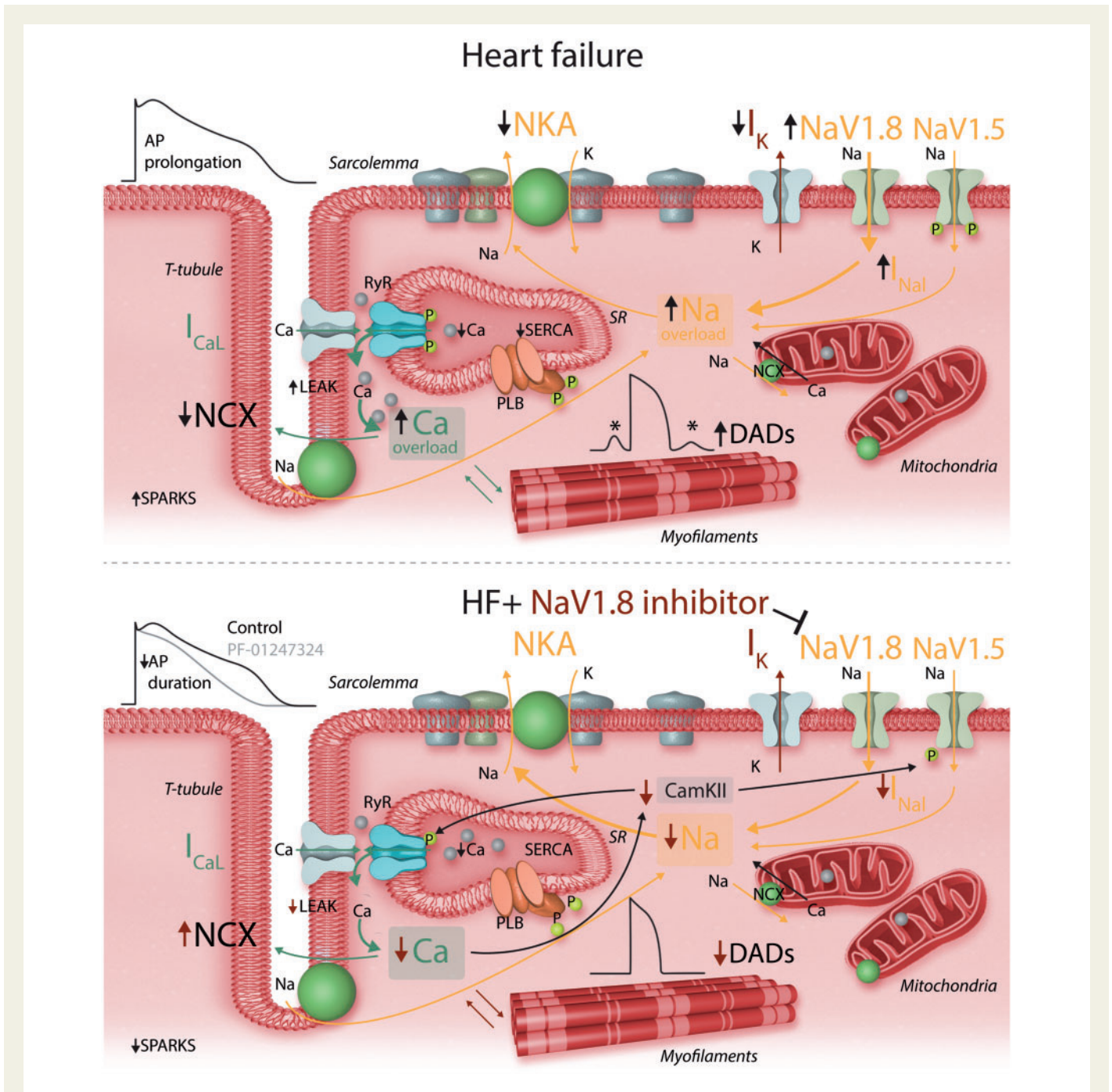


Figure 1 NaV1.8 in heart failure. Cartoon depicting the molecular basis of cardiomyocyte electrical remodelling in HF and the role of NaV1.8. Top panel shows lower K currents and increased I_{NaL} cause AP prolongation in HF myocytes. Increased expression of NaV1.8 channels contribute to elevate I_{NaL} , that in turn causes Na^+ overload; increased cytosolic $[Na^+]$ impairs Na^+/Ca^{2+} exchanger (NCX) function and contribute to increase diastolic $[Ca^{2+}]$ that in turn increases the rate of Ca^{2+} sparks and the risk of DADs and arrhythmias. Lower panel shows effects of NaV1.8 inhibition. NaV1.8 block reduces I_{NaL} , thus lowering cytosolic $[Na^+]$; the reduced Na^+ normalizes NCX function and contribute to reduce diastolic $[Ca^{2+}]$. The latter causes a reduction of the rate of Ca^{2+} sparks and leak through the RyR, thereby reducing DADs and arrhythmic events. Some of these effects might be mediated by the reduced activity of calmodulin kinase II (CaMKII). The traces have been reproduced with permission from Refs.^{12,13}

samples. Measurements on human cells were conducted by pre-incubating them with the drug or the vehicle, thus precluding coupled measurements; this approach, however, was needed to avoid inconsistent results due to degradation of myocytes upon repeated measurements, and the effects of the drugs were ascertained by comparing data

from the two groups of myocytes (drug and vehicle treated) with solid multi-level hierarchical statistical techniques.¹² Additionally, no measurements were performed in non-failing non-hypertrophic human myocytes, which were previously used to ascertain the selectivity of other I_{NaL} inhibitors.^{12,14} Future studies in non-failing human samples using

NaV1.8 inhibitors will help to define the physiological role of NaV1.8 current in the human ventricle. The work lacks the analysis of the effects of NaV1.8 inhibitors on steady-state Ca^{2+} -transients and contractile function: following I_{NaL} inhibition, we expect shortening of Ca^{2+} -transient decay, accelerated relaxation and lower diastolic tension at high pacing rates.^{11,12,14} As a follow-up to this work, it would be useful to assess whether the increased expression of NaV1.8 is present in cardiac samples from patients with different cardiac diseases, such as in hypertrophic cardiomyopathy^{12,14} or atrial fibrillation, where ranolazine shows a remarkable antiarrhythmic profile. A direct comparison of selective NaV1.8 blockers with ranolazine in the same disease model would ascertain the possible therapeutic implications of NaV1.8 inhibitors. Interestingly, ranolazine was shown to reduce both NaV1.5 and NaV1.8-dependent I_{NaL} .¹⁵ Finally, *in vivo* test using the orally-available PF-01247324 should be performed in relevant animal models of HF.

Conflict of interest: none declared.

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