RESEARCH LETTER

Increased susceptibility to ventricular arrhythmia at low–normal and moderately low levels of extracellular potassium in catecholaminergic polymorphic ventricular tachycardia

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Recent studies have shown that the predominant arrhythmogenic mechanism in hypokalemia is through inhibition of cardiac Na^+/K^+ ATPase [Figure 1A(1)]. This results in accumulation of intracellular Na^+, which reduces the concentration gradient across the sodium/calcium exchanger [Figure 1A(2)]. The resultant Ca^{2+} buildup activates CaMKII, an enzyme that facilitates further Na^+ and Ca^{2+} accumulation by activating cardiac ryanodine receptors (RyR2), L-type Ca^{2+} channels, phospholamban, and the late sodium current [Figure 1A(3)]. Intracellular Ca^{2+} is loaded into the sarcoplasmic reticulum (SR) [Figure 1A(4)], causing inappropriate diastolic release of Ca^{2+} via RyR2 [Figure 1A(5)], triggering arrhythmia.[1] Catecholaminergic polymorphic ventricular tachycardia (CPVT) is a life-threatening inherited arrhythmia syndrome, most commonly caused by genetic variants in RyR2. These variants cause enhanced intracellular Ca^{2+} leak from the SR, predisposing patients to arrhythmia, particularly during adrenergic stimulation.

Given their genetic predisposition to intracellular Ca^{2+} loading, CPVT patients are likely to be more susceptible to ventricular arrhythmia when exposed to additional Ca^{2+} loading from hypokalemia compared to healthy people. Although break-through arrhythmias in CPVT are most associated with adrenergic stimulation, arrhythmias can be triggered by hypokalemia in treated CPVT. A 17-year-old girl with CPVT controlled with 40 mg of nadolol twice daily and 150 mg flecainide twice daily presented to the emergency department with a cardiac arrest. She carried a class IV, likely pathogenic, mutation in RyR2 (F4851L). The most likely cardiac arrest trigger was determined to be a serum potassium level of 3.1 mmol/L on arrival. She was compliant with her medication, with infrequent ectopy noted on her last exercise test. Serial QTc measurements pre- and post-arrest were between 430 and 460 ms. No obvious explanation was found for the hypokalemia, so it was thought to be secondary to unintentional decreased nutritional intake. Her electrocardiogram (ECG) post-arrest showed polymorphic ectopy (Figure 1B), which normalized after treatment with potassium chloride.

This study tests the hypothesis that hypokalemia-induced ventricular arrhythmia is more likely to occur in a murine model of CPVT than in control animals. Whole-heart Langendorff preparations isolated from C57BL/6J mice (controls) or C57BL/6J mice with a point mutation in RyR2 (R2474S) were perfused with Krebs–Henseleit solution containing normal (4.0 mmol/L) [K^+] for 30 minutes, during which no arrhythmias occurred, then perfused with either low–normal (3.5 mmol/L) or moderately low (3.0 mmol/L) [K^+]. Action potentials and pseudo-ECGs were recorded simultaneously (methodology detailed previously).[2] Time to occurrence of the first spontaneous ventricular arrhythmia was compared between control and CPVT mice, at both concentrations of K^+. The percentage of mice that developed ventricular arrhythmia was also compared between groups. Mice of either sex were used (aged 5–6 months) (Jackson Laboratories, Bar Harbor, ME). Experiments and animal care protocols conformed to the Guide for Care and Use of

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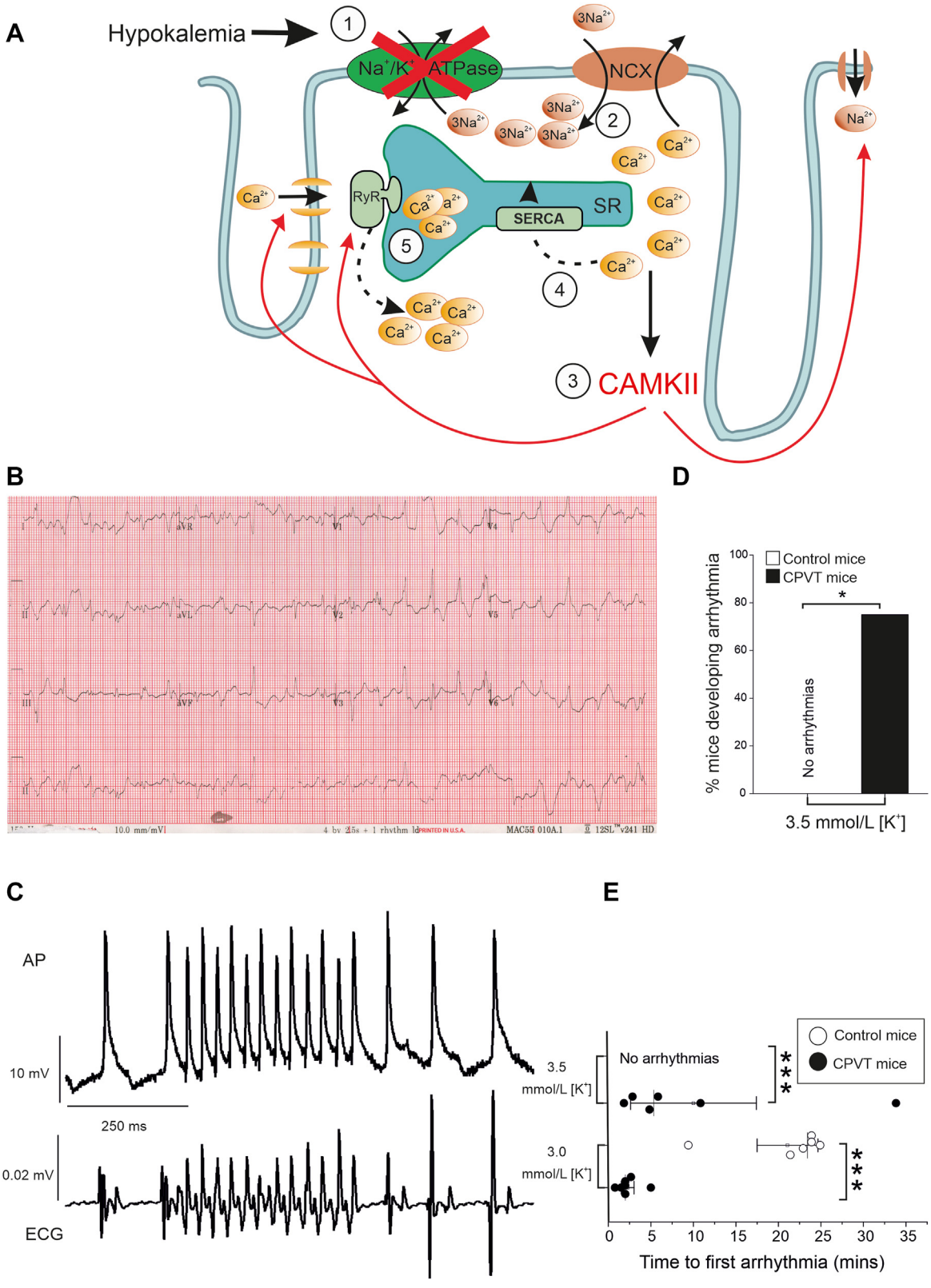

Figure 1 **A:** Schematic diagram of a cardiomyocyte exposed to hypokalemia. **B:** ECG showing polymorphic ectopy after a cardiac arrest in a patient with catecholaminergic polymorphic ventricular tachycardia (CPVT). **C:** Example of bidirectional ventricular tachycardia, recorded from an R2474S CPVT mouse with corresponding action potential (AP) traces. **D:** Percentage of explanted hearts from control and CPVT mice that developed ventricular arrhythmia when perfused with 3.5 mmol/L [K^+]. **E:** Time to development of first ventricular arrhythmia in explanted hearts from control and CPVT mice, perfused with either 3.5 or 3.0 mmol/L [K^+]. NCX = sodium/calcium exchanger; RyR2 = ryanodine receptor 2; SR = sarcoplasmic reticulum.

Laboratory Animals and were approved by the local Institutional Animal Care and Use Committee. The Mann-Whitney rank sum test was used for statistical comparison of time to first arrhythmia between groups, and the z test was used to compare the proportion of mice that developed arrhythmia (SigmaPlot Version 13.0, Systat Software, San Jose, CA). $P < .05$ value was considered significant.

Arrhythmias recorded were those typically seen in hypokalemia and CPVT, including polymorphic and bidirectional ventricular tachycardia (Figure 1C). In low–normal (3.5 mmol/L) [K^+], no control mice (n = 7) developed ventricular arrhythmia, even after 1 hour of perfusion, whereas 75% of the CPVT mice (n = 8) developed arrhythmia ($P = .015$) (Figure 1D). In 3.5 mmol/L [K^+], the CPVT mice had mean ± SEM time to first arrhythmia of 10.2 ± 4.9 minutes ($P = .001$) (Figure 1E). In 3 mmol/L [K^+], a high percentage of both control and CPVT animals developed arrhythmia (75% vs 88%, respectively; P = NS; n = 8 animals per group), but the time to first arrhythmia was significantly different between groups. Mean time to first arrhythmia was 21.2 ± 2.4 minutes in control animals and 2.3 ± 0.5 minutes in CPVT mice ($P = .001$) (Figure 1E). Thus, CPVT mice developed arrhythmias at low–normal [K^+], whereas control mice did not. At moderately low [K^+], CPVT mice were significantly more sensitive to ventricular arrhythmia.

This study provides the first experimental demonstration of increased susceptibility to ventricular arrhythmia in the setting of hypokalemia in CPVT. Because it would be unethical to expose CPVT patients to hypokalemia, these murine data make a case for maintaining a serum potassium >4 mmol/L in CPVT patients.

References

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