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### Title

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### Permalink

<https://escholarship.org/uc/item/3tn6b54f>

### Journal

Circulation Arrhythmia and Electrophysiology, 10(3)

### ISSN

1941-3149

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### Publication Date

2017-03-01

### DOI

10.1161/circep.116.004667

Peer reviewed

## Electrophysiology of Hypokalemia and Hyperkalemia

James N. Weiss, MD; Zhilin Qu, PhD; Kalyanam Shivkumar, MD, PhD

Potassium ( $K^+$ ) was first isolated as an element in 1807 by Sir Humphrey Davy when he electrolyzed potash (plant ashes soaked in pots of water), from which its name is derived. Despite the organic origin of its isolation, however, the role of  $K^+$  in biology was not elucidated until the 20th century. In this article, we discuss the basic science underlying the effects of both hypo- and hyperkalemia on cardiac excitability and arrhythmias. As the major intracellular cation,  $K^+$  is concentrated 30- to 40-fold over its extracellular concentration by the activity of  $Na^+$ - $K^+$  ATPase in the plasma membrane, which hydrolyzes ATP to pump 3  $Na^+$  ions out of the cell in exchange for 2 extracellular  $K^+$  ions into the cell, generating an outward current in the process. Because most cells express time-independent  $K^+$  ion channels in their plasma membrane, the high selective permeability to  $K^+$  over other ions generates a negative resting membrane potential ( $E_m$ ) approaching the  $K^+$  equilibrium potential ( $E_K$ ) as determined by the Nernst equation ( $-95$  mV for extracellular and intracellular  $[K^+]$  of 4.0 and 140 mmol/L, respectively). In excitable tissues such as the heart, the negative resting  $E_m$  stabilizes working atrial and ventricular myocytes during diastole, preventing spontaneous action potentials (APs) from causing premature extrasystoles. For this reason, serum  $[K^+]$  is closely regulated physiologically, with normal values ranging from 3.5 to 5.0 mmol/L. Outside of this range, lower and higher values of serum  $[K^+]$  have electrophysiological effects that commonly promote cardiac arrhythmias, not solely because of direct effects of  $K^+$ , but also because the cellular balances of  $K^+$ ,  $Na^+$ , and  $Ca^{2+}$  are interlinked through  $Na^+$ - $K^+$  ATPase and  $Na^+$ - $Ca^{2+}$  exchange (Figure 1A). Thus, hypo- and hyperkalemia directly impact  $Na^+$  and  $Ca^{2+}$  and  $K^+$  balances. In this article, we discuss how these relationships promote cardiac arrhythmias. First, we review how hypokalemia not only reduces repolarization reserve by suppressing  $K^+$  conductances, but also significantly inhibits  $Na^+$ - $K^+$  ATPase activity, causing intracellular  $Na^+$  and  $Ca^{2+}$  accumulation. Increased intracellular  $Ca^{2+}$  loading activates  $Ca^{2+}$ -calmodulin kinase (CaMK) signaling to further reduce repolarization reserve by inducing late  $Na^+$  and  $Ca^{2+}$  currents. This positive feedback loop promotes early afterdepolarization (EAD)-mediated arrhythmias, especially when  $K^+$  channel-blocking drugs are present, and delayed afterdepolarization (DAD)-mediated arrhythmias and automaticity. We then turn to hyperkalemia, both systemic and interstitial. We discuss how resting membrane depolarization by systemic

hyperkalemia promotes conduction block and reentry and may also promote phase 2 reentry. Finally, we describe how interstitial hyperkalemia, a prominent feature of acute myocardial ischemia, contributes to injury currents causing electrocardiographic ST-segment elevation and TQ-segment depression that promote arrhythmias, including phase 2 reentry similar to Brugada and other early repolarization syndromes. Differences between responses of conduction system tissues and atrial and ventricular myocardium to changes in extracellular  $[K^+]$  are also noted.

### Hypokalemia

Hypokalemia is most commonly encountered clinically as a complication of diuretic therapy<sup>2</sup> used to treat hypertension, heart failure, renal disease, and other conditions. Its direct electrophysiological effects include resting membrane hyperpolarization,  $Na^+$ - $K^+$  ATPase inhibition, and suppression of  $K^+$  channel conductances resulting in AP duration (APD) prolongation, reduced repolarization reserve, EAD, DADs, and automaticity.

### Arrhythmia Mechanisms

Reduced repolarization reserve predisposes the heart to EADs (Figure 1B) and EAD-mediated arrhythmias, including Torsades de pointes and polymorphic ventricular tachycardia (VT), which can degenerate to ventricular fibrillation (VF) causing sudden cardiac death (Figure 2).<sup>1</sup> Reductions in repolarization reserve prolong APD in a heterogeneous manner, both because ion channel expression is heterogeneous throughout the atria and ventricles<sup>3</sup> and because EADs are intrinsically chaotic, occurring irregularly instead of reliably with every beat.<sup>4</sup> Because of the gap junction coupling in cardiac tissue that prevents adjacent myocytes from exhibiting markedly different APD, the chaotic behavior causes some regions to exhibit EADs synchronously, whereas other nearby regions do not. This dynamical process has been termed regional chaos synchronization and generates marked dispersion of repolarization because areas with long APD due to EADs are juxtaposed next to regions much shorter APD without EADs<sup>4,5</sup> (Figure 3).<sup>6</sup> Moreover, if His-Purkinje fibers or regions of myocardium with EADs reach the threshold for triggered activity, the resulting extrasystoles can propagate into recovered regions without EADs but may block when propagating into other regions with

Received December 19, 2016; accepted February 6, 2017.

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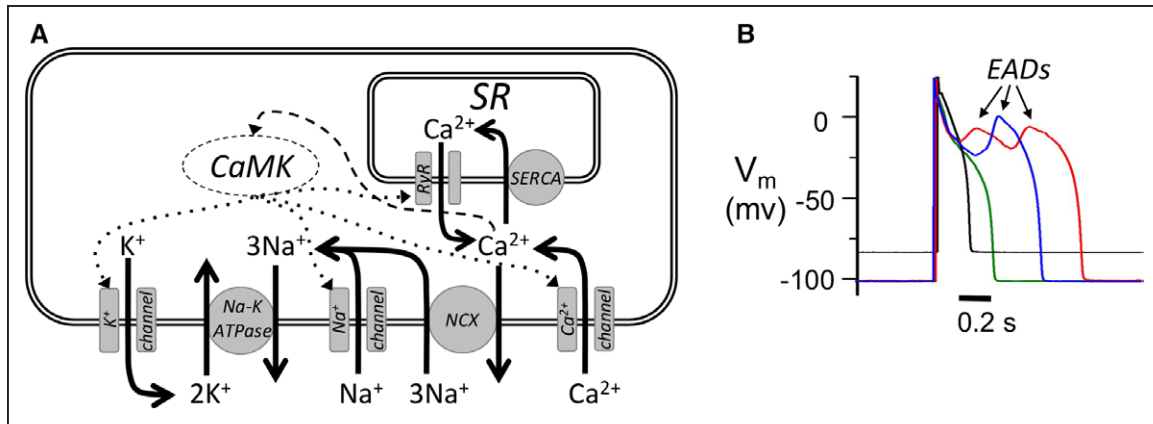
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(*Circ Arrhythm Electrophysiol*. 2017;10:e004667. DOI: 10.1161/CIRCEP.116.004667.)

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*Circ Arrhythm Electrophysiol* is available at <http://circep.ahajournals.org>

DOI: 10.1161/CIRCEP.116.004667



**Figure 1. A**, Interconnectedness of  $K^+$ ,  $Na^+$ , and  $Ca^{2+}$  balances in the cardiac myocyte. Outward  $K^+$  loss through  $K^+$  channels (left) is recovered by the  $Na^+$ - $K^+$  ATPase removing 3  $Na^+$  ions in exchange for 2  $K^+$  ions. Some  $Na^+$  ions enter the cell via  $Na^+$  channels, but most via  $Na^+$ - $Ca^{2+}$  exchange (NCX) during diastole, which exchanges 1  $Ca^{2+}$  ion for 3  $Na^+$  ions. In the steady state, the  $Ca^{2+}$  removed by NCX balances the  $Ca^{2+}$  entering the cell via  $Ca^{2+}$  channels. Most  $Ca^{2+}$  in the cell recycles between the sarcoplasmic reticulum (SR) and cytoplasm, with uptake by sarcoplasmic reticulum  $Ca^{2+}$  ATPase (SERCA) and release through ryanodine receptors (RyR). Cytoplasmic free  $Ca^{2+}$  activates  $Ca^{2+}$ -calmodulin kinase (CaMK), which regulates the properties of  $Na^+$ ,  $Ca^{2+}$ , and  $K^+$  channels, and RyR in the SR (dotted arrows). **B**, Effects of hypokalemia on the action potential (AP). Superimposed AP recordings from an isolated rabbit ventricular myocyte with  $[K^+]_o = 5.4$  mmol/L (black trace) vs  $[K^+]_o = 2.7$  mmol/L (red trace), showing hyperpolarized  $E_m$  and early afterdepolarizations (EADs), the latter suppressed by the CaMK blocker KN-93 (green trace), but not by inactive KN-92 (blue trace). Adapted from Pezhouman et al<sup>1</sup> with permission of the publisher. Copyright © 2015, American Heart Association. Authorization for this adaptation has been obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.

subthreshold EADs, thereby initiating reentry (Figure 3, black arrows). Under these conditions, reentry can have a special property called biexcitability,<sup>7</sup> in which 2 types of unstable rotors coexist. Incomplete repolarization allows slow meandering rotors to propagate using the L-type  $Ca^{2+}$  current (manifesting as Torsades de pointes or polymorphic VT), whereas full repolarization allows fast rotors to propagate using the  $Na^+$  current (manifesting as polymorphic VT or VF). This arrhythmia mechanism is called mixed focal-reentrant fibrillation (as opposed the multiple wavelet or mother rotor fibrillation) because the unstable rotors often self-terminate, but new rotors are then initiated by ongoing

EAD-mediated triggered activity arising from His-Purkinje tissue or ventricular myocardium.<sup>4,5</sup>

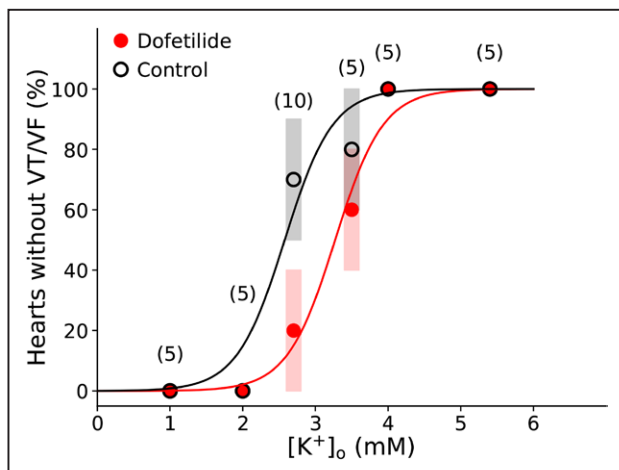
Even moderate hypokalemia (2.5–3.0 mmol/L) can be highly arrhythmogenic in normal hearts. In isolated rabbit and rat hearts, we found that modestly reducing  $[K^+]_o$  to 2.7 mmol/L resulted in spontaneous EADs, polymorphic VT, and VF in approximately over 50% of hearts studied, whereas severe hypokalemia (2.0 mmol/L) caused VF in 100%<sup>1</sup> (Figure 2).

### Molecular Factors Underlying Hypokalemia-Induced Arrhythmias

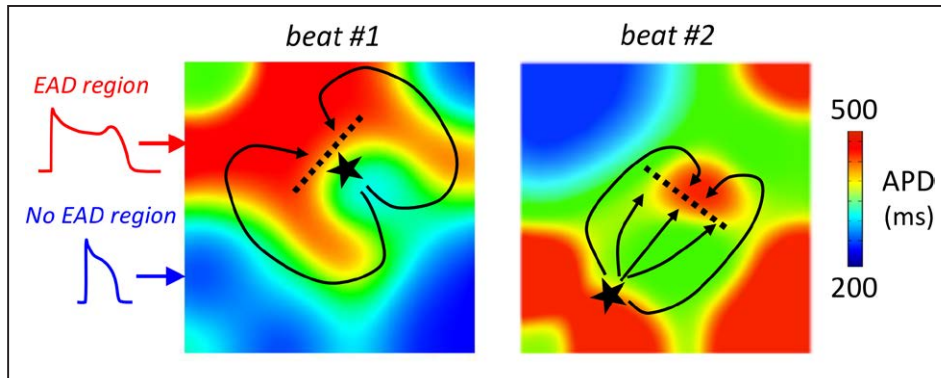
The reduction in repolarization reserve by hypokalemia has classically been attributed to direct suppression of  $K^+$  channel conductances, but recent evidence indicates that indirect effects of hypokalemia leading to activation of late  $Na^+$  and  $Ca^{2+}$  currents play a key role as well.<sup>1</sup> Together, these 2 factors are synergistic in reducing repolarization reserve sufficiently to induce EADs and EAD-mediated arrhythmias, including Torsades de pointes, polymorphic VT, and VF.

### Suppression of $K^+$ Channel Conductances by Hypokalemia

Many  $K^+$  channels, including the inward rectifier  $K^+$  current  $I_{K1}$ , the rapid component of the delayed rectifier  $K^+$  current  $I_{Kr}$ , and the transient outward current  $I_{to}$ , exhibit a strong allosteric dependence on extracellular  $K^+$  concentration  $[K^+]_o$ .<sup>8–12</sup> In inward rectifier  $K^+$  channels (eg, Kir2.1 encoded by the KCNJ2 gene), outward current through the channel is regulated by voltage-dependent block of the pore by cytoplasmic  $Mg^{2+}$  and polyamines that bind to the negative charges in the pore's cytoplasmic vestibule and prevent passage of  $K^+$  ions. Extracellular  $K^+$  ions entering the pore from the outside electrostatically destabilize and knockoff these blocking cations from their binding sites, restoring



**Figure 2.**  $[K^+]_o$  dependence of hypokalemia-induced ventricular tachycardia (VT)/ventricular fibrillation (VF) in isolated rabbit hearts, without or with dofetilide. When  $[K^+]_o$  was lowered, the incidence of VT/VF within 90 min progressively increased to 100% at 2.0 and 1.0 mmol/L (black circles). Dofetilide (1  $\mu$ mol/L) shifted the dose-response curve to the right. Reprinted from Pezhouman et al<sup>1</sup> with permission of the publisher. Copyright © 2015, American Heart Association.



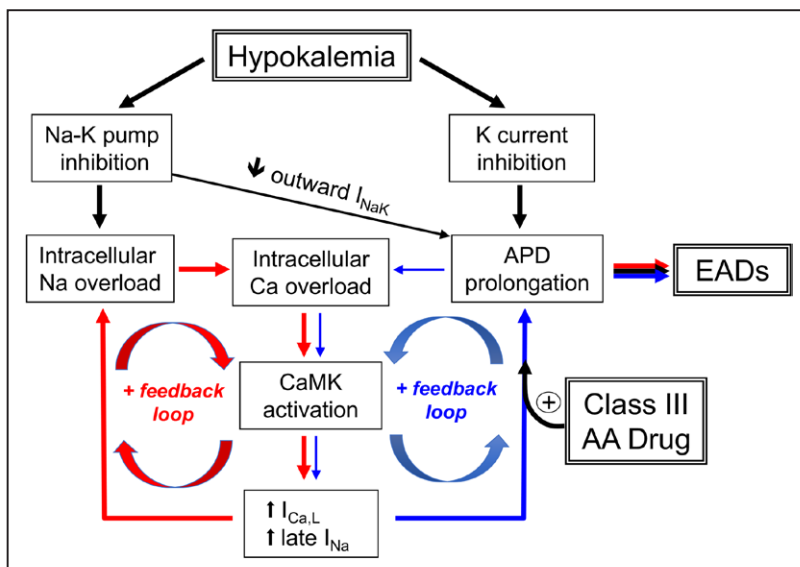
**Figure 3.** Regional chaos synchronization of early afterdepolarizations (EADs) in tissue. In simulated paced homogeneous cardiac tissue, electrotonic coupling causes regional chaos synchronization to generate EAD islands (red regions), separated by regions without EADs (blue), whose position and size vary from beat to beat. Beat No. 1 illustrates a scenario in which a triggered premature ventricular contraction (★) arising from an EAD island blocks superiorly (dashed line) but conducts inferiorly (solid line), subsequently reentering the blocked region to induce reentry. Beat No. 2 illustrates a scenario in which the triggered premature ventricular contraction arising from an EAD island encounters another EAD island, resulting in conduction block (dashed line) and reentry (solid lines). Adapted from Weiss et al<sup>6</sup> with permission of the publisher. Copyright © 2015, Elsevier. Authorization for this adaptation has been obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.

outward  $K^+$  flow.<sup>13</sup> Thus, even though hypokalemia hyperpolarizes  $E_K$ , increasing the driving force for outward  $K^+$  flow ( $E_m - E_K$ ), the increased stability of blocking cations in the pore decreases the conductance more powerfully, resulting in decreased outward  $K^+$  current.

The mechanism by which extracellular  $K^+$  acutely regulates the conductance of voltage-dependent  $K^+$  channels, such as  $I_{Kr}$  (Kv11.1 encoded by KCHN2) and  $I_{to}$  (Kv1.4, Kv4.2, Kv4.3 encoded by KCNA4, KCND2, KCND3), is different. Hypokalemia speeds rapid inactivation of  $I_{Kr}$ <sup>10</sup> and slows reactivation kinetics of  $I_{to}$ ,<sup>11</sup> reducing outward repolarizing current even with moderate hypokalemia.<sup>12</sup> Hypokalemia also downregulates  $I_{Kr}$  expression within hours.<sup>14</sup> Thus, despite increasing the driving force for  $K^+$  efflux, hypokalemia reduces the number of conducting  $K^+$  channels during repolarization. His-Purkinje fibers are particularly susceptible to EADs, DADs, and automaticity because of their lower resting  $K^+$  conductance (less  $I_{K1}$ ) compared with ventricular myocardium.<sup>15</sup>

### Na<sup>+</sup>-K<sup>+</sup> ATPase Inhibition by Hypokalemia

The rate at which Na<sup>+</sup>-K<sup>+</sup> ATPase transports ions depends both on the affinities of the extracellular and intracellular binding sites for Na<sup>+</sup>/K<sup>+</sup> and  $E_m$  because the transport cycle moves 1 net positive charge outward. For the predominant  $\alpha 1$  isoform of Na<sup>+</sup>-K<sup>+</sup> ATPase in heart,<sup>16,17</sup> the external  $K^+$  binding site is half maximally saturated at  $[K^+]_o = 1.9$  mmol/L, operating at half-maximal pumping rate at this concentration. Reducing  $[K^+]_o$  from 4.5 to 2.7 mmol/L decreases ion pumping rate by about 20%<sup>18</sup> (and by >50% for the  $\alpha 2$  isoform that is half maximally saturated at 2.9 mmol/L).<sup>16</sup> In addition, hypokalemia hyperpolarizes  $E_m$ , from  $-82$  to  $-100$  mV in isolated rabbit ventricular myocytes when  $[K^+]_o$  is reduced from 4.5 to 2.7 mmol/L (Figure 1B). Because Na<sup>+</sup>-K<sup>+</sup> ATPase generates a net outward current and is inhibited by hyperpolarization, the combined effect reduced  $K^+$  binding and hyperpolarization is predicted to reduce Na<sup>+</sup>-K<sup>+</sup> ATPase ion pumping rate by 43%.<sup>18</sup> This agrees quantitatively with experimental measurements in isolated rat ventricular myocytes<sup>19</sup> reporting an



**Figure 4.** Hypokalemia-induced positive feedback loops (red and blue arrows) promoting intracellular Na<sup>+</sup> and Ca overload, Ca<sup>2+</sup>-calmodulin kinase (CaMK) activation and early afterdepolarizations (EADs) during hypokalemia. The potentiation of the blue positive feedback loop by class III antiarrhythmic (AA) drugs is also shown.  $I_{NaK}$  = Na<sup>+</sup>-K<sup>+</sup> ATPase outward current. APD indicates action potential duration. Reprinted from Pezhouman et al<sup>1</sup> with permission of the publisher. Copyright © 2015, American Heart Association.

≈50% suppression of Na<sup>+</sup>-K<sup>+</sup> ATPase current when [K<sup>+</sup>]<sub>o</sub> was reduced from 5.4 to 2.7 mmol/L. The consequence was a slow rise in intracellular [Na<sup>+</sup>] that inhibited the ability of the Na<sup>+</sup>-Ca<sup>2+</sup> exchanger to remove Ca<sup>2+</sup> from the cell resulting in spontaneous diastolic Ca<sup>2+</sup> waves.

### Intracellular Ca<sup>2+</sup> Overload and CaMK Activation

Hypokalemia prolongs APD by reducing outward current through both K<sup>+</sup> channels and Na<sup>+</sup>-K<sup>+</sup> ATPase. The prolonged APD results in increased Ca<sup>2+</sup> influx through Ca<sup>2+</sup> channels. At the same time, intracellular Ca<sup>2+</sup> removal via Na<sup>+</sup>-Ca<sup>2+</sup> exchange is compromised by the elevated intracellular [Na<sup>+</sup>] from Na<sup>+</sup>-K<sup>+</sup> ATPase inhibition. Together, these factors cause an increase in cytoplasmic [Ca<sup>2+</sup>]<sup>19</sup> sufficient to activate CaMK, as documented directly in rabbit hearts exposed to 2.7 mmol/L [K<sup>+</sup>]<sub>o</sub><sup>18</sup> (Figure 4). When activated, CaMK phosphorylates a variety of protein targets, including Na<sup>+</sup> channels, L-type Ca<sup>2+</sup> channels, and ryanodine receptors<sup>20</sup> (Figure 1). Na<sup>+</sup> channel phosphorylation by CaMKII increases late Na<sup>+</sup> current which further decreases repolarization reserve and also further exacerbates intracellular Na<sup>+</sup> loading.<sup>21</sup> L-type Ca<sup>2+</sup> channel phosphorylation by CaMKII both increases current amplitude and slows inactivation,<sup>20</sup> increasing the Ca<sup>2+</sup> window current that plays a critical role in EAD generation.<sup>22–24</sup> Ryanodine receptors phosphorylation by CaMKII increases ryanodine receptors leakiness, further elevating diastolic [Ca<sup>2+</sup>] and promoting Ca<sup>2+</sup> waves and DADs.<sup>20</sup> At the same time, hyperkalemia reduces the outward current hump of inward rectifier K<sup>+</sup> channels and shifts its peak to a more negative voltage,<sup>25</sup> requiring less opposing inward current to depolarize E<sub>m</sub>. This effect, combined with the enhancement of inward Na<sup>+</sup>-Ca<sup>2+</sup> exchange current by hypokalemia-induced hyperpolarization of E<sub>m</sub>, lowers the threshold for DADs to cause triggered activity.<sup>25</sup> CaMK has other targets as well,<sup>20</sup> whose role in the genesis of EADs, DADs, and automaticity is less clear, but may also be important. Thus, the effect of CaMK activation during hypokalemia is to create the positive feedback scenario illustrated in Figure 4 that further reduces repolarization reserve and exacerbates intracellular Ca<sup>2+</sup> overload, culminating in the appearance of afterdepolarization-mediated arrhythmias. Purkinje fibers are particularly sensitive because of their already low I<sub>K1</sub> density and reduced repolarization reserve compared with ventricular myocardium.<sup>15</sup> In our rabbit heart experiments, the role of CaMK activation was critical because blocking CaMK with KN-93 completely prevented hypokalemia-induced VT/VF in both myocytes (Figure 1B) and isolated hearts,<sup>1</sup> as did the selective late Na<sup>+</sup> current blocker GS-967.

### Hypokalemia and Class III Antiarrhythmic Drugs

Hypokalemia is well known to potentiate the proarrhythmic effects of class III antiarrhythmic drugs,<sup>26,27</sup> especially in diseased hearts. This is not surprising because hypokalemia further reduces the conductance of K<sup>+</sup> channels not already blocked by the drug. In addition, affinity of some class III antiarrhythmic drugs is increased by hypokalemia.<sup>28</sup> Most experimental models in which EAD-mediated arrhythmias were induced by K<sup>+</sup> channel-blocking drugs in normal heart tissue have included hypokalemia (and often hypomagnesemia) as a cofactor. In our isolated rabbit heart preparation, the

class III antiarrhythmic drug dofetilide, despite significantly prolonging APD, failed to induce EAD-mediated arrhythmias when extracellular [K<sup>+</sup>] was normal.<sup>1</sup> Rather dofetilide sensitized the heart to hypokalemia, such that VT/VF occurred at a higher (but still abnormal) [K<sup>+</sup>]<sub>o</sub> when dofetilide was present (Figure 2).

Other evidence also suggests that drug-induced suppression of K<sup>+</sup> currents alone may not be sufficient to induce EAD-mediated arrhythmias. Anderson and coworkers<sup>29,30</sup> previously showed that CaMK activation by the K<sup>+</sup> channel blocker clofilium played key role in EAD formation in isolated rabbit hearts. Moreover, CaMK inhibitors abolished clofilium-induced EADs. Recently, Yang et al<sup>31</sup> reported that various class III antiarrhythmic drugs such as dofetilide contribute to EAD formation by activating the late Na<sup>+</sup> current (I<sub>Na</sub>) via phosphoinositide 3-kinase inhibition. Thus, the concomitant activation of pathological late Na<sup>+</sup> or Ca<sup>2+</sup> currents by CaMK, phosphoinositide 3-kinase, or other signaling pathways seems to be an essential corequirement for eliciting EAD-mediated arrhythmias by either hypokalemia or class III drugs. These findings may provide insight into why failing hearts, in which CaMK activity is chronically elevated,<sup>20</sup> are presensitized to the proarrhythmic effects of class III antiarrhythmic drugs even when serum [K<sup>+</sup>] is normal. Finally, targeting late I<sub>Na</sub> to break the CaMK-facilitated positive feedback cycle promoting EAD formation (Figure 4) may be a promising antiarrhythmic strategy.

### Hyperkalemia

Hyperkalemia can be systemic or interstitial (confined to cardiac or other tissue as a result of acute global or regional ischemia). Both settings confer a high arrhythmia risk, whose mechanisms are discussed below.

#### Systemic Hyperkalemia

Systemic hyperkalemia (mild 5.5–6.0, moderate 6.0–7.0, severe >7.0 mmol/L) is most commonly encountered clinically in chronic and acute renal failure, K<sup>+</sup> supplementation for diuretic therapy, diuretic therapy with K<sup>+</sup>-sparing drugs such as spironolactone and triamterene, therapy with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers in cardiorenal disease, acute digitalis toxicity, massive hemolysis or muscle trauma, etc. Because one or more of these conditions are often present in chronic heart failure, they combine with the inherently increased arrhythmia susceptibility of diseased myocardium to further enhance risk.

#### Electrophysiological Effects

The major cardiac electrophysiological effects of systemic hyperkalemia are depolarization of E<sub>m</sub> as E<sub>K</sub> becomes less negative (+18 mV change for a doubling of [K<sup>+</sup>]<sub>o</sub> from 4.0 to 8.0 mmol/L), APD shortening and altered conduction velocity (CV). APD shortening is because of the allosteric effect of [K<sup>+</sup>]<sub>o</sub> at increasing K<sup>+</sup> channel conductances (despite a decreased driving force E<sub>m</sub>-E<sub>K</sub>),<sup>9,10</sup> thereby creating excess repolarization reserve. APD shortening by hyperkalemia initially decreases the effective refractory period, but as hyperkalemia worsens, increased K<sup>+</sup> channel conductances can induce postrepolarization refractoriness, such that the AP remains

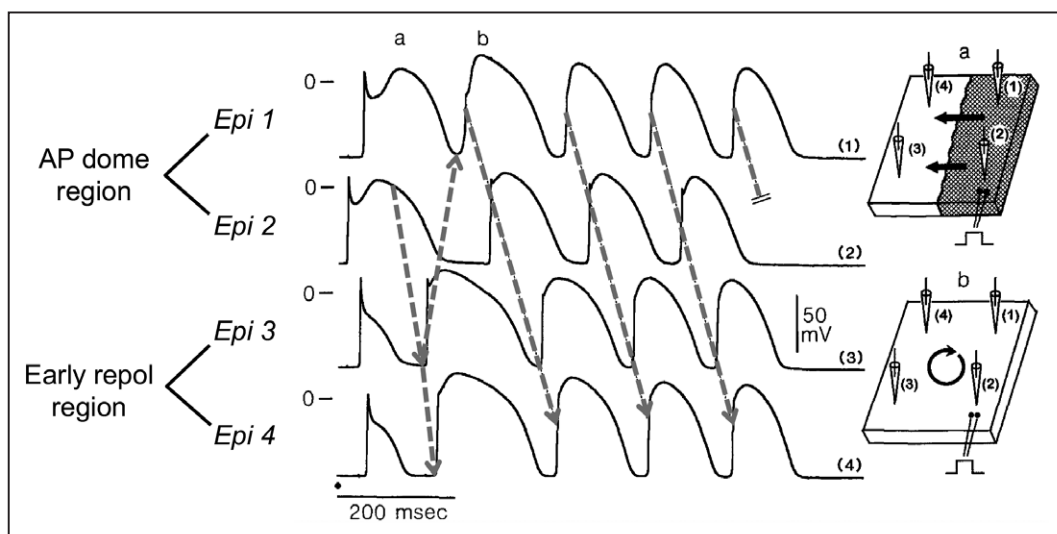
refractory for a period of time after full repolarization has occurred, prolonging the effective refractory period. The effect of hyperkalemia on CV is biphasic, determined jointly by (1) the voltage difference between  $E_m$  and the  $\text{Na}^+$  channel activation threshold (around  $-55$  mV) and (2) the effect of  $E_m$  on the steady-state inactivation of  $\text{Na}^+$  channels, which increases with depolarization so that fewer  $\text{Na}^+$  channels are available to be activated during the AP upstroke. Up to  $\approx 8$  mmol/L, the first factor dominates such that hyperkalemia-induced depolarization of  $E_m$  accelerates CV. At higher  $[\text{K}^+]_o$ , however, the second factor of decreased  $\text{Na}^+$  channel availability becomes more important, causing CV slowing eventually to the point of propagation failure and inexcitability at  $[\text{K}^+]_o > 14$  mmol/L.<sup>32</sup> Despite its biphasic effects on CV, however, hyperkalemia uniformly accentuates CV restitution, that is, the dependence of CV on the previous diastolic interval. This is because the time required for  $\text{Na}^+$  channels to recover from inactivation after repolarization prolongs as resting  $E_m$  depolarizes, such that fewer  $\text{Na}^+$  channels are available to contribute to the AP upstroke at short diastolic intervals. Thus, although CV may be accelerated by hyperkalemia at normal heart rates, premature beats exhibit slowed CV because of incomplete  $\text{Na}^+$  channel recovery from inactivation. The arrhythmogenic consequences of these changes are described below.

### Arrhythmia Mechanisms

As hyperkalemia worsens, the ECG first demonstrates peaked T waves resulting from global APD shortening causing more synchronous repolarization across the ventricular wall. Subsequently, the P wave broadens and decreases in amplitude, eventually disappearing, and the QRS widens because of CV slowing. Severe hyperkalemia ( $[\text{K}^+]_o > 7.0$  mmol/L) can lead to heart block, asystole, and VT/VF. In humans, the precise level of hyperkalemia producing (or not producing) these changes varies considerably. For example, in trained athletes, short duration maximal exercise to exhaustion increased

serum  $[\text{K}^+]$  to an average of 8.2 mmol/L at peak exercise, which recovered with a half-time of 25 s post-exercise without apparent arrhythmias (perhaps protected by the high catecholamine state stimulating  $\text{Na}^+\text{-K}^+$  ATPase activity<sup>33</sup>), although electrocardiograms were not recorded.<sup>34</sup> Yet in a hospitalized patient, a serum  $[\text{K}^+]$  of 8 mmol/L is considered a dire medical emergency. It is not uncommon for systemic hyperkalemia to cause the P wave to disappear and the QRS to widen at serum  $[\text{K}^+]$  between 7 and 8 mmol/L, that is, below the threshold at which hyperkalemia causes CV slowing in animal models. Although visible P waves may disappear completely, conduction from the sinus node to ventricle may persist (sinoventricular conduction), taken as circumstantial evidence favoring specialized hyperkalemia-resistant atrial internodal tracts connecting the sinoatrial node to the atrioventricular node.<sup>35</sup> Pacemaking by the sinus node is less sensitive to hyperkalemia because of its low resting  $\text{K}^+$  conductance, as reflected in its partially depolarized resting potential ( $-50$  to  $-60$  mV) and slow response ( $\text{Ca}^{2+}$  current dependent) AP.<sup>36</sup> However, the conduction through the atrioventricular node is often impaired,<sup>37</sup> which has been attributed to potentiation of adenosine-sensitive inward rectifier  $\text{K}^+$  channels (Kir3 family encoded by *KCNJ3*) by hyperkalemia<sup>38</sup> and may also apply to the sinus node. Compared with nodal tissue, His-Purkinje tissue has higher resting  $\text{K}^+$  conductance, and its secondary pacemaking capability (driven by the hyperpolarization-activated nonselective cation current  $I_f$  encoded by the HCN gene family) is suppressed by hyperkalemia, such that infranodal escape pacemakers become unreliable after heart block develops, which, together with propagation failure, can cause frank asystole.

Several mechanisms predispose hyperkalemic hearts to reentrant tachyarrhythmias. Decreased  $\text{Na}^+$  channel availability after premature extrasystoles can result in localized conduction block initiating reentry. As heart rate increases, the accentuation of CV restitution by hyperkalemia, combined



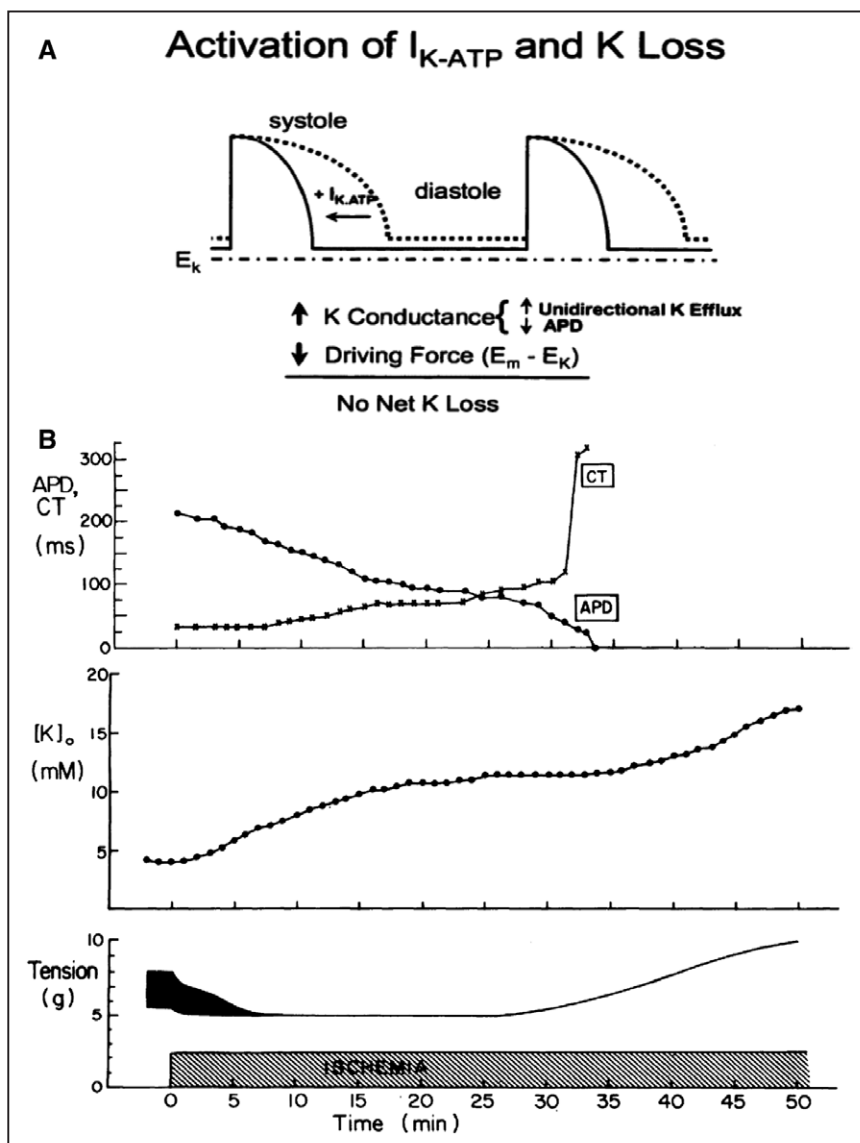
**Figure 5.** Phase 2 reentry during simulated ischemia in canine epicardium. Traces show action potential (AP) recordings from 4 sites (Epi 1–4) in a canine epicardial sheet exposed to simulated ischemia ( $[\text{K}^+]_o = 6$  mmol/L, hypoxia,  $\text{pH} = 6.8$ ). Sites 1 and 2 exhibit normal APs with accentuated AP domes, whereas sites 3 and 4 show early repolarization. Arrows show reexcitation of site 3 by the AP dome at site 2, inducing phase 2 reentry that self-terminates after 4 beats. Adapted from Lukas and Antzelevitch<sup>42</sup> with permission of the publisher. Copyright © 1996, Oxford University Press. Authorization for this adaptation has been obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.

with postrepolarization refractoriness, may predispose the heart to spatially discordant APD alternans, the classic mechanism causing localized conduction block and initiation of reentrant VT/VF during rapid pacing.<sup>39,40</sup> To our knowledge, however, this mechanism has not been demonstrated experimentally for hyperkalemia. By increasing repolarization reserve, hyperkalemia also potentiates all-or-none early repolarization of the AP, potentially predisposing the heart to phase 2 reentry, as in Brugada, Short QT, and Early Repolarization (J wave) Syndromes.<sup>41</sup> It is interesting that phase 2 reentry was originally described in hearts exposed to simulated global ischemia in which hyperkalemia (6 mmol/L) was included as a cofactor together with hypoxia and acidosis<sup>42</sup> (Figure 5). However, whether hyperkalemia alone is capable of inducing phase 2 reentry and initiating VF has not, to our knowledge, been systematically investigated, even though hyperkalemia is classified as an acquired form of Short QT Syndrome.<sup>43</sup> It is intriguing to speculate that the effectiveness of  $\text{Ca}^{2+}$  at stabilizing the heart during systemic hyperkalemia may be related in part to its enhancement of the L-type  $\text{Ca}^{2+}$  current, thereby

suppressing all-or-none repolarization of the AP that is critical for the development of phase 2 reentry. Sympathetic enhancement of the L-type  $\text{Ca}^{2+}$  current during exercise might similarly protect the heart from phase 2 reentry-mediated arrhythmias during exercise-induced hyperkalemia. Further experimental studies are needed to better clarify the specific mechanisms of tachyarrhythmia initiation by systemic hyperkalemia. In simulated ventricles, once reentry has been initiated, hyperkalemia tends to stabilize spiral/scroll wave reentry by flattening APD restitution slope.<sup>44</sup> The shorter APD increases the dominant frequency until CV slowing becomes prominent. The latter setting tends to promote the sinusoidal appearance of VT on the ECG in severe hyperkalemia.

### Interstitial Hyperkalemia

Interstitial hyperkalemia refers to elevated interstitial  $[\text{K}^+]$  in tissue with normal serum  $[\text{K}^+]$  in the circulation. Interstitial hyperkalemia is a prominent feature of acute myocardial ischemia due to global or regional cessation of coronary blood. During acute myocardial ischemia, intracellular  $\text{Na}^+$  ( $[\text{Na}^+]_i$ )



**Figure 6.** A, Schematic illustrating how action potential duration (APD) shortening because of ATP-sensitive  $\text{K}^+$  current ( $I_{\text{K-ATP}}$ ) activation offsets net cellular  $\text{K}^+$  loss by decreasing the average driving force  $E_m - E_K$  for  $\text{K}^+$  efflux over the cardiac cycle. B, APD shortening, conduction time (CT) delay, tension development, and interstitial  $[\text{K}^+]_o$  accumulation vs time during acute global ischemia in rabbit ventricle. Reprinted from Weiss and Shine.<sup>48</sup> Copyright © 1982, the American Physiological Society.

accumulates because of a net imbalance involving both increased  $\text{Na}^+$  influx and decreased  $\text{Na}^+\text{-K}^+$  ATPase reserve caused by the fall in tissue ATP levels, although the relative contributions are still debated. When  $[\text{Na}^+]_i$  increases, however, a counter charge movement (ie, concomitant efflux of a positively charged ion or influx of a negatively charged ion) is also required because a 1 mmol/L increase in positive charge from  $\text{Na}^+$  ions would depolarize membrane voltage by  $>30$  V if uncompensated. As the most ubiquitous intracellular cation with a high membrane permeability,  $\text{K}^+$  serves the bulk of this charge-compensating role.<sup>45</sup> Without washout by coronary blood flow, the net  $\text{K}^+$  efflux causes interstitial  $[\text{K}^+]_o$  to accumulate rapidly, typically reaching 10 to 15 mmol/L in the first 10 minutes of ischemia<sup>46,47</sup> (Figure 6).<sup>48</sup> Interstitial hyperkalemia during acute ischemia has all of the electrophysiological actions described for systemic hyperkalemia, complicated by additional changes related to hypoxia, acidosis, and other ischemic components.<sup>44,48</sup> In particular, APD shortening is accelerated by the activation of sarcolemmal ATP-sensitive K ( $\text{K}_{\text{ATP}}$ ) channels because of the ischemic fall in the cytoplasmic ATP/ADP ratio. The activation of sarcolemmal  $\text{K}_{\text{ATP}}$  channels, however, does not itself accelerate the net  $\text{K}^+$  loss during ischemia.<sup>45</sup> This is because the APD shortening induced by the increase in  $\text{K}^+$  conductance is offset by the decrease in driving force  $E_m - E_K$  for  $\text{K}^+$  efflux over the cardiac cycle because of the prolongation of diastole (Figure 6A). APD shortening is also accelerated by intracellular acidosis during ischemia, which suppresses both L-type  $\text{Ca}^{2+}$  and  $\text{Na}^+$  currents. Other ischemic components, such as catecholamines, adenosine, fatty acid metabolites, lysophospholipids, etc., also contribute to complex, temporally evolving electrophysiological changes.<sup>49</sup> The net result is more rapid APD shortening, onset of postrepolarization refractoriness, CV slowing, and conduction block, typically leading to inexcitability within 15 to 25 minutes (Figure 6B).

Acute global ischemia (or hypoxia with maintained coronary blood flow to wash out ischemic metabolites), however, is less arrhythmogenic than acute regional ischemia after coronary artery occlusion. The link between ischemic  $[\text{K}^+]_o$  accumulation and arrhythmias after coronary occlusion was

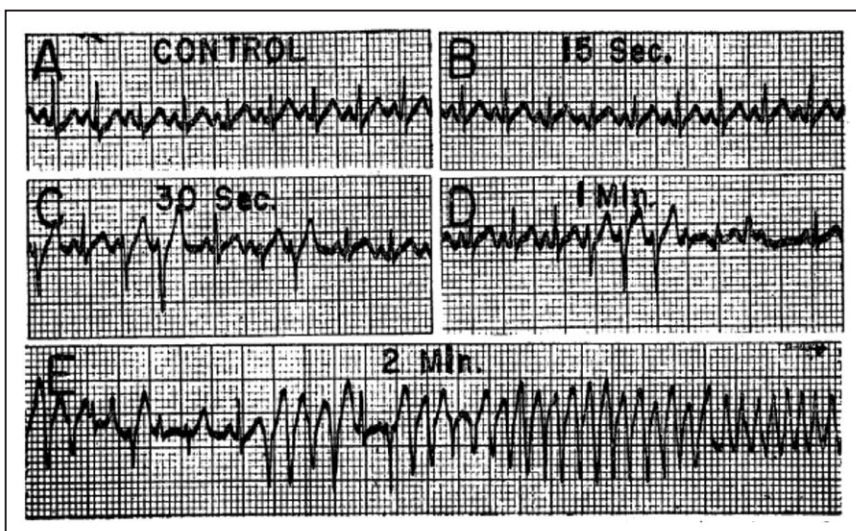
first delineated by Harris et al<sup>50</sup> (Figure 7). Subsequent studies with  $\text{K}^+$ -selective electrodes documented that  $[\text{K}^+]_o$  increased to 10 to 15 mmol/L in the central ischemic zone within the first 10 minutes of coronary occlusion, creating a steep  $[\text{K}^+]_o$  gradient between ischemic and adjacent nonischemic tissue.<sup>46</sup> As  $[\text{K}^+]_o$  increases, the subepicardial tissue layer, with its greater repolarization reserve because of higher expression of the transient outward current  $I_{\text{to}}$ , becomes inexcitable before the subendocardial tissue layer.<sup>51</sup> After 10 to 15 minutes,  $[\text{K}^+]_o$  reaches a plateau followed by a secondary rise after 20 to 30 minutes associated with contracture and irreversible injury on reperfusion.<sup>47</sup> This sequence accounts for both the electrocardiographic changes and early arrhythmia phases after coronary occlusion, as described below.

### Electrocardiographic Changes

When APD shortens in the ischemic region because of  $[\text{K}^+]_o$  accumulation,  $\text{K}_{\text{ATP}}$  channel activation, and other ischemic factors, the overlying T wave becomes peaked as in systemic hyperkalemia, followed by ST-segment elevation. ST-segment elevation is a somewhat misleading term because standard electrocardiographic recordings are high pass filtered to remove baseline drift, obfuscating the contribution of TQ depression to the apparent ST elevation. When direct current electrocardiograms are recorded, as much as half of the apparent ST elevation is caused by TQ depression.<sup>52</sup> This is a direct reflection of  $[\text{K}^+]_o$  accumulation in the ischemic region, which depolarizes the diastolic  $E_m$  relative to nonischemic tissue.<sup>53</sup> This voltage difference causes a diastolic injury current to flow through gap junctions across the border zone, depressing the TQ segment. During systole, APD shortening in ischemic tissue also generates a systolic injury current of opposite polarity to the diastolic injury current. The combined effect is to depress the TQ segment and elevate the ST segment. The abnormal repolarization in the ischemic area also commonly inverts the T wave.

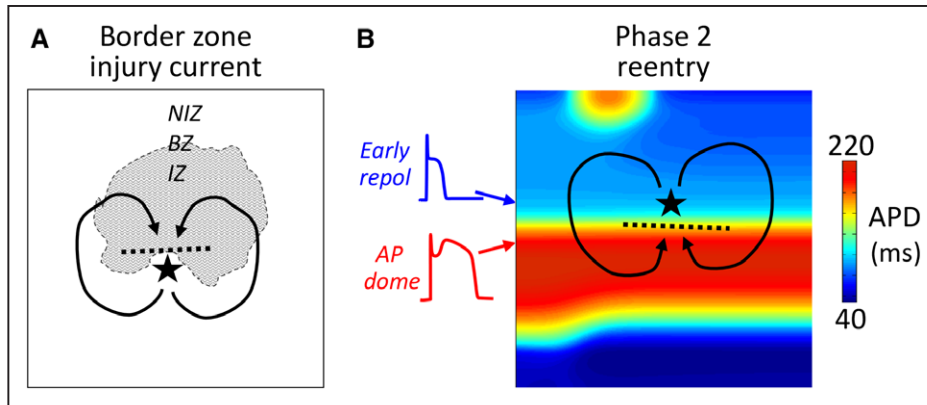
### Arrhythmia Mechanisms

In addition to being a marker of acute myocardial ischemia, the injury currents causing ST-segment elevation/TQ depression



**Figure 7.** Ventricular arrhythmias after injection of KCl (2.8 mg/kg) into the left anterior descending coronary artery of a dog at the times indicated in A–E. Reprinted from Harris et al<sup>50</sup> with permission of the publisher. Copyright © 1954, the American Association for the Advancement of Science.





**Figure 8.** Initiation of reentry during acute ischemia. **A**, Injury current across the border zone (BZ) excites adjacent repolarized tissue in the nonischemic zone (NIZ) to trigger a premature ventricular contraction (★) which propagates through the NIZ and reenters the ischemic zone (IZ) to initiate reentry. **B**, In ischemic subepicardial tissue, regions of all-or-none early repolarization with very short action potential duration (APD; blue) are juxtaposed to adjacent regions with normal APD and accentuated action potential (AP) domes (red). The AP dome propagates into the repolarized region to trigger a closely coupled premature ventricular contraction (★) that propagates laterally until the normal AP region repolarizes and then reenters this region to initiate phase 2 reentry.

also play a direct causal role in ischemic arrhythmogenesis. After coronary occlusion, the diastolic injury current caused by difference in resting  $E_m$  between ischemic and nonischemic tissue depolarizes the neighboring nonischemic tissue. In nonischemic areas, where the injury current density is highest, the depolarization may be sufficient to trigger a premature ventricular contraction, potentially initiating reentry, especially if the CV is depressed in the ischemic region (Figure 8A).<sup>52</sup> In addition, as  $[K^+]_o$  accumulation and  $K_{ATP}$  channel activation increase repolarization reserve, the subepicardial tissue layer, with its greater intrinsic repolarization reserve because of  $I_{to}$ , becomes susceptible to all-or-one repolarization and phase 2 reentry,<sup>42</sup> which can precipitate VF (Figures 5 and 8B).

In summary, the interaction between the depolarized ischemic region with elevated  $[K^+]_o$  and normally polarized nonischemic regions creates marked electrophysiological dispersion in resting  $E_m$ , APD, effective refractory period, and CV. These changes generate both triggers and an arrhythmogenic substrate promoting initiation of reentry, resulting in a high incidence of ventricular ectopy, VT, and VF during the first 25 to 30 minutes after acute coronary occlusion (called Harris phase 1 arrhythmias<sup>54</sup>). These early arrhythmias are the major cause of mortality in patients with acute myocardial infarction who die before reaching the hospital (around 60% of all deaths from acute myocardial infarction<sup>55</sup>). After 20 to 30 minutes of ischemia, however, gap junctions between ischemic myocytes become dephosphorylated and close, electrically isolating ischemic myocytes from their neighbors. At this point, corresponding to the secondary rise in  $[K^+]_o$  (Figure 6B), the ischemic region becomes inexcitable and no longer capable of transmitting injury currents across the border zone into nonischemic tissue, causing the arrhythmias to cease. However, arrhythmias often return 6 to 8 hours later because of automaticity arising from surviving but hypoxic subendocardial Purkinje fibers (called Harris phase 2 arrhythmias<sup>49,54</sup>).

### Synopsis

Up to 20% of patients admitted to the hospital exhibit hypokalemia,<sup>56</sup> and 3.5% exhibit hyperkalemia.<sup>57</sup> Both have powerful

electrophysiological effects promoting cardiac arrhythmias. Hypokalemia ( $[K^+]_o < 3.5$  mmol/L) reduces repolarization reserve by directly inhibiting  $K^+$  channel conductances and indirectly by suppressing  $Na^+K^+$  ATPase. The latter results in intracellular  $Na^+$  and  $Ca^{2+}$  loading activating CaMK signaling whose targets include  $Na^+$  and  $Ca^{2+}$  channels, initiating positive feedback cascades that further reduce repolarization reserve to the range promoting EADs, DADs, and afterdepolarization-mediated arrhythmias (Figure 4). The proarrhythmic effects of class III antiarrhythmic drugs are increased by elevated CaMK activity during hypokalemia and heart failure. In animal models, blocking CaMK or the late  $Na^+$  current activated by CaMK is an effective strategy to suppress afterdepolarization-mediated arrhythmias induced by hypokalemia and class III antiarrhythmic drugs.

In contrast, systemic hyperkalemia ( $[K^+]_o > 5.5$  mmol/L) enhances repolarization reserve by increasing  $K^+$  channel conductance, shortening APD, and inducing postrepolarization refractoriness, manifested electrocardiographically by peaked T waves. Hyperkalemia also depolarizes resting membrane potential, which first accelerates but then slows CV at  $[K^+]_o > 8$  mmol/L, manifested electrocardiographically by broadening and disappearance of the P wave (sinoventricular conduction) and QRS widening. Hyperkalemia also accentuates CV restitution, even when CV is accelerated, such that premature extrasystoles conduct more slowly and are more likely to develop conduction block. Accentuated CV restitution, together with postrepolarization refractoriness, may also make hyperkalemic tissue more susceptible to arrhythmogenic spatially discordant repolarization alternans. When combined with hypoxia and acidosis to simulate global ischemia, hyperkalemia can promote phase 2 reentry by further increasing repolarization reserve in epicardial ventricular tissue (Figure 5).<sup>42</sup> Whether hyperkalemia alone causes phase 2 reentry remains to be determined.

Systemic and global interstitial hyperkalemia are less arrhythmogenic than regional interstitial hyperkalemia after coronary occlusion. After coronary occlusion, interstitial  $[K^+]_o$  rises rapidly at a rate of 1.0 to 1.5 mmol  $L^{-1} min^{-1}$  in the

central ischemic zone. APD shortening and resting membrane potential depolarization cause both diastolic and systolic injury currents to flow across the border zone. These injury currents appear electrocardiographically as ST elevation, but actually represent a combination of TQ depression and ST elevation.<sup>52</sup> Injury currents flowing across the border zone can reexcite nonischemic recovered tissue to induce extrasystoles that initiate reentry (Figure 8A). Interstitial hyperkalemia also promotes all-or-none early repolarization in the ischemic subepicardium, inducing phase 2 reentry and VT/VF (Figure 8B), analogous to Brugada Short QT and Early Repolarization Syndromes.<sup>41</sup> These arrhythmogenic effects of interstitial hyperkalemia play a critical role in the majority of sudden cardiac deaths because of VT/VF in patients who never reach the hospital after an acute coronary occlusion.<sup>55</sup>

### Sources of Funding

This work was supported by National Institutes of Health/National Heart, Lung, and Blood Institute grant P01 HL079831 and the Laubisch and Kawata Endowments (J.N. Weiss).

### Disclosures

None.

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KEY WORDS: hyperkalemia ■ hypokalemia ■ ischemia ■ potassium channels ■ sodium

## Electrophysiology of Hypokalemia and Hyperkalemia

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*Circ Arrhythm Electrophysiol.* 2017;10:  
doi: 10.1161/CIRCEP.116.004667

*Circulation: Arrhythmia and Electrophysiology* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

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Print ISSN: 1941-3149. Online ISSN: 1941-3084

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