CONTEMPORARY REVIEW

Neurohormonal Regulation of $I_{Ks}$ in Heart Failure: Implications for Ventricular Arrhythmogenesis and Sudden Cardiac Death

Tyler Shugg, PharmD, PhD; Andy Hudmon, PhD; Brian R. Overholser, PharmD

ABSTRACT: Heart failure (HF) results in sustained alterations in neurohormonal signaling, including enhanced signaling through the sympathetic nervous system and renin-angiotensin-aldosterone system pathways. While enhanced sympathetic nervous system and renin-angiotensin-aldosterone system activity initially help compensate for the failing myocardium, sustained signaling through these pathways ultimately contributes to HF pathophysiology. HF remains a leading cause of mortality, with arrhythmogenic sudden cardiac death comprising a common mechanism of HF-related death. The propensity for arrhythmia development in HF occurs secondary to cardiac electrical remodeling that involves pathological regulation of ventricular ion channels, including the slow component of the delayed rectifier potassium current, that contribute to action potential duration prolongation. To elucidate a mechanistic explanation for how HF-mediated electrical remodeling predisposes to arrhythmia development, a multitude of investigations have investigated the specific regulatory effects of HF-associated stimuli, including enhanced sympathetic nervous system and renin-angiotensin-aldosterone system signaling, on the slow component of the delayed rectifier potassium current. The objective of this review is to summarize the current knowledge related to the regulation of the slow component of the delayed rectifier potassium current in response to HF-associated stimuli, including the intracellular pathways involved and the specific regulatory mechanisms.

Key Words: arrhythmias ■ heart failure ■ $I_{Ks}$ ■ KCNQ1 ■ renin-angiotensin-aldosterone system ■ sympathetic nervous system

Heart failure (HF) refers to a clinically heterogeneous group of pathologic conditions that result in reduced cardiac output and a subsequent reduction in the systemic circulation of oxygenated blood.1 HF affects nearly 6 million people in the United States and constitutes a leading cause of morbidity, mortality, hospitalization, and healthcare expenditure.2 HF imparts a 6- to 9-fold increase in the risk for sudden cardiac death (SCD) that occurs secondary to the development of ventricular arrhythmias, such as ventricular tachycardia (including torsades de pointes) and ventricular fibrillation.3,4 Animal models of HF as well as cardiomyocytes isolated from failing hearts consistently demonstrate prolongation of cardiac action potential duration (APD), which is a risk factor for the development of ventricular arrhythmias.5,6 Though HF mortality occurs through a variety of mechanisms, arrhythmogenic SCD accounts for up to 40% of mortality in patients with severe HF.4

HF is associated with pathological structural (ie, changes in the expression of contractile and extracellular matrix proteins) and electrical (ie, changes in the expression and function of calcium handling proteins, gap junctions, and ion channels) cardiac remodeling that predispose the failing heart to arrhythmogenesis.7 These remodeling processes largely stem from HF-associated changes in neurohormonal signaling and dysregulated calcium homeostasis.8 In particular, sustained elevations in the sympathetic nervous system (SNS) and renin-angiotensin-aldosterone system...
Cardiac ion channels mediate propagation of autonomous electrical signals in the heart, thereby providing coordinated electrical stimuli that trigger synchronized contraction of cardiac muscle. In this way, ion channels are critical physiologic regulators of cardiac rhythm and contractility. The human ventricle contains many species of ion channels that contribute to cardiomyocyte membrane potential during specific phases of the ventricular action potential via conductance of sodium, calcium, and potassium ions, as illustrated in Figure 1A in the healthy heart.\(^\text{14}\) Currents conducted by delayed rectifier potassium channels, including \(I_{\text{Ks}}\) (Figure 1B), are the primary contributors to the rapid repolarization phase of the ventricular action potential (phase 3) that is responsible for returning cardiomyocytes to resting membrane potential in preparation for subsequent depolarizing electrical stimuli (ie, heartbeats). Accordingly, alterations in ventricular ionic currents in heart failure (summarized in Figure 1C), including reductions in delayed rectifier potassium currents, prolong ventricular APD and thereby prolong the QT interval on the surface ECG.\(^\text{14}\)

Given the essential role of ion channels in regulating cardiac rhythm and contractility, dysregulation of ion channel function by HF-associated stimuli underlies increased arrhythmogenesis in HF, including increased development of ventricular arrhythmias.\(^\text{5,8}\) Though conflicting data exist, research investigations have largely found reductions in both species of ventricular delayed rectifier potassium currents in limited human studies and in animal and cellular HF models. Specifically, both increased angiotensin II signaling and sustained \(\beta\)-AR stimulation have been demonstrated to inhibit both the rapid component of the delayed rectifier potassium current \(I_{\text{Kr}}\) and \(I_{\text{Ks}}\).\(^\text{15–19}\) These findings are supported by studies in various models, including isolated ventricular cardiomyocytes from patients with HF, that demonstrate reductions in \(I_{\text{Ks}}\) and prolongation of APD in HF.\(^\text{6}\) HF-associated reductions in \(I_{\text{Ks}}\) may be of particular clinical importance since \(I_{\text{Kr}}\) is also reduced in HF, making the contributions of \(I_{\text{Ks}}\) to phase 3 repolarization in the ventricle more critical.\(^\text{20,21}\)

### SIGNIFICANCE OF I\(_{\text{KS}}\) IN HEALTH AND DISEASE

\(I_{\text{Ks}}\) is conducted through a voltage-gated potassium channel that is formed via protein-protein interaction of the pore-forming subunit, KCNQ1 (gene product of \(\text{KCNQ1}\); located on chromosome 11p), with the beta subunit, KCNE1 (product of \(\text{KCNQ1}\); 21q).\(^\text{22}\) KCNQ1 and KCNE1 are expressed in both human atria and ventricles, where \(I_{\text{Ks}}\) plays an essential role in phase 3 cardiac repolarization.\(^\text{23}\) In the ventricular action potential, \(I_{\text{Ks}}\) is a major contributor to the ventricular “repolarization reserve” by providing redundant current to maintain rapid repolarization during increases in cardiac rate or during conditions in which other ventricular potassium currents are reduced (eg, pharmacological

---

**Nonstandard Abbreviations and Acronyms**

| Acronym | Description |
|---------|-------------|
| APD     | action potential duration |
| ARBs    | angiotensin II receptor blockers |
| AT\(_1\) | angiotensin II type 1 receptor |
| CaM     | calcium-bound calmodulin |
| CaMKII  | calcium/calmodulin-dependent protein kinase II |
| Epac    | exchange protein activated by cyclic adenosine monophosphate |
| \(I_{\text{Kr}}\) | rapid component of the delayed rectifier potassium current |
| \(I_{\text{Ks}}\) | slow component of the delayed rectifier potassium current |
| \(I_{\text{Na}}\) | voltage-gated sodium current |
| MR      | mineralocorticoid receptor |
| \(\text{PIP}_2\) | phosphatidylinositol 4,5-bisphosphate |
| PKA     | protein kinase A |
| PKC     | protein kinase C |
| PKC-\(\epsilon\) | epsilon isoform of protein kinase C |
| RAAS    | renin-angiotensin-aldosterone system |
| SCD     | sudden cardiac death |
| SNS     | sympathetic nervous system |
| SUMO    | small ubiquitin-like modifier |
| \(\beta\)-AR | beta-adrenergic receptor |

(RAAS) pathways, as occur in HF, are intimately involved in HF pathophysiology.\(^\text{9}\) The roles of the SNS and RAAS in mediating HF disease progression are evidenced by the fact that medications targeting increased catecholaminergic \((\beta\)-AR [beta-adrenergic receptor] blockers) and angiotensin II (ACE [angiotensin-converting enzyme] inhibitors or angiotensin II receptor blockers [ARBs]) signaling confer mortality benefit and remain standards of care in HF therapy.\(^\text{10–12}\) While the mechanistic basis for the pathophysiologic role of alterations in neurohormonal signaling in HF is not completely understood, various investigations have demonstrated that sustained SNS and RAAS activation inhibit a variety of species of ion channels that are important regulators of the cardiac action potential.\(^\text{13}\) In particular, the potential for HF-associated changes in neurohormonal signaling to inhibit L-type calcium channels and delayed rectifier potassium channels, including those responsible for the slow component of the delayed rectifier potassium current \(I_{\text{Ks}}\), have been well established.\(^\text{13}\)
inhibition of $I_{Kr}$). In accordance with its contributions to the repolarization reserve, $I_{Ks}$ contributes only modestly to repolarization during normal resting heart rates (during which time $I_{Kr}$ is the predominant repolarizing current). However, $I_{Ks}$ has the potential to be acutely activated by the SNS to increase the rate of ventricular repolarization to compensate for increases in cardiac rate. This role is evidenced by the fact that reductions in $I_{Ks}$ may result in APD prolongation and the development of potentially fatal ventricular arrhythmias, particularly during sustained adrenergic tone. For example, loss-of-function mutations in $KCNQ1$, referred to as long QT syndrome phenotype 1, constitute the most common causes of congenital long QT syndrome and predispose patients to the development of ventricular arrhythmias and SCD that typically occur during periods of sustained adrenergic stimulation (eg, swimming). Channel activation to increase $I_{Ks}$ in response to acute release of norepinephrine and other catecholamines comprises a key physiologic mechanism to enhance repolarization during rapid heart rates. Increases in $I_{Ks}$ during rapid heart rates involve multiple mechanisms, including enhancement of $I_{Ks}$ current.
amplitude during individual ventricular depolarizations and accumulation of $I_{KS}$ during rapid pacing attributable to incomplete current deactivation.\textsuperscript{29} $I_{KS}$ activation during acute or intermittent SNS activation is mediated by catecholaminergic activation of $\beta$-ARs (primarily cardiac $\beta_1$-ARs) and involves a PKA (protein kinase A)-dependent signaling complex that has been well characterized.\textsuperscript{30}

In contrast to acute and intermittent $\beta$-AR signaling, sustained $\beta$-AR stimulation, as occurs as part of the pathophysiology of HF, has consistently been demonstrated to reduce $I_{KS}$.\textsuperscript{15,19} A number of studies have also shown that sustained increases in angiotensin II signaling, a major signaling molecule of the RAAS pathway that is also upregulated in HF, also result in reduced $I_{KS}$.\textsuperscript{16-18} Regardless of mechanism, reductions in $I_{KS}$ have been demonstrated to prolong APD and increase arrhythmia development in animal HF models.\textsuperscript{31} In addition, cardiomyocytes isolated from explanted hearts from patients with HF have also demonstrated reduced $I_{KS}$.\textsuperscript{6,32} Disturbances in $I_{KS}$ may contribute to known mechanisms of arrhythmia development, including transmural dispersion of repolarization,\textsuperscript{33,34} since KCNQ1 and KCNE1 have both demonstrated transmural differences in expression in human ventricular myocardium.\textsuperscript{35,36} Experiments in explanted human hearts have demonstrated that the contribution of $I_{KS}$ to ventricular repolarization is enhanced both during $\beta$-AR stimulation and in conditions where $I_{Kr}$ is reduced.\textsuperscript{37} Given its increased contribution to repolarization in HF, reductions in $I_{KS}$ have been shown to potentiate transmural dispersion of repolarization, though conflicting reports exist.\textsuperscript{37-39} Therefore, reductions in $I_{KS}$ in response to various neurohormonal triggers involved in HF pathogenesis may account for increases in the risk of ventricular arrhythmogenesis and SCD seen in HF.

### CELLULAR SIGNALING PATHWAYS INVOLVED IN $I_{KS}$ REGULATION IN HF

HF results in a multitude of alterations in neurohormonal signaling that, while initially are adaptive to maintain cardiac output in the failing heart, ultimately lead to cardiac remodeling and disease progression.\textsuperscript{7} In particular, chronic activation of the SNS and RAAS signaling pathways are key mediators of HF pathophysiology, and pharmacological targeting of these pathways remains the standard of care for preventing disease progression and HF-related morbidity and mortality.\textsuperscript{10} Sustained activation of the SNS and RAAS pathways have also been demonstrated to regulate $I_{KS}$ potentially contributing to enhanced arrhythmogenesis in patients with HF. Table 1 summarizes changes in $I_{KS}$ in response to HF-associated neurohormonal signaling.

Multiple investigations have identified regulation of $I_{KS}$ in response to SNS signaling, mediated through cardiac $\alpha$-ARs and $\beta$-ARs. Alterations in $I_{KS}$ by enhanced catecholaminergic signaling through $\alpha$-ARs, mediated primarily through cardiac $\alpha_1$-ARs, are less well established relative to $\beta$-AR signaling. Acute activation of $\alpha_1$-ARs has been demonstrated to reduce $I_{KS}$ by a mechanism that is mediated through PKC (protein kinase C)– and AMP kinase–dependent signaling and involves (1) downregulation of KCNQ1 and possibly KCNE1\textsuperscript{46,50} and (2) impaired $I_{KS}$ via depletion of phosphatidylinositol-4,5-bisphosphate (PIP$_2$).\textsuperscript{47,51} The implications of sustained $\alpha_1$-AR stimulation on $I_{KS}$ remain largely unknown, however; while sustained $\alpha_1$-AR

| Signaling Molecule | Receptors Involved | Duration | Effect | Reference |
|--------------------|--------------------|----------|--------|-----------|
| Angiotensin II     | Angiotensin II type 1 receptor | Acute    | $\uparrow I_{KS}$ | Zankov et al\textsuperscript{40} |
|                     |                    |          | $\downarrow I_{KS}$ | Matavel et al\textsuperscript{41} |
| Aldosterone        | Angiotensin II type 1 receptor | Chronic  | $\downarrow I_{KS}$ | Guo et al\textsuperscript{42} |
|                     | Mineralocorticoid receptor | Chronic  | $\downarrow I_{KS}$ | Li et al\textsuperscript{43} |
| Catecholamines     | $\alpha_1$-Adrenergic receptor | Acute    | $\downarrow I_{KS}$ | Kurakami et al\textsuperscript{46} |
|                     | $\beta$-Adrenergic receptor | Acute    | $\uparrow I_{KS}$ | Marx et al\textsuperscript{47} |
|                     | $\beta$-Adrenergic receptor | Chronic  | $\downarrow I_{KS}$ | Aflaki et al\textsuperscript{15} |
| Endothelin         | Endothelin receptor  | Acute    | $\uparrow I_{KS}$ | Habuchi et al\textsuperscript{48} |
|                     |                    |          | $\downarrow I_{KS}$ | Washizuka et al\textsuperscript{49} |
stimulation might be expected to reduce \( I_{Ks} \) via both subunit downregulation of KCNQ1 and KCNE1 and depletion of PIP2, evidence has shown (1) the potential for desensitization of PIP2 hydrolysis downstream of chronic \( \alpha_1 \)-AR signaling\(^{17} \) and (2) the ability of CaM (calcium-bound calmodulin) to interact with the PIP2 binding site on the KCNQ1 carboxyl terminus to stabilize \( I_{Ks} \).\(^{51} \) Acute \( \beta \)-AR stimulation has been consistently shown to enhance \( I_{Ks} \) through the aforementioned PKA pathway.\(^{15,19} \) In contrast, sustained \( \beta \)-AR stimulation has been demonstrated to reduce \( I_{Ks} \) through 2 distinct pathways: the first involving activation of the Epac (exchange protein activated by cAMP) and the second involving activation of CaMKII (calcium/calmodulin-dependent protein kinase II).\(^{15,19} \)

Sustained elevations in RAAS signaling, mediated largely through activation of the \( \alpha_1 \) (angiotensin II type 1 receptor) by angiotensin II, have also been demonstrated to affect \( I_{Ks} \). Conflicting data exist regarding the role of acute angiotensin II treatment on regulating \( I_{Ks} \), with investigations demonstrating both enhancements, mediated by phosphorylation of KCNE1 S102, with investigations demonstrating both enhancements, mediated by phosphorylation of KCNE1 S95, T96, or both and KCNE1 S102.\(^{17,42,43} \) Sustained treatment with angiotensin II, though less widely studied, has been demonstrated to reduce \( I_{Ks} \) through a mechanism involving cellular depletion of PIP2 in response to \( G_{i} \)-coupled \( \alpha_1 \) signaling.\(^{41} \) Chronic aldosterone exposure has also been found to reduce \( I_{Ks} \) via decreased expression of both KCNQ1 and KCNE1.\(^{45} \) Interestingly, aldosterone’s inhibitory effects on \( I_{Ks} \) have been shown to be mediated by signaling through both the MR (mineralocorticoid receptor) and \( \alpha_1 \)-AR signaling.\(^{44,45} \) This finding supports previously described crosstalk between MR activation and subsequent activation of angiotensin II/\( \alpha_1 \) signaling.\(^{53-55} \)

HF also results in chronic elevation of other signaling hormones, including atrial and brain natriuretic peptides, arginine vasopressin, and endothelin. Results from 2 studies assessing the effects of acute endothelin exposure on \( I_{Ks} \) within isolated guinea pig cardiomyocytes are conflicting, with one study demonstrating \( I_{Ks} \) enhancement and the other showing \( I_{Ks} \) reduction.\(^{48,49} \) The effect of chronic endothelin signaling on \( I_{Ks} \) has not been investigated. Similarly, the potential for acute or sustained exposure of atrial natriuretic peptide, brain natriuretic peptide, and vasopressin to regulate \( I_{Ks} \) have not been studied.

**POTENTIAL FOR CROSSTALK AMONG \( I_{Ks} \) REGULATORY PATHWAYS**

Given that HF-associated changes in neurohormonal signaling have been demonstrated to regulate \( I_{Ks} \) through a variety of pathways, there exists the potential for crosstalk among signaling pathways that regulate \( I_{Ks} \). Most notably, the potential for crosstalk between cardiac \( \alpha_1 \)-ARs and \( \alpha_1 \) receptors, as detailed in Figure 2A, has been consistently demonstrated in response to HF stimuli.\(^{56,57} \) Specific to \( I_{Ks} \), acute activation of both \( \alpha_1 \)-ARs and \( \alpha_1 \) receptors have been demonstrated to produce reductions in \( I_{Ks} \) through pathways that involve PKC activation and phosphorylation of KCNE1 S102.\(^{17,50,52} \) Accordingly, simultaneous signaling through acute activation of both pathways may bypass homeostatic mechanisms (eg, downregulation of receptors) involved in either pathway and thus further reduce \( I_{Ks} \).

Evidence also supports crosstalk between \( \alpha_1 \) receptor and cardiac \( \beta \)-AR signaling, including the potential for heterodimerization of the G-protein alpha subunits \( G_{i} \) and \( G_{s} \) downstream of \( \alpha_1 \) signaling.\(^{58-60} \) As previously mentioned, sustained activation of \( \beta \)-AR and \( \alpha_1 \) receptors have been demonstrated to reduce \( I_{Ks} \) through distinct mechanisms.\(^{15,17,19} \) However, these signaling pathways have been demonstrated to share a common downstream signaling molecule, CaMKII, that is known to be upregulated in HF and has been implicated in HF pathophysiology.\(^{61,62} \) The delta isoform of CaMKII (\( \delta \)CaMKII) is known to be activated downstream of AT1 receptor signaling in cardiomyocytes via a mechanism that involves oxidation of methionine 281 or methionine 282 on the enzyme.\(^{63-65} \) Conversely, sustained \( \beta \)-AR signaling activates the delta isoform of CaMKII through a pathway that involves autophosphorylation at T287 downstream of Epac and PKC-\( \epsilon \) signaling.\(^{64,66-68} \) Therefore, as described in Figure 2B, \( I_{Ks} \) reductions may also result from \( \delta \)CaMKII activation downstream of both \( \alpha_1 \) and \( \beta \)-AR signaling.

Finally, results from Lv et al\(^{14} \) suggest the potential for \( \alpha_1 \) activation downstream of sustained aldosterone activation of the MR. Mechanistically, these results are supported by previous findings that prolonged activation of the MR by aldosterone resulted in increased AT1 receptor density\(^{53} \) and increased gene expression of ACE.\(^{54,55} \) Both of these effects are predicted to increase signaling through \( \alpha_1 \) receptors, as shown in Figure 2C, which has been consistently shown to contribute to pathologic cardiac remodeling processes in HF.\(^{69,70} \) In addition, sustained MR activation has been independently linked to cardiac fibrosis\(^{71} \) and adverse HF outcomes.\(^{72,73} \)
alterations in neurohormonal signaling, may pathologically regulate IKS. These mechanistic analyses have largely focused on (1) changes in the expression of KCNQ1, KCNE1, and other KCNE isoforms; (2) posttranslational regulation of KCNQ1 and KCNE1 subunits; and (3) effects on the interactions among IKS-related proteins, including interaction of KCNQ1 and KCNE1 with each other and with various accessory proteins. Regardless of mechanism, the arrhythmogenic potential of reductions in IKS has been corroborated within investigations that have shown the development of ventricular arrhythmias during pharmacological inhibition of IKS and in canine and rabbit HF models wherein IKS is reduced.31 Below, we discuss the existing literature for each regulatory mechanism.

CHANGES IN KCNQ1 AND KCNE EXPRESSION IN HF

Although IKS reductions and APD prolongation have been consistently observed clinically and in cellular and animal HF models, the mechanism supporting IKS reduction remains elusive. In particular, changes in the expression of KCNQ1 and KCNE1 within animal HF models and samples from patients with HF have shown conflicting results, as summarized in Table 2. The results from animal studies, in which HF has been simulated by atrioventricular blockade, tachycardiac pacing, coronary artery occlusion, coronary artery microembolization, or treatment with the compounds isoproterenol (β-AR agonist) or aldosterone (MR agonist), have generally been mixed. Multiple studies have found reductions in mRNA and protein expression of KCNQ1 and KCNE1, while others have demonstrated no change in expression.15,21,34,45,74–78 In contrast, human studies that have analyzed ventricular tissue explanted from patients with HF have demonstrated either no change or increases in the mRNA expression of KCNQ1 and KCNE1 relative to healthy controls.32,79

Additionally, multiple KCNE isoforms, including KCNE2, KCNE3, KCNE4, and KCNE5, are expressed in human ventricular cardiomyocytes and may form heteromeric channels with KCNQ1 and KCNE1 to alter IKS.80–82 Coexpression of KCNQ2, KCNE4, and KCNE5 along with KCNQ1 and KCNE1 reduce IKS amplitude, whereas coexpression of KCNE3 with KCNQ1/KCNE1 has been shown to enhance IKS amplitude.81–83 While data describing HF-associated changes in these KCNE isoforms are sparse, one investigation found that mRNA expression of KCNQ2 and KCNE5 were reduced approximately 3- and 4-fold, respectively, in explanted left ventricular tissue from patients with
dilated or ischemic cardiomyopathy relative to healthy tissue.\textsuperscript{81} In contrast, mRNA expression of KCNE3 and KCNE4 were enhanced approximately 5- and 2-fold, respectively, in the cardiomyopathic left ventricle.\textsuperscript{81}

In summary, reductions in mRNA and protein expression of KCNQ1, KCNE1, and other KCNE isoforms in patients with HF and in animal HF models have not been consistently reproduced. These inconsistent findings are likely attributable to differences related to the HF model and the method of HF simulation. Regardless, these inconsistencies, along with the fact that the limited clinical data do not support reduced expression of KCNQ1 and KCNE1, suggest that alternative or additional molecular mechanism may mediate reduced $I_{\text{KS}}$ in HF.

**POSTTRANSLATIONAL REGULATION OF $I_{\text{KS}}$ IN HF**

A number of investigations have assessed the potential for aberrant posttranslational regulation of KCNQ1 and KCNE1 subunits to mediate reductions in $I_{\text{KS}}$ in response to HF-associated changes in neurohormonal signaling. These studies have identified regulatory sites on the intracellular amino and carboxyl termini of KCNQ1 and the intracellular carboxyl terminus of KCNE1 with functional implications for $I_{\text{KS}}$. Figure 3 diagrams the KCNQ1 and KCNE1 subunits, showing demonstrated sites of posttranslational regulation in response to HF-related stimuli.

**Biology of KCNQ1**

The KCNQ1 subunit is 676 amino acids in length and contains a 120-residue intracellular amino terminus and a 325-residue intracellular carboxyl terminus.\textsuperscript{84} These termini are separated by a transmembrane region with 6 membrane-spanning domains, with the region connecting the fifth and sixth segments serving as the pore and multiple positively charged residues in the fourth segment serving as the voltage sensor.\textsuperscript{85} The canonical $I_{\text{KS}}$ channel is formed when 4 KCNQ1 subunits coassemble via protein-protein interactions with 2 KCNE1 auxiliary

---

**Table 2. Studies Assessing Changes in the Expression of KCNQ1 and KCNE1 in Animal or Human Models of HF**

| HF Simulation Method | Experimental Model | Percent Change in mRNA Expression | Percent Change in Protein Expression | Authors |
|----------------------|--------------------|-----------------------------------|-------------------------------------|---------|
| Chronic aldosterone treatment | Guinea pig left ventricle | ↓60%*| ↓60%* | Lv et al\textsuperscript{45} |
| Chronic atrioventricular block | Canine ventricle | ↓80% | ↓70% | Ramakers et al\textsuperscript{44} |
| Chronic atrioventricular block + bradycardiac pacing | Rabbit left ventricle | ↓53% | ↓43% | Tsuji et al\textsuperscript{47} |
| Chronic atrioventricular block + tachycardiac pacing | Rabbit right ventricle | ↓76% | ↓58% | Tsuji et al\textsuperscript{47} |
| Chronic atrioventricular block + tachycardiac pacing | Rabbit left ventricle | ↓61% | ↓43% | Tsuji et al\textsuperscript{47} |
| Chronic atrioventricular block + tachycardiac pacing | Rabbit right ventricle | ↓64% | ↓74% | Tsuji et al\textsuperscript{47} |
| Chronic ischemia (coronary artery occlusion) | Rabbit myocardium | ↔ | ↔ | Guo et al\textsuperscript{77} |
| Chronic ischemia (coronary microembolization) | Canine myocardium | NS | NS | Liu et al\textsuperscript{86} |
| Chronic isoproterenol treatment | Guinea pig ventricle | ↔ | ↓45% | Afifi et al\textsuperscript{75} |
| Chronic isoproterenol treatment | Guinea pig ventricle | ↔ | NS | Sołtysinska et al\textsuperscript{84} |
| Tachycardiac pacing | Canine left ventricle | ↔ | ↔ | Akar et al\textsuperscript{88} |
| Tachycardiac pacing | Rabbit ventricle | ↔ | ↔ | Rose et al\textsuperscript{89} |
| None (clinical heart failure) | Human left ventricle | ↑160% | NS | Boriak et al\textsuperscript{72} |
| None (clinical heart failure) | Human left ventricle | ↑400%* | 1400%* | Lundquist et al\textsuperscript{81} |
| None (clinical heart failure) | Human right ventricle | ↔ | NS | Boriak et al\textsuperscript{72} |
| None (clinical heart failure) | Human right ventricle | ↔ | ↑25% | Watanabe et al\textsuperscript{92} |

\(↑\) indicates increased expression; \(↓\), decreased expression; ↔, no significant change in expression; HF, heart failure; and NS, not studied.

\*Numerical results for the change in expression of KCNQ1 and KCNE1 were not presented in the Lv et al and Lundquist et al articles. The presented percentages were estimated based on the presented graphical results.

\† Because of limitations in detecting KCNE1 within protein immunoblot experiments, Guo et al\textsuperscript{77} did not report results for changes in KCNE1 protein expression.

\‡ Liu et al found no change in expression of the predominant KCNQ1 isoform (KCNQ1.1), but did observe an increase in expression of a truncated KCNQ1 isoform (KCNQ1.2), which they predicted to inhibit $I_{\text{KS}}$ in a dominant-negative fashion.
subunits. The intracellular amino and carboxyl termini of KCNQ1 contain residues and domains that are critical for channel function, including domains that affect (1) the biophysical properties of $I_{Ks}$ current, (2) coassembly of KCNQ1 tetramers, (3) trafficking of KCNQ1 channels, and (4) interaction of KCNQ1 subunits with KCNE1 and other interacting proteins and molecules (eg, PIP2 and CaM). Given the established functional importance of the intracellular domains of KCNQ1, multiple investigations have assessed the potential for experimental models of HF to regulate the intracellular regions of KCNQ1 and thereby affect $I_{Ks}$.

**Posttranslational Regulation of KCNQ1 in HF**

Posttranslational regulation of the intracellular amino and carboxyl termini of KCNQ1 has been demonstrated to regulate $I_{Ks}$ in cellular and animal models in response to HF-related signaling cascades. Specifically, the KCNQ1 amino terminus contains residues, including S27 and possibly S92, that mediate activation of $I_{Ks}$ during acute $\beta$-AR stimulation via a well-characterized signaling complex that includes PKA, alpha-kinase anchoring protein 9 (also called yotiao), protein phosphatase 1, phosphodiesterase 4D3, and adenylate cyclase 9. However, it is has been consistently demonstrated that responsiveness to $\beta$-AR signaling becomes reduced or “uncoupled” during sustained $\beta$-AR stimulation by a mechanism that involves downregulation of $G_{\alpha}$, these findings suggest that PKA-mediated enhancement of $I_{Ks}$ during acute $\beta$-AR stimulation, which plays a critical physiologic role in shortening ventricular repolarization during rapid heart rates, is diminished during HF and may contribute to pathological electrical remodeling. Site-specific phosphorylation of the KCNQ1 amino terminus has also been shown to regulate $I_{Ks}$ in response to enhanced angiotensin II signaling. Acute increases in angiotensin II signaling alter $I_{Ks}$ via a signaling cascade that involves PKC, with a recent investigation by Gou et al implicating the PKC-ε (episilon isoform of protein kinase C) as the regulator via a pathway that involves phosphorylation of S95, T96, or both on the amino terminus of KCNQ1 and a carboxyl residue (S102) on KCNE1. It should be reemphasized that the implications of acute angiotensin II exposure on $I_{Ks}$ have demonstrated conflicting results, with 2 studies demonstrating $I_{Ks}$ enhancement and 3 others finding $I_{Ks}$ reductions.

Posttranslational regulation of the KCNQ1 carboxyl terminus in response to HF-related signaling has also been described. Sustained $\beta$-AR stimulation was recently shown to reduce $I_{Ks}$ via a mechanism that involves δCAMKII-mediated phosphorylation of S484 on the KCNQ1 carboxyl terminus. Ubiquitination of...
a PY motif by the E3 ubiquitin-protein ligase NEDD4-2 (neural precursor cell expressed developmentally downregulated 4-like) in the distal KCNQ1 carboxyl terminus (L659-Y662) has also been demonstrated to reduce I_{KS} via downregulation of KCNQ1 plasma membrane expression.46,97 More recently, findings by Kurakami et al.48 elucidated the signaling pathway involved in KCNQ1 ubiquitination, which involves AMP kinase and PKC and occurs secondary to acute \( \alpha_1 \)-AR activation. The effects of sustained \( \alpha_1 \)-AR activation on KCNQ1 ubiquitination and plasma membrane expression have not been studied. Finally, an investigation by Xiong et al.98 has identified the SUMO (small ubiquitin-related modifier) protein as a key regulator of activation gating. “SUMOylation,” the process by which an interacting protein is covalently bound by a SUMO protein, has been demonstrated at K424 on each KCNQ1 subunit (incorporating up to four SUMO proteins in a functional \( I_\text{KS} \) channel) in a process that is KCNE1-dependent.98 The regulatory role of SUMOylation on \( I_\text{KS} \) may be of significance in HF since past investigations have found that SUMO proteins, and thereby the process of SUMOylation, are downregulated in HF; decreased SUMOylation in HF has been shown to result in pathological changes in processes involved in cardiac contractility and stress adaptation, including specific pathological regulation of the sarco/endoplasmic reticulum Ca\(^{2+}\)-ATPase.99,100

**Biology of KCNE1**

The KCNE1 subunit is 129 amino acids in length and contains a 44 residue extracellular amino terminus and a 58 residue intracellular carboxyl terminus.101 These termini are separated by a single membrane-spanning transmembrane domain.101 Functional interaction with KCNQ1 involves multiple locations within the transmembrane domain and carboxyl terminus of KCNE1 and produces the characteristic properties of physiologic \( I_\text{KS} \), including slowing of channel activation, increasing conductance, and reducing or eliminating channel inactivation relative to currents produced by KCNQ1 alone.22,101,102 Based on the necessity of KCNQ1-KCNE1 interaction for proper channel function, investigations have assessed the functional implications of posttranslational modifications of KCNE1 in response to HF-related signaling pathways.

**Posttranslational Regulation of KCNE1 in HF**

Multiple investigations have elucidated a role for \( \alpha_1 \)-AR signaling in mediating reductions in \( I_\text{KS} \) via a mechanism that involves PKC-dependent phosphorylation of KCNE1 S102.50,52 While the exact isoform of PKC that phosphorylates S102 has not been fully elucidated, it has been demonstrated to be a calcium-dependent PKC isoform, such as alpha (PKC-\( \alpha \)), which is the predominant isoform expressed in the heart, or beta (PKC-\( \beta \)), which is upregulated in HF.103–105 Regardless of the specific PKC isoform involved, \( I_\text{KS} \) reduction in response to \( \alpha_1 \)-AR stimulation mechanistically involves enhanced clathrin- and dynamin-dependent endocytosis of plasma membrane-bound KCNQ1-KCNE1 channel complexes.50,52

**HF EFFECTS ON INTERACTION AMONG \( I_\text{KS} \)-RELATED PROTEINS**

In addition to changes in KCNQ1 and KCNE1 expression or posttranslational subunit regulation, HF-associated changes in neurohormonal signaling have also been demonstrated to modulate the interaction of KCNQ1 and KCNE1 with each other and other interacting proteins. These alterations may have important implications for \( I_\text{KS} \) in HF.

**HF-Associated Modulation of the KCNQ1-KCNE1 Subunit Interaction**

HF-associated signaling changes may modulate the protein-protein interaction between KCNQ1 and KCNE1 subunits and thereby reduce \( I_\text{KS} \). Work by Dvir et al.90 which investigated the mechanisms for how long QT syndrome mutations in the KCNQ1 and KCNE1 carboxyl termini affect \( I_\text{KS} \), demonstrated an important role for PIP\(_2\) in facilitating interaction of KCNQ1 and KCNE1. The importance of PIP\(_2\) in regulating \( I_\text{KS} \) was also demonstrated by Kienitz et al.47 Their work found \( I_\text{KS} \) reductions following sustained \( \alpha_1 \)-AR stimulation via enzymatic depletion of cellular PIP\(_2\) through a pathway involving chronic PKC activation, which is a known pathologic regulator in HF.106,107 Accordingly, HF-associated increases in SNS signaling are predicted to disrupt the KCNQ1-KCNE1 subunit interaction by depleting cellular stores of PIP\(_2\), thereby reducing \( I_\text{KS} \).

**HF-Associated Modulation of KCNQ1-KCNE1 Interaction With Other Interacting Proteins**

HF-associated changes in neurohormonal signaling have also been demonstrated to impact the functional interaction between KCNQ1-KCNE1 complexes and other interacting proteins necessary for channel function. For instance, an investigation by Aye et al.108 demonstrated that, relative to tissue from control hearts, explanted heart tissue in patients with HF showed impaired interaction of PKA with alpha-kinase anchoring protein 9, thus potentially blunting \( I_\text{KS} \) via PKA-mediated (and alpha-kinase anchoring
protein 9–dependent) phosphorylation of KCNQ1 S27 during acute or intermittent rises in adrenergic signaling. Reductions in alpha-kinase anchoring protein 9–dependent IKs responsiveness to acute β-AR stimulation are predicted to exacerbate an already decreased responsiveness to β-AR stimulation in HF (ie, because of PKA uncoupling secondary to reduced Gs expression). Together, these HF-mediated signaling adaptations are predicted to act in concert to impart an increased risk of QT prolongation and ventricular arrhythmogenesis.74

HF-associated changes may also influence interaction of KCNQ1 with CaM, a calcium-binding second messenger that is a regulator of IKs inactivation gating and channel assembly.89 Specifically, CaM has been shown to interact with KCNQ1 via 2 CaM-binding domains within helices A and B of the KCNQ1 carboxyl terminus in a process that is required for channel tetramerization.89,109 Given the essential role of CaM in regulating IKs, reduced expression of CaM, as has been consistently demonstrated in HF, may be involved in the pathologic regulation of IKs in HF.79,110

CONCLUSION

HF imparts an enormous health burden, and cardiac electrical remodeling underlies a major mechanism of HF-related pathophysiology.2,4 HF is associated with alterations in neurohormonal signaling, including sustained elevations in SNS and RAAS signaling, that prolong APD and predispose to arrhythmogenic SCD via pathologic regulation of ion channels, including IKs.7,13 Herein, we present the current experimental evidence related to the regulation of IKs during normal physiology and in response to HF-associated stimuli. Specifically, we focus on (1) the cellular receptors and intracellular pathways involved in HF pathophysiology and (2) the specific mechanisms through which HF-associated neurohormonal signaling impact IKs. By aggregating findings from the basic science and clinical literature, we provide a comprehensive review of both the pathologic regulation of IKs in HF and the resulting clinical implications on electrical instability and arrhythmogenesis.

Although this review summarizes the literature related to pathological remodeling to alter IKs, HF is also known to pathologically regulate a wide variety of ion channels and calcium-handling proteins, which contribute to HF-associated ventricular arrhythmogenesis. Past investigations have convincingly demonstrated pathological regulation of ventricular sodium (eg, late INa), calcium (eg, ICa,L), and potassium currents (eg, the transient outward potassium current, IKr, the inward rectifier potassium current) along with calcium-handling proteins, including the ryanodine receptor, the sodium–calcium exchanger, and sarco/endoplasmic reticulum Ca2+-ATPase, in HF.6,21,111-115 HF-associated changes in affected ion currents are summarized in Figure 1C. Given that HF results in deficits in other repolarizing ion currents, including IKs, and the inward rectifier potassium current, the proarrhythmic potential of reductions in IKs is enhanced in HF.20,21,25 Indeed, it has been demonstrated that HF-associated reductions in IKs contribute to the proarrhythmic effects of other calcium-related ion carriers that are activated in response to β-AR stimulation (ie, ICa,L, the sodium–calcium exchanger).116,117 Therefore, the enhanced ventricular electrical instability and arrhythmogenesis characteristic of HF stem from complex interaction of multiple ionic currents that undergo pathological remodeling in HF.

While the therapeutic success of targeting SNS and RAAS signaling in HF is well documented,11,12 progress toward the understanding of HF pathophysiology continues to elucidate novel potential therapeutic targets. In particular, advances in basic science research have revealed putative therapeutic targets downstream of membrane-bound receptors that have the potential to overcome challenges associated with signaling pathway crosstalk, such as Epac and CaMKII.118,119 As detailed in this review, the potential benefits of these promising therapeutic targets may be, at least in part, attributable to their ability to prevent or ameliorate pathological IKs remodeling. Further research is needed to explore the therapeutic potential of these novel targets in preventing and improving clinical outcomes in HF, including arrhythmogenic SCD.

ARTICLE INFORMATION

Affiliations
From the Division of Clinical Pharmacology, Indiana University School of Medicine, Indianapolis, IN (T.S., B.R.O.); Department of Medicinal Chemistry and Molecular Pharmacology (A.H.) and Department of Pharmacy Practice, Purdue University College of Pharmacy, Indianapolis, IN (B.R.O.).

Sources of Funding
This work was supported in part by a grant from the National Institutes of Health, National Heart, Lung, and Blood Institute; R03 HL141619.

Disclosures
None.

REFERENCES

1. Francis GS, Cogswell R, Thenappan T. The heterogeneity of heart failure: will enhanced phenotyping be necessary for future clinical trial success? J Am Coll Cardiol. 2014;64:1775–1776.

2. Benjamin EJ, Virani SS, Callaway CW, Chamberlain AM, Chang AR, Cheng S, Chiue S, Cushman M, Delling FN, Deo R, et al. Heart disease and stroke statistics–2018 update: a report from the American Heart Association. Circulation. 2018;137:e67–e492.
3. Saltzman HE. Arrhythmias and heart failure. Circulation. 2013;128:133–133.

4. Tomaselli GF, Zipes DP. What causes sudden death in heart failure? Circ Res. 2004;95:754–763.

5. Coronel R, Wilders R, Verkerk AO, Wiegerinck RF, Benoist D, Bernus O. Electrophysiological changes in heart failure and their implications for arrhythmogenesis. Biochim Biophys Acta. 2013;1832:2432–2441.

6. Li GR, Lau CP, Leung TK, Nattel S. Ionic current abnormalities associated with prolonged action potentials in cardiomyocytes from diseased human right ventricles. Heart Rhythm. 2004;1:1480–1488.

7. Cutler MJ, Rosenbaum DS, Dunlap ME. Structural and electrical remodeling as therapeutic targets in heart failure. J Electrocardiol. 2007;40:51–57.

8. Nattel S, Maguy A, Le Bouter S, Yeh YH. Arrhythmogenic ion-channel remodeling in the heart: heart failure, myocardial infarction, and atrial fibrillation. Physiol Rev. 2007;87:425–456.

9. Packer M. The neurohormonal hypothesis: a theory to explain the mechanism of disease progression in heart failure. J Am Coll Cardiol. 1992;20:248–254.

10. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Colvin MM, Drazner MH, Filipatos GS, Fonarow GC, Givertz MM, et al. 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines and the heart failure society of America. Circulation. 2017;136:936–997.

11. Shibata MC, Flather MD, Wang D. Systematic review of the impact of beta blockers on mortality and hospital admissions in heart failure. Eur J Heart Fail. 2001;3:351–357.

12. Garg R, Yusuf S. Overview of randomized trials of angiotensin-converting enzyme inhibitors on mortality and morbidity in patients with heart failure. Collaborative Group on ACE Inhibitor Trials. JAMA. 1995;273:1450–1456.

13. Kurokawa J, Abriel H. Neurohormonal regulation of cardiac ion channels in chronic heart failure. J Cardiovasc Pharmacol. 2009;54:98–105.

14. Katz AM. Physiology of the heart, 5th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2011.

15. Atlasi M, Qi XY, Xiao L, Ordog B, Tadevosyan A, Luo X, Maguy A, Shi Y, Tardif JC, Nattel S. Exchange protein directly activated by cAMP mediates slow delayed rectifier current remodeling by sustained beta-adrenergic activation in guinea pig hearts. Circ Res. 2014;114:993–1003.

16. Gonzalez-Juanatey JR, Garcia-Acuna JM, Pose A, Varela A, Calvo C, Cabezás-Cerrato J, de la Pena MG. Reduction of QT and QTc dispersion during long-term treatment of systemic hypertension with enalapril. Am J Cardiol. 1998;81:170–174.

17. Gou K, Wang W, Zou S, Qi Y, Xu Y. Protein kinase C epsilon mediates the inhibition of angiotensin II on the slowly activating delayed-rectifier potassium current through channel phosphorylation. J Mol Cell Cardiol. 2018;116:165–174.

18. Rivard K, Paradis P, Nemer M, Fiset C. Cardiac-specific overexpression of the human type 1 angiotensin II receptor causes delayed repolarization. Cardiovasc Res. 2008;78:53–62.

19. Shugh T, Johnson DE, Shao M, Lai X, Witzmann F, Cummins TR. Regulation of IKS During Heart Failure

20. Banyasz T, Jian Z, Horvath B, Kabrhaz S, Izu LT, Chen-Izu Y. Beta-adrenergic stimulation reverses the I Kr-I Ks dominant pattern during cardiac action potential. Pflugers Arch. 2014;466:2067–2076.

21. Volders PG, Stengl M, van Opstal JM, Gerlach U, Spåtens RL, Beeckman JD, Sidipo KR, Vos MA. Probing the contribution of I Ks to canine ventricular repolarization: key role for beta-adrenergic receptor stimulation. Circulation. 2003;107:2753–2760.

22. Splawski I, Shen J, Timothy KW, Lehmann MH, Priori S, Robinson JL, Moss AJ, Schwartz PJ, Tobin JA, Vincent GM, et al. Spectrum of mutations in long-QT syndrome genes. KVLQT1, HERG, SCN5A, KCNE1, and KCNE2. Circulation. 2000;102:1178–1185.

23. Stengl M, Volders PG, Thomsen MB, Spåtens RL, Sidipo KR, Vos MA. Accumulation of slowly activating delayed rectifier potassium current (I Ks) in canine ventricular myocytes. J Physiol. 2003;551:777–786.

24. Marx SO, Kurokawa J, Reiken S, Mutoke H, D’Amiento J, Marks AR, Kass RS. Requirement of a macromolecular signaling complex for beta-adrenergic receptor modulation of the KCNQ1–KCNQ1 potassium channel. Science. 2002;295:496–499.

25. Cheng HC, Incandona J. Models of torsades de pointes: effects of FPL64176, DPD20116, dofetilide, and chromanol 293B in isolated rabbit and guinea pig hearts. J Pharmacol Toxicol Methods. 2006;50:174–184.

26. Watanabe E, Yasaki K, Kamiya K, Yamaguchi T, Sakuma I, Honjo H, Ozaki Y, Morimoto S, Hishida H, Kodama I. Upregulation of KCNE1 induces QT interval prolongation in patients with chronic heart failure. Circulation. 2007;117:471–478.

27. Lee HC, Rych Y, Po-Yung Y, Shou SH, Chang JG, Cui J. Modulation of KCNQ1 alternative splicing regulates cardiac Iks and action potential repolarization. Heart Rhythm. 2013;10:1220–1228.

28. Ramakers C, Vos MA, Doevedans PA, Schoenmakers M, Wu YS, Sciicchitano S, Iodice A, Thomas GP, Antzelevitch C, Dumaine R. Coordinated down-regulation of KCNQ1 and KCNE1 expression contributes to reduction of I Ks in canine hypertrophied hearts. Cardiovasc Res. 2003;57:486–496.

29. Liu DW, Antzelevitch C. Characteristics of the delayed rectifier current (I Ks and I Kr) in canine ventricular epicardial, midmyocardial, and endocardial myocytes. A weaker I Kr contributes to the longer action potential of the M cell. Circ Res. 1996;78:351–365.

30. Szabó G, Szentandrássy N, Biro T, Tóth BI, Czifra G, Magyar J, Bányász T, Kovács L. Nánnási P. Asymmetrical distribution of ion channels in canine and human left-ventricular wall: epicardium versus midmyocardium. Pflugers Archiv: Eur J Physiol. 2005;450:307–316.

31. Kang C, Badieaneu A, Brennan JA, Gloshat C, Qiao Y, Trayanova NA, Efimov IR. Beta-adrenergic stimulation augments transmural dispersion of repolarization via modulation of delayed rectifier currents I Ks and I Kr in the human ventricle. Sci Rep. 2017;7:15922.

32. Barkashov OK, Antzelevitch C, Prominent I Ks in epicardium and endocardium contributes to development of transmural dispersion of repolarization but protects against development of early afterdepolarizations. J Cardiovasc Electrophysiol. 2002;13:172–177.

33. Pajouh M, Wilson LD, Poezing S, Johnson NJ, Rosenbaum DS. Iks blockade reduces dispersion of repolarization in heart failure. Heart Rhythm. 2005;2:731–738.

34. Zankov DP, Omatsu-Kanbe M, Isono T, Toyoda F, Ding WG, Matsuura H, Morimoto S, Hishida H, Kodama I. Upregulation of KCNE1 biphasic regulation of IKs by Gq-coupled receptors. J Physiol. 2004;551:777–786.

35. Szabó G, Szentandrássy N, Biro T, Tóth BI, Czifra G, Magyar J, Bányász T, Kovács L. Nánnási P. Asymmetrical distribution of ion channels in canine and human left-ventricular wall: epicardium versus midmyocardium. Pflugers Archiv: Eur J Physiol. 2005;450:307–316.
46. Kurakami K, Norota I, Nasu F, Ohshima S, Nagasawa Y, Konno Y, Obara Y, Ishii K. KCNQ1 is internalized by activation of alpha1-adrenergic receptors. Biochem Pharmacol. 2019;169:113628.

47. Kienitz MC, Vladimirova D, Muller C, Pott L, Rinne A. Receptor species-dependent desensitization controls KCNQ1/KCNEl K+ channels as downstream effectors of Gq protein-coupled receptors. J Biol Chem. 2016;291:26410–26426.

48. Habuchi Y, Tanaka H, Furukawa T, Tsujimura Y, Takahashi H, Yoshimura M. Endothelin enhances delayed potassium current via phospholipase C in guinea pig ventricular myocytes. Am J Physiol. 1992;262:H345–H354.

49. Washizuka T, Horie M, Wataniuki M, Sasayama S. Endothelin-1 inhibits the slow component of cardiac delayed rectifier K+ currents via a pertussis toxin-sensitive mechanism. Circ Res. 1997;81:211–218.

50. Kanda VA, Purtell K, Abbott GW. Protein kinase C downregulates I(Ks) by stimulating KCNQ1/KCNEl potassium channel endocytosis. Heart Rhythm. 2011;8:1641–1647.

51. Tobelaim WS, Dvir M, Lebel G, Cui M, Buki T, Peretz A, Marom M, Haitin Y, Logothetis DE, Hirsch JA, et al. Ca2+ and IP3 interactions at the proximal C-terminus of Kcs channels. Circulation. 2017;11:686–695.

52. Ronzier E, Parks XX, Lopes CM. KCNEl subunit phosphorylation leads to I(Ks) internalization in response to chronic calcium-dependent PKG activation. Biochem J. 2019;418:398A.

53. Uillan ME, Schelling JR, Linas SL. Aldosterone enhances angiotensin II receptor binding and inositol phosphate responses. Hypertension. 1992;20:67–73.

54. Sugiyama T, Yoshimoto T, Tsuchiya K, Gochou N, Hirono Y, Tateno T, Obara Y, Ishii K. KCNQ1 is internalized by activation of alpha1 adrenergic receptors. PLoS One. 2014;9:e94257.

55. Harada E, Yoshimura M, Yasue H, Nakagawa O, Nakagawa M, Harada M, Mizuno Y, Nakayama M, Shimasaki Y, Ito T, et al. Aldosterone induces angiotensin-converting-enzyme gene expression in cultured neonatal rat cardiomyocytes. Circulation. 2001;104:137–139.

56. Vittorio TJ, Fudim M, Wagman G, Kosmas CE. Alpha-1 adrenoceptor-angiotensin II type 1 receptor cross-talk and its relevance in clinical medicine. Cardiol Rev. 2014;22:51–55.

57. Henegar JR, Brower GL, Kabour A, Janicki JS. Catecholamine response to chronic ANG II infusion and its role in myocyte and coronary vascular damage. Am J Physiol. 1995;268:H1564–H1569.

58. Schuetz WE, Xue H, Reid JF, Rollebot JB, Anderson S, Mader SL. Angiotensin II enhances beta-adrenergic receptor-mediated vasorelaxation in aortas from young but not old rats. Am J Physiol Heart Circ Physiol. 2000;279:H2807–H2814.

59. Ostrom RS, Naugle JE, Hase M, Gregorian C, Swaney JS, Insel P, Luttrell LM, Rockman HA. Dual inhibition of beta-adrenergic and angiotensin II signaling in intact cardiomyocytes. J Cardiovasc Pharmacol. 2010;56:598–603.

60. Hoch B, Meyer R, Hetzer R, Krause EG, Karczewski P. Identification of I(Ks) by stimulating KCNQ1/KCNEl potassium channel endocytosis. Heart Rhythm. 2011;8:1641–1647.

61. Shugg et al. Regulation of IKS During Heart Failure. J Cardiovasc Pharmacol. 2003;278:24461–24468.

62. Baltas LG, Karczewski P, Bartel S, Krause EG. The endogenous cardiac sarcoplasmic reticulum Ca2+-calmodulin-dependent kinase is activated in response to beta-adrenergic stimulation and becomes Ca2+-independent in intact beating hearts. FEBS Lett. 1997;409:131–136.

63. Curran J, Hinton MJ, Rios E, Berts DM, Shannon TR. Beta-adrenergic enhancement of sarcoplasmic reticulum calcium leak in cardiac myocytes is mediated by Ca2+-calmodulin-dependent protein kinase. Circ Res. 2007;100:391–398.

64. Dias E, Fisher-Mistler R, Richard S, Benitah JP, et al. The CaM binding protein Epac modulates Ca2+ sparks by a Ca2+-calmodulin kinase signaling pathway in rat cardiac myocytes. J Physiol. 2001;538:685–694.

65. Wollert CK, Drexler H. The renin-angiotensin system and experimental heart failure. Cardiovasc Res. 1999;43:838–849.

66. Ohta K, Kim S, Wainiibuchi H, Ganten D, Iwao H. Contribution of local renin-angiotensin system to cardiac hypertrophy, phenotypic modulation, and remodeling in TGR (mRen2)27 transgenic rats. Circulation. 1996;94:785–791.

67. Tesch GH, Young MJ. Mineralocorticoid receptor signaling as a therapeutic target for renal and cardiac fibrosis. Front Pharmacol. 2017:8;313.
86. Yu H, Lin Z, Mattmann ME, Zou B, Tenenore C, Zhang H, Wu M, McManus OB, Kass RS, Lindsley CW, et al. Dynamic subunit stoichiometry confers a progressive continuum of pharmacological sensitivity by KCNQ potassium channels. Proc Natl Acad Sci U S A. 2013;110:8732–8737.

87. Schwake M, Athanasiadou D, Beimgreben C, Blanz J, Beck C, Jentach TJ, Safiq P, Friedrich T. Structural determinants of M-type KCNQ (K\textsuperscript{+}) channel assembly. J Neurosci. 2006;26:3757–3766.

88. Howard RJ, Clark KA, Holton JM, Minor DL Jr. Structural insights into KCNQ (K\textsuperscript{+}) channel assembly and channelopathy. Neuron. 2007;53:663–675.

89. Ghosh S, Nunziato DA, Pitt GS. KCNQ1 assembly and function is blocked by long-QT syndrome mutations that disrupt interaction with calmodulin. Circ Res. 2006;98:1045–1054.

90. Dvir M, Strulovich R, Sachyani D, Ben-Tal Cohen I, Hainit Y, Dessauer C, Pongs O, Kass R, Hirsh JA, Attai B. Long QT mutations at the interface between KCNQ1 helix C and KCNE1 disrupt K(\textsuperscript{+}) regulation by PKA and PIP(2). J Cell Sci. 2014;127:3943–3955.

91. Lundby A, Andersen MN, Steffensen AB, Horn H, Kelstrup CD, Shugg et al. Regulation of IKs During Heart Failure. Circulation. 2017;135:114–132.

92. Schwake M, Athanasiadou D, Beimgreben C, Blanz J, Beck C, Jentsch TJ, Saftig P, Friedrich T. Structural determinants of M-type KCNQ (K\textsuperscript{+}) channel assembly. J Neurosci. 2006;26:3757–3766.

93. Li Y, Hof T, Baldwin TA, Chen L, Kass RS, Dessauer CW. Regulation of IKs potassium current by isoproterenol in adult cardiomyocytes requires type 9 adenylyl cyclase. Proc Natl Acad Sci U S A. 2004;101:16374–16378.

94. Pogwizd SM, Bers DM. Calcium cycling in heart failure: the arrhythmia focus on IKs downregulation and blunted beta-adrenergic activation. J Cardiovasc Electrophysiol. 2004;15:1290–1302.

95. Baro I, Abriel H. The KCNQ1 potassium channel is down-regulated by ubiquitylating enzymes of the Nedd4/Nedd4-like family. Cardiovasc Res. 2009;82:582–589.

96. Aye TT, Soni S, van Veen TA, van der Heyden MA, Cappadona S, Varro A, de Weger RA, de Jonge N, Vos MA, Beck C, et al. Reorganized PKA-AKAP associations in the failing human heart. J Cell Mol Cardiol. 2012;52:511–518.

97. Fowler MB, Laser JA, Hopkins GL, Minobe W, Bristow MR. Evaluation of Norepinephrine’s actions in cardiomyocytes. Circ Res. 1989;64:1741–1748.

98. Xiong D, Li T, Dai H, arena AF, Plant LD, Goldstein SAN. SUMOylation of alpha subunits of G protein-coupled receptors by ubiquitin-like SUMO systems. Proc Natl Acad Sci U S A. 2004;101:1383–1388.

99. Schwake M, Athanasiadou D, Beimgreben C, Blanz J, Beck C, Jentsch TJ, Saftig P, Friedrich T. Structural determinants of M-type KCNQ (K\textsuperscript{+}) channel assembly. J Neurosci. 2006;26:3757–3766.

100. Li Y, Hof T, Baldwin TA, Chen L, Kass RS, Dessauer CW. Regulation of IKs potassium current by isoproterenol in adult cardiomyocytes requires type 9 adenylyl cyclase. Circ Res. 2009;105:2631–2638.

101. Jeck CD, Zimmermann R, Schaper J, Schaper W. Decreased expression of calmodulin mRNA in human end-stage heart failure. J Mol Cell Cardiol. 1994;26:99–107.

102. Ruggeri ZM, Zieske A, Shaffer S, Zieske R. The role of IFN-gamma in the regulation of IKs potassium current by isoproterenol in adult cardiomyocytes. Am J Physiol. 2002;283:H1741–H1748.

103. Ou J, Rice JJ, Ruwald MH, Parks XX, Ronzier E, Moss AJ, Zareba W, Lopes CM. Impaired IKs channel activation by Ca(2+) dependent PKC shows correlation with emotion/arousal-triggered events in LQT1. J Mol Cell Cardiol. 2015;79:203–211.

104. Braz JC, Gregory K, Pathak A, Zhao W, Sahin B, Klevitsky R, Kimball TF, Lorenzen J, Naim AC, Liggert SB, et al. PKC-alpha regulates cardiac contractility and propensity toward heart failure. Nat Med. 2004;10:248–254.

105. Fowler MB, Laser JA, Hopkins GL, Minobe W, Bristow MR. Evaluation of Norepinephrine’s actions in cardiomyocytes. Circ Res. 1989;64:1741–1748.

106. Athanasiadou D, Schwake M, Beimgreben C, Blanz J, Beck C, Jentsch TJ, Saftig P, Friedrich T. Structural determinants of M-type KCNQ (K\textsuperscript{+}) channel assembly. J Neurosci. 2006;26:3757–3766.

107. Athanasiadou D, Schwake M, Beimgreben C, Blanz J, Beck C, Jentsch TJ, Saftig P, Friedrich T. Structural determinants of M-type KCNQ (K\textsuperscript{+}) channel assembly. J Neurosci. 2006;26:3757–3766.