This new edition of Essential Cardiac Electrophysiology: The Self-Assessment Approach continues the successful formula of the first edition, providing a concise and thorough overview of electrophysiology supplemented by challenging questions readers can use to test their knowledge and prepare for examinations.

Comprehensively updated and significantly expanded to include the latest recommendations, findings from leading-edge research, emergent diagnostic tools, and new therapeutic options, Essential Cardiac Electrophysiology: The Self-Assessment Approach now offers coverage of some of hottest topics in EP, including:

- HCN channels
- Congenital and paroxysmal AV blocks
- Left atrial flutter
- Electrophysiologic assessment of AVNRT and AVRT
- Bystander v/s participating accessory pathway
- VT ablation
- Short QS syndrome
- Genetics of ARVD
- Early repolarization and ventricular fibrillation
- Aortic cusp VT
- Commotio cordis
- Weight loss supplements and cardiac arrhythmias

Fact-based and clinically-focused, Essential Cardiac Electrophysiology: The Self-Assessment Approach is an ideal reference for all members of the EP care team, from cardiac care nurses and technicians to EP and cardiology fellows to practicing electrophysiologists. Packed with questions designed to aid readers’ understanding of key concepts and retention of essential facts, it is an excellent study aid for those preparing for board examination or other EP certifications.
Dedication

To all the students of cardiac electrophysiology
and
To my mentors: Dr. Fred Morady, Dr. Mark Josephson,
Dr. Masood Akhtar, Dr. Warren Jackman, Dr. James Maloney,
Dr. Christopher Wyndham, Dr Eric Prystowsky, Dr George Klein and
Dr Kalyanam Shivkumar
and
To my wife Karuna whose patience and understanding made
this project possible.
and
To my children Moeen, Sakena and Zameer
and my grandchildren Neela and Sameer Yidroose
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Foreword

The second edition of *Essentials of Cardiac Electrophysiology* continues in the same format as the first edition – a concise review in bullet-point fashion of the most important facts dealing with all major topics in clinical cardiac electrophysiology and with selected basic electrophysiology topics that are the most relevant to clinical electrophysiologists. The second edition has been enhanced both by expanding some of the topics previously covered and by the addition of some new topics. For example, additional information useful for those wishing to review cardiac membrane channels has been provided. A notable number of issues directly related to clinical practice have been expanded upon or added, including post-maze arrhythmias, the genetics of atrial fibrillation, new oral anticoagulants, left ventricular non-compaction, the use of magnetic resonance imaging in patients with a device, and management of high defibrillation thresholds.

All in all, this book remains a very useful resource for those seeking a concise review of the most important information on virtually any topic important to clinical cardiac electrophysiologists.

Fred Morady, MD
McKay Professor of Cardiovascular Disease
Professor of Medicine
University of Michigan Health System
Ann Arbor, MI, USA
Preface

*There are known knowns, there are known unknowns, but there are also unknown unknowns*

**DONALD RUMSFELD**

I use this quotation with some trepidation because of its use in justifying the Iraq war. But I feel it also describes the state of knowledge in many scientific fields including cardiac electrophysiology.

There has been an exponential increase of information in all facets of cardiac electrophysiology. When the first edition of *Essential Cardiac Electrophysiology* was published there were seven known types of long QT syndromes; by the time this edition went into press the list had expanded to 12 different types of long QT syndromes.

The question is invariably raised as to why we need another book on cardiac electrophysiology when, with the availability of the world wide web and smart handheld devices, the information can be accessed anytime anywhere within a few seconds. The answer to this question lies in the ability of this text to assimilate, synthesize and present only factual and relevant information.

As Albert Einstein has eloquently said, “Everything should be made as simple as possible, but not one bit simpler.”

Learning is best accomplished by testing, reiteration, and concentration on essential information, accomplished in this book by using a self-assessment approach, illustrations, tables and an enumeration of factual information in bullet format rather than by verbose description.

The first edition has been immensely popular among cardiac electrophysiology and cardiology fellows, residents, and medical students. Keeping the same format, this edition has been expanded by 50% with new information, multiple-choice questions and illustrations.

This has been a long and immensely time-consuming project. The rewards are not financial. These rewards are realized in the form of compliments from students and encouraging remarks from their mentors.

Any project of this magnitude is likely to have errors and or omissions. Any constructive criticism, comments, and suggestions are always welcomed.

Please send comments, critiques and suggestions to, ‘essentiallep@gmail.com’.

*Zainul Abedin*
Acknowledgements

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I am grateful to Ms. Susan Fernandez for secretarial assistance; and to Mr. Thomas Hartman, Ms. Kate Newell, Ms. Cathryn Gates and Ms. Mahabunnisa Mohamed and other members of Wiley-Blackwell editorial, publishing and marketing team.
## Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>4-AP</td>
<td>4-Aminopyridine</td>
</tr>
<tr>
<td>AAD</td>
<td>Antiarrhythmic drugs</td>
</tr>
<tr>
<td>AAG</td>
<td>Alpha1 acid glycoprotein</td>
</tr>
<tr>
<td>ABC</td>
<td>ATP binding cassette protein</td>
</tr>
<tr>
<td>Ach</td>
<td>Acetylcholine</td>
</tr>
<tr>
<td>Ado</td>
<td>Adenosine</td>
</tr>
<tr>
<td>AF</td>
<td>Atrial fibrillation</td>
</tr>
<tr>
<td>AIvR</td>
<td>Accelerated idioventricular rhythm</td>
</tr>
<tr>
<td>AJT</td>
<td>Automatic junctional tachycardia</td>
</tr>
<tr>
<td>AKAP</td>
<td>A kinase anchoring proteins</td>
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<tr>
<td>AP</td>
<td>Action potential</td>
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<td>AP</td>
<td>Accessory pathway</td>
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<td>APD</td>
<td>Action potential duration</td>
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<tr>
<td>ARP</td>
<td>Atrial refractory period</td>
</tr>
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<td>ARVD/C</td>
<td>Arrhythmogenic right ventricular dysplasia/cardiomyopathy</td>
</tr>
<tr>
<td>AT</td>
<td>Atrial tachycardia</td>
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<tr>
<td>AT-II</td>
<td>Angiotensin II</td>
</tr>
<tr>
<td>Atp</td>
<td>Adenosine triphosphate</td>
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<tr>
<td>ATP</td>
<td>Anti tachycardia pacing</td>
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<td>Andersen–Tawil Syndrome</td>
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<tr>
<td>AVD</td>
<td>AV dissociation</td>
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<td>Atrioventricular node</td>
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<td>AVNRT</td>
<td>AVN re-entry tachycardia</td>
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<td>AVRT</td>
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<td>Bundle branch block</td>
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<td>Bundle branch re-entry VT</td>
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<td>BRS</td>
<td>Baroreflex sensitivity</td>
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<td>Ca</td>
<td>Calcium</td>
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<tr>
<td>CAD</td>
<td>Coronary artery disease</td>
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<tr>
<td>cAMP</td>
<td>Cyclic adenosine monophosphate</td>
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<tr>
<td>CANS</td>
<td>Cardiac autonomic nervous system</td>
</tr>
<tr>
<td>CHF</td>
<td>Congestive heart failure</td>
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<tr>
<td>CHB</td>
<td>Complete heart block</td>
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<tr>
<td>CICR</td>
<td>Calcium induced calcium release</td>
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<tr>
<td>CL</td>
<td>Cycle length</td>
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<td>Cl−</td>
<td>Chloride</td>
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<td>CPVT</td>
<td>Catecholaminergic polymorphic ventricular tachycardia</td>
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<td>CS</td>
<td>Coronary sinus</td>
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<tr>
<td>CSF</td>
<td>Cerebrospinal fluid</td>
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<td>CSNRT</td>
<td>Corrected sinus node recovery time</td>
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</table>
Abbreviations

CX Connexion
CYP Cytochrome P
DAD Delayed after-depolarization
DCM Dilated cardiomyopathy
DFT Defibrillation threshold
EAD Early after depolarization
EAM Electroanatomical map
EF Ejection fraction
EHL Elimination half life
ER Eustachian ridge
ERP Effective refractory period
HB His bundle
HCM Hypertrophic cardiomyopathy
HCN Hyperpolarization activated cyclic nucleotide gated
HERG Human ether related a-go-go gene protein
HPS His Purkinje system
HRV Heart rate variability
HRT Heart rate turbulence
$I_{Ca,T}$ Ca current transient or short acting
$I_{Ca,L}$ Ca current long acting
ICE Intracardiac echocardiography
ICD Implantable cardioverter-defibrillator
$I_h$ Hyperpolarizing cation current
$I_K$ Potassium current
$I_{K1}$ Inward rectifying potassium current
$I_{Kach}$ Acetylcholine mediated potassium current
$I_{K,ATP}$ ATP dependent potassium current
$I_{Kp}$ Time independent background plateau current
$I_{Kr}$ Rapidly activating potassium current
$I_{Ks}$ Slowly activating potassium current
$I_{Kur}$ Ultra rapid potassium current
$I_{Na}$ Sodium current
IP3 Inositol triphosphate
IST Inappropriate sinus tachycardia
$I_{to}$ Transient outward current
IVC Inferior vena cava
K Potassium
KvLQT1 Voltage-dependent potassium controlling protein
LAFB Left anterior fascicular block
LCSD Left cardiac sympathetic denervation
LIPV Left inferior pulmonary vein
LOC Loss of consciousness
LQTS Long QT Syndrome
LSPV Left superior pulmonary vein
LVH Left ventricular hypertrophy
LVOT Left ventricular outflow tract
<table>
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<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>M</td>
<td>Muscarinic</td>
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<tr>
<td>MHC</td>
<td>Myosin heavy chain</td>
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<td>MDP</td>
<td>Maximum diastolic potential</td>
</tr>
<tr>
<td>MI</td>
<td>Myocardial infarction</td>
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<tr>
<td>MinK</td>
<td>Minimal potassium current controlling protein</td>
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<tr>
<td>MnCl₂</td>
<td>Manganese chloride</td>
</tr>
<tr>
<td>MTR</td>
<td>Maximum tracking rate</td>
</tr>
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<td>MVT</td>
<td>Monomorphous VT</td>
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<tr>
<td>Na</td>
<td>Sodium</td>
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<tr>
<td>NAPA</td>
<td>$N$-acetylprocainamide</td>
</tr>
<tr>
<td>NAT</td>
<td>$N$-acetyltransferase</td>
</tr>
<tr>
<td>NCX</td>
<td>Sodium and calcium exchange</td>
</tr>
<tr>
<td>NCC</td>
<td>Noncoronary cusp</td>
</tr>
<tr>
<td>NSVT</td>
<td>Nonsustained VT</td>
</tr>
<tr>
<td>P</td>
<td>Purinergic</td>
</tr>
<tr>
<td>PAC</td>
<td>Premature atrial contractions</td>
</tr>
<tr>
<td>PAVB</td>
<td>Paroxysmal AV block</td>
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<tr>
<td>PCA</td>
<td>Pulseless cardiac electrical activity</td>
</tr>
<tr>
<td>PCCD</td>
<td>Progressive cardiac conduction disease</td>
</tr>
<tr>
<td>PES</td>
<td>Programmed electrical stimulation</td>
</tr>
<tr>
<td>PG</td>
<td>P glycoprotein</td>
</tr>
<tr>
<td>PJRT</td>
<td>Permanent form of junctional reciprocating tachycardia</td>
</tr>
<tr>
<td>PKA</td>
<td>Protein kinase A</td>
</tr>
<tr>
<td>PPI</td>
<td>Post pacing interval</td>
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<td>PVARP</td>
<td>Postventricular atrial refractory period</td>
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<tr>
<td>PVC</td>
<td>Premature ventricular contractions</td>
</tr>
<tr>
<td>QTc</td>
<td>Corrected QT interval</td>
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<tr>
<td>RB</td>
<td>Right bundle</td>
</tr>
<tr>
<td>RCC</td>
<td>Right coronary cusp</td>
</tr>
<tr>
<td>RCM</td>
<td>Restrictive cardiomyopathy</td>
</tr>
<tr>
<td>RF</td>
<td>Radiofrequency</td>
</tr>
<tr>
<td>RNA</td>
<td>Ribonucleic acid</td>
</tr>
<tr>
<td>RSPV</td>
<td>Right superior pulmonary vein</td>
</tr>
<tr>
<td>RVOT</td>
<td>Right ventricular outflow tract</td>
</tr>
<tr>
<td>RyR2</td>
<td>Ryanodine receptor</td>
</tr>
<tr>
<td>SACT</td>
<td>Sino atrial conduction time</td>
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<tr>
<td>SAECG</td>
<td>Signal average ECG</td>
</tr>
<tr>
<td>SAN</td>
<td>Sinoatrial node</td>
</tr>
<tr>
<td>SCD</td>
<td>Sudden cardiac death</td>
</tr>
<tr>
<td>SCRC</td>
<td>Sarcoplasmic Ca release channel</td>
</tr>
<tr>
<td>SND</td>
<td>Sinus node dysfunction</td>
</tr>
<tr>
<td>SMVT</td>
<td>Sustained monomorphic VT</td>
</tr>
<tr>
<td>SNRT</td>
<td>Sinus node recovery time</td>
</tr>
<tr>
<td>SQTS</td>
<td>Short QT syndrome</td>
</tr>
<tr>
<td>SR</td>
<td>Sarcoplasmic reticulum</td>
</tr>
<tr>
<td>SSS</td>
<td>Sick sinus syndrome</td>
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<td>Abbreviation</td>
<td>Description</td>
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<tr>
<td>SUR</td>
<td>Sulfonylurea receptor</td>
</tr>
<tr>
<td>SVC</td>
<td>Superior vena cava</td>
</tr>
<tr>
<td>SVT</td>
<td>Supraventricular tachycardia</td>
</tr>
<tr>
<td>TA</td>
<td>Tricuspid annulus</td>
</tr>
<tr>
<td>TCL</td>
<td>Tachycardia cycle length</td>
</tr>
<tr>
<td>TDP</td>
<td>Torsades de Pointes</td>
</tr>
<tr>
<td>TDR</td>
<td>Transmural dispersion of repolarization</td>
</tr>
<tr>
<td>TEE</td>
<td>Transesophageal echocardiography</td>
</tr>
<tr>
<td>TIA</td>
<td>Transient ischemic attack</td>
</tr>
<tr>
<td>TWA</td>
<td>T wave alternans</td>
</tr>
<tr>
<td>ULV</td>
<td>Upper limit of vulnerability</td>
</tr>
<tr>
<td>VA</td>
<td>Ventriculoatrial</td>
</tr>
<tr>
<td>VF</td>
<td>Ventricular fibrillation</td>
</tr>
<tr>
<td>VRP</td>
<td>Ventricular refractory period</td>
</tr>
<tr>
<td>VT</td>
<td>Ventricular tachycardia</td>
</tr>
<tr>
<td>WCT</td>
<td>Wide complex tachycardia</td>
</tr>
<tr>
<td>WPW</td>
<td>Wolff–Parkinson–White syndrome</td>
</tr>
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</table>
CHAPTER 1
Ions channels and currents

Self-assessment questions

1.1 Potassium channels and currents

1 In normal Purkinje fibers which one of the following currents is responsible for normal automaticity?
   A $I_f$, hyperpolarization-activated cyclic nucleotide gated current
   B $I_{CaL}$, L-type calcium current
   C $I_{Na}$, rapid inward sodium current
   D $I_k$, delayed rectifier potassium current
   E $I_{to}$, transient outward current

2 Abnormal potassium channel function is unlikely to cause
   A Deafness.
   B Short QT interval.
   C Long QT interval.
   D Catecholaminergic polymorphic ventricular tachycardia.

3 Osborn waves seen in hypothermia are the result of:
   A Uneven distribution of $I_{to}$ in endocardium and epicardium.
   B Sarcoplasmic calcium overload.
   C Metabolic acidosis.
   D Loss of function of the sodium channel.

4 Which of the following is the result of outward movement of the potassium ions across the cell membrane?
   A Repolarizing current.
   B Depolarizing current.
   C Prolongation of the QT interval.
   D Prominent U waves.
5 In a diagram of AP shown below, which one of the following currents is active where arrow is pointing?

\[ \text{A} \quad I_{to} \]
\[ \text{B} \quad I_{K1} \]
\[ \text{C} \quad I_{Na} \]
\[ \text{D} \quad I_{Ca} \]

6 Which one of the following genes controls the expression of $I_{Kr}$?
\[ \text{A} \quad KCNQ1 (KvLQT1) \]
\[ \text{B} \quad KCNH2 (HERG) \]
\[ \text{C} \quad SCN5A \]
\[ \text{D} \quad MinK \]

7 Which one of the following actions is likely to activate $I_{KATP}$ current?
\[ \text{A} \quad \text{Rise in intracellular ATP} \]
\[ \text{B} \quad \text{Rise in intracellular calcium} \]
\[ \text{C} \quad \text{Fall of Intracellular ATP} \]
\[ \text{D} \quad \text{Fall of Intracellular calcium} \]

8 How does congestive heart failure affect depolarizing/repolarizing currents?
\[ \text{A} \quad \text{Outward Repolarizing currents are reduced} \]
\[ \text{B} \quad \text{Inward depolarizing currents are reduced} \]
\[ \text{C} \quad \text{Outward repolarizing currents are increased} \]
\[ \text{D} \quad \text{APD is decreased} \]

9 Which one of the following is least likely to occur with prolongation of plateau phase of the AP?
\[ \text{A} \quad \text{Increased strength of contraction} \]
\[ \text{B} \quad \text{Increase in conduction velocity} \]
\[ \text{C} \quad \text{Increased duration of contraction} \]
\[ \text{D} \quad \text{Increased refractoriness} \]

10 Which one of the following is likely to increase the activity of $I_{Kr}$?
\[ \text{A} \quad \text{Increased extracellular potassium} \]
\[ \text{B} \quad \text{Exposure to Sotalol} \]
C Decrease extracellular potassium
D Increase in chloride current

11 When does the reverse use dependent block occur?
A It occurs with repeated activation of channel
B It occurs when sodium channel is blocked
C It occurs at slow heart rate but not at fast heart rate
D It occurs in the presence of catecholamines

12 Which one of the following is least likely attribute of $I_{to}$?
A It is present in ventricular epicardium but not in endocardium
B It is responsible for spike and dome characteristic
C It is blocked by Ranolazine
D It is also present in human atrium

13 Which one of the following is associated with Brugada syndrome?
A Defect in SCN5A gene
B Loss of $I_{Kr}$
C ST segment depression is precordial leads
D Deafness

14 Which one of the following agents/actions is likely to block $I_{ks}$?
A Aminophylline
B Indapamide
C Activation of protein kinase C
D Erythromycin
E Increase in intracellular calcium

1.2 Sodium channels and currents

1 Chronic exposure to Na channel blocking antiarrhythmic drugs may result in:
A Increase in sodium channel messenger RNA, which counteracts the effects of channel blockade.
B Hyponatremia at cellular level.
C Decrease in Na/K ATPase.
D Decrease in sodium channel messenger RNA, resulting in steady state-level.

2 Which of the following statement about Na/K ATPase is incorrect?
A It is an enzyme responsible for the maintenance of Na$^+$ and K$^+$ concentration gradients in the cells.
B Its operation produces an inwardly directed current as 1 Na$^+$ ion is removed from the cell in exchange for the influx of 3 K$^+$.
C The sodium pump performance determines the level of intracellular Na$^+$ level and, consequently, cardiac inotropic status.
D Changes in intracellular Na$^+$ levels influence the activity of the cardiac Na$^+$-Ca$^{2+}$ exchanger.
3 SCN5A mutation resulting in loss of function is responsible for which one of the following rhythm disorders?
   A Progressive cardiac conduction disease (PCCD).
   B Long QT syndrome.
   C Catecholaminergic polymorphic ventricular tachycardia.
   D Paroxysmal atrial fibrillation.

4 Which one of the following currents is likely to occur when the Na moves across the cell membrane and into the cell?
   A Inward current
   B Outward current
   C Repolarizing current
   D Hyperpolarizing current

5 A patient receiving a Na channel blocker develops AF with rapid ventricular response. What changes on ECG can be anticipated to occur?
   A Narrowing of the QRS complex during tachycardia
   B Widening of the QRS complex during tachycardia
   C Prolongation of the QT interval
   D Shortening of the QT interval

6 What is likely to happen when a Na channel is blocked?
   A Increase in intracellular Ca and increased contractility
   B Increase in EAD and DAD
   C Decrease in contractility
   D Increase in extracellular Na

7 Which one of the following is not associated with Brugada syndrome?
   A Mutation in SCN5A resulting in loss of function
   B Increase in Ito current
   C Inhibition of ICa during the plateau phase
   D Mutation in SCN5A, resulting in gain of function

8 What type of channel block, by lidocaine, results in effective suppression of arrhythmias during myocardial ischemia?
   A Inactivated state block
   B Resting state block
   C Open state block
   D Closed state block

9 Which one of the following agents is likely to be effective in treating flecainide induced VT?
   A IV magnesium
   B IV lidocaine
   C IV amiodarone
   D IV digoxin
10 Which one of the following metabolic abnormalities is likely to decrease lidocaine dissociation from the channel sites?
   A Acidosi
   B Ischemia
   C Hyperkalemia
   D Hyponatremia

11 What electrophysiologic manifestations can be expected when $I_{Nab}$ (the slow component of the background Na current) is blocked?
   A Lengthening of the QT interval
   B Positive inotropy
   C Occurrence of EAD
   D Bradycardia

12 Which one of the following interventions is likely to promote occurrence of TDP in patients with LQT3?
   A Beta blocker induced bradycardia
   B Permanent pacemaker
   C Mexiletine
   D Exercise-induced sinus tachycardia

1.3 Calcium channels and currents

1 In which one of the following electrical activities there is no contribution from calcium current $I_{CaL}$?
   A EAD
   B Electrical remodeling of the atrium during AF
   C DAD
   D Depolarization of the SA and AV nodes

2 Which of the following statements is incorrect?
   A β-Adrenergic agonists increase $I_{CaL}$ channel activity
   B Beta-blockers act as Ca channel blockers
   C Parasympathetic stimulation decreases $I_{CaL}$ activity
   D T-type Ca channel density is increased by growth hormone, endothelin, and pressure overload

3 Which of the following agents has no effect on T-type Ca channel?
   A Amiloride
   B Flunarizine
   C Mibefradil
   D Digoxin

4 Which one of the following statements regarding calcium homeostasis in cardiac myocyte is incorrect?
   A Ca$^{2+}$-ATPase contributes substantially to diastolic Ca$^{2+}$ removal from cardiac myocyte.
B Ca\textsuperscript{2+} in SR lumen is bound to the low-affinity calcium-binding protein calsequestrin  
C Ca\textsuperscript{2+} signal is generated by Ca\textsuperscript{2+} influx through voltage-dependent L-type calcium channels.  
D Sarcoplasmic reticulum is the major reservoir of the calcium.

5 Which one of the following agents increases sensitization to RyR2?  
A Tetracaine  
B Rapamycin  
C Caffeine  
D Doxorubicin

6 Which one of the following statement about ivabradine is incorrect?  
A It produces bradycardia  
B cAMP overload will nullify its effect  
C It produces visual signs and symptoms  
D It has negative inotropic effect.
1.1 Potassium channels/currents\textsuperscript{1,2}

- There are more than eight types of potassium currents.
- Plateau phase of the action potential depends on the balance between inward (depolarizing) and outward (repolarizing) currents.
- Potassium currents (outward movement of the K through the potassium channels) are the main contributors to repolarization.
- Activity of potassium channel could be either time-dependent or voltage-dependent (\(K_v\)).
- Voltage-gated potassium (\(K_v\)) channels consist of a tetrameric assembly of \(\alpha\) subunits (Figure 1.1). Each \(\alpha\) subunit contains six membrane-spanning segments, S1 to S6, with both amino (N) and carboxyl (C) termini located on the intracellular side of the membrane.
- Segments S1 to S4 confer voltage-sensing properties to these channels, whereas S5 and S6 are critical for forming the channel.
- \(K_v\) channels fluctuate between open conducting (activated) state(s) and nonconducting state(s), with the kinetics of the transitions depending critically on membrane voltage and channel structure.
- Nonconducting states can be classified as either closed (deactivated) or inactivated states.
- During the course of an action potential, closed \(K_v\) channels activate or open in response to membrane depolarization and subsequently enter the inactivated state in a time-dependent manner. Re-entry into the closed state requires membrane repolarization.
- The voltage- and time-dependent transition between these different conformational functional states is called gating.
- Potassium channels catalyze selective transport of \(K^+\) ions across lipid bilayers while remaining impermeable to other biologic cations.
- AP duration determines amount of calcium influx and tissue refractoriness. It is inversely related to heart rate. Prolongation of AP plateau increases the strength and duration of contraction. It also increases refractoriness.
- In congestive heart failure and in left ventricular hypertrophy repolarizing outward currents are reduced by 50\%. This increases APD and results in EAD and arrhythmias. Use of class III drugs in patients with CHF needs reevaluation as intended target (K channels) is down regulated or absent.
- In atrial fibrillation repolarizing outward currents (\(I_{Kr}, I_{to}\)) are reduced. Reduction of these currents may exacerbate arrhythmic effect of hypokalemia and hypomagnesemia.
- Potassium channel expression is decreased in hypothyroid and hypoadrenal states.

**Delayed and inwardly rectifying voltage sensitive potassium channels**\textsuperscript{2}

- Rectification is a diode like property of unidirectional current flow which could be inward or outwards. It limits outward flow of potassium through \(I_{Kr}\) and \(I_{Ks}\) during plateau. Delayed rectifier potassium channels have slow onset of action.
Figure 1.1 α-Subunits of cardiac ion channels. (a) α-Subunits of Na\(^+\) and Ca\(^{2+}\) channels consists of four serially linked homologous domains (DI–DIV), each containing six transmembrane segments (S1–S6). (b, c) α-Subunits of channels responsible for \(I_{\text{to}}\), \(I_{\text{Kur}}\), \(I_{\text{Kr}}\), \(I_{\text{Ks}}\), \(I_{\text{K1}}\), and \(I_{\text{i}}\) consist of one single domain with six (B) or two (C) \((I_{\text{K1}})\) transmembrane segments. Four subunits (domains) co-assemble to form one functional channel. (Reproduced with permission.)
• Voltage gated potassium channels are activated during upstroke of AP.
• Rapidly activating and inactivating voltage sensitive transient outward current $I_{to}$ produces phase 1 of repolarization.
• Inward rectifier $I_{K1}$, slowly activating delayed rectifier potassium current, which includes fast inactivating rapid component $I_{Kr}$ and slow component $I_{Ks}$, contributes to plateau and phase 3 of AP.
• K channels carry positive charge which triggers a voltage sensor.
• Potassium channels are closed at resting potential and open after depolarization.
• Two types of voltage-gated channels play major role in repolarization.
  1 Transient outward current ($I_{to}$) which is characterized by rapid activation and inactivation.
  2 Delayed rectifier $I_{K}$ which has several components (Figure 1.2)
    - $I_{Kr}$ is a rapidly activating current with inward rectification.
    - $I_{Ks}$ is a slowly activating current
    - $I_{Kur}$ is an ultra rapid current.

**Transient outward potassium current ($I_{to}$)**

- $I_{to}$ supports early repolarization during phase 1. The transient nature of $I_{to}$ is secondary to its fast activation and inactivation upon depolarization.
- There are two types of $I_{to}$ currents, $I_{to1}$ and $I_{to2}$
- A calcium-activated chloride current ($I_{to2}$) and a classical calcium-independent potassium current ($I_{to1}$) (referred to as $I_{to}$)
- The calcium-independent $I_{to}$ is of two types: a “rapid” or “fast” $I_{to,fast}$ and a slower form, $I_{to,slow}$
- $I_{to,slow}$ is smaller than $I_{to,fast}$
- $I_{to,fast}$ recovers rapidly from inactivation, and its $\alpha$-subunit (Kv4.3) is encoded by KCND3. $I_{to,slow}$ recovers slowly from inactivation; its $\alpha$-subunit (Kv1.4) is encoded by KCNA4.
Kv4.3 and Kv1.4 contain one domain with six transmembrane segments. Four subunits co-assemble to form one channel.

Kv4.3 is strongly expressed in the epicardium and is responsible for shorter AP duration there compared to endocardium, where Kv1.4 expression is weak.

This creates a transmural voltage gradient between epicardium and endocardium.

$\text{i}_{\text{to,f}}$ is the primary determinant of the time course of early repolarization (phase 1) of atrial and ventricular action potentials and it varies greatly between regions of the heart.

Early repolarization modulates L-type calcium current magnitude, thereby regulating excitation-contraction coupling and myocardial contractility.

$I_{\text{to,f}}$ expression is greater in epicardium, right ventricle and the base of the heart, and less in the septum, left ventricular endocardium, and apex of the heart.

Regional variations in $I_{\text{to,f}}$ results in the heterogeneity of action potential, which are responsible for orderly ventricular repolarization.

Variation in $I_{\text{to,f}}$ is responsible for the regional modulation of contractility.

Electrical heterogeneity associated with the transmural $I_{\text{to,f}}$ gradient contributes to synchronization of repolarization and force generation across the ventricular wall.

The effects of $I_{\text{to,f}}$ levels on contractility are related to voltage-dependent modulation of sodium-calcium exchanger which reverses direction during the early repolarization phase.

The early repolarization period, which is dependent on $I_{\text{to,f}}$ levels, controls both the amplitude and the timing of Ca$^{2+}$ release from the SR.

Reductions in the $I_{\text{to,f}}$ and the loss of the notch lead to a slowing of SR Ca$^{2+}$ release.

The distribution of $I_{\text{to,f}}$ in the ventricle synchronizes the timing of force generation between different regions of the ventricle, thereby enhancing mechanical efficiency.

Generalized downregulation of $I_{\text{to,f}}$ occurs in heart failure, slowing the time course of force generation, resulting in reduced myocardial performance.

Chronic exposure of ventricular myocytes to $\alpha$-adrenergic agonists (such as phenylephrine) reduces $I_{\text{to,f}}$. It also decreased K$\sqrt{4.2}$, K$\sqrt{4.3}$, and KChIP2 expression.

$\alpha$-adrenergic agonists increase $I_{\text{to,s}}$ and Kv1.4 expression

Angiotensin II (AT-II) type 1 (AT-1) receptors stimulation reduces $I_{\text{to,f}}$.

Hypothyroidism prolongs action potential duration reduces $I_{\text{to,f}}$ and decreases K$\sqrt{4.2}$ expression, whereas hyperthyroidism has the reverse effect.

Aldosterone, induces downregulation of $I_{\text{to,f}}$.

Electrical remodeling in heart disease involves downregulation of $I_{\text{to,f}}$ and reductions in K$\sqrt{4.2}$, K$\sqrt{4.3}$, and KChIP2. This has been linked to the hypertrophy through the activation of the calcineurin–nuclear factor of activated T cells (NFAT) pathway.

$I_{\text{to}}$ is present in ventricular epicardium but not in endocardium. It is responsible for spike and dome morphology of AP in epicardium.
• In human atrium it recovers rapidly from inactivation thus allowing rapid repolarization at fast heart rate.
• Flecainide, quinidine and ambasilide inhibit \( I_{to} \). Flecainide binds to inactivated \( I_{to} \). It also demonstrates fast unbinding. Quinidine binds to open channel, its slow recovery from block causes rate dependent effect.
• Inhibition of \( I_{to} \) prolongs repolarization in diseased human ventricle.
• A gain of function in \( I_{to} \) secondary to a mutation in KCNE3 contributes to a Brugada phenotype.

\( I_{to} \) mutation and inherited diseases
• \( KCNE3 \) mutation may be responsible for Brugada syndrome. \( K_v4.3 \), gain of function mutation increases \( I_{to} \) fast.
• Increased \( I_{to,f} \) induces ST-segment elevation in Brugada syndrome by aggravating transmural voltage gradients.
• \( KCNE3 \) mutation has been identified in familial AF. Mutation increases \( I_{to,f} \) and may cause AF by shortening AP duration.

\( I_{to} \) expression in acquired cardiac diseases
• \( I_{to} \) is reduced in AF, myocardial infarction, and heart failure.
• In myocardial infarction, Ito is down-regulated by the increased activity of calcineurin, a phosphatase that regulates gene transcription by dephosphorylating transcription factors.
• Sustained tachycardia in heart failure reduces \( I_{to} \).
• Ito may be reduced and contribute to QT interval prolongation in diabetes, insulin therapy partially restores Ito, maybe by enhancing \( K_v4.3 \) expression.

\( I_{to} \) and J wave
• J wave (Osborn wave), elevated J point and T wave alternans may be due to transmural gradient between epicardium and endocardium as a result of uneven distribution of \( I_{to} \).
• Prominent J wave are often seen in presence of hypothermia and hypercalcemia.
• The heterogeneity of repolarization generated by \( I_{to,f} \) also explains the cardiac T wave memory and Osborne or J wave formation.

Rapidly activating delayed rectifier \( I_{Kr} \)
• \( KCNH2 \), also called the human-ether-a-go-go-related gene (hERG), encodes the \( \alpha \)-subunit (Kv11.1) of the channel carrying \( I_{Kr} \).
• \( I_{Kr} \) activation upon depolarization is not rapid, but inactivation is fast, resulting in a small outward \( K^+ \) current near the end of the AP upstroke.
• During early repolarization, the channel rapidly recovers from inactivation to produce large \( I_{Kr} \) amplitudes during AP phases 2 and 3. Channel deactivates (closes) slowly (in contrast to inactivation, deactivation is a voltage-independent process).
• \( I_{Kr} \) is responsible for repolarization of most cardiac cells.
• Interaction of Kv11.1 with its β-subunit MiRP1 (encoded by KCNE2) induces earlier activation and accelerates deactivation.
• It is blocked by methane sulfonamide, class III agents (D. Sotalol).
• Inward rectification of $I_{kr}$ results in small outward current.
• It plays an important role in atrial pacemaker cells. It rapidly recovers from inactivation and it peaks at –40 mV.
• KCNH2 (HERG, Human ether related-a-go-go gene) is responsible for the $I_{kr}$ current.
• $I_{kr}$ is increased in the presence of elevated extracellular potassium. Normally increased extracellular potassium will decrease outward potassium current by decreasing chemical gradient but activity of $I_{kr}$ is increased.
• Increase in serum potassium by 1.4 mEq/L decreases QTc by 24% and decreases QT dispersion.
• Efficacy of $I_{kr}$ blockers is limited by inverse rate dependency. These drugs are more effective at slower heart rate. High heart rate increases the prevalence of $I_{ks}$, which is insensitive to $I_{kr}$ blockers, thus neutralizes the potassium blocking effects of the $I_{kr}$ blockers.
• Effect of $I_{ks}$ but not $I_{kr}$ is enhanced by β-adrenergic stimulation. Thus effects of pure $I_{ks}$ blockers will be antagonized by sympathetic stimulation.
• Selective $I_{kr}$ blockers (d-Sotalol) lose efficiency at high rate and during sympathetic stimulation.
• $I_{kr}$ and $I_{ks}$ are present in human atrium and ventricle.
• During phase 3 repolarization, the channels recover from inactivation creating a large repolarizing current, which hastens repolarization and opposes any depolarizing force that would prolong repolarization or create EADs.
• KCNH2 coassembles with MinK-related peptide 1 (MiRP1) (i.e., KCNE2), giving it gating, conductance, regulation, and biphasic inhibition by the methanesulfonilide class III antiarrhythmic drug.

**$I_{kr}$ mutation in inherited diseases**
• Loss-of-function mutations in $I_{kr}$ due to defects in KCNH2, (LQT2) or MiRP1 (LQT6) results in congenital long QT syndromes.
• Gain-of-function mutations in KCNH2 are associated with short QT syndrome 1 (SQTS1).
• KCNH2 mutations reduce $I_{kr}$ KCNH2 Mutation impairs potassium channel by altering protein Kv11.1.

**$I_{kr}$ expression in acquired diseases**
• In myocardial infarction, Kv11.1 mRNA levels and $I_{kr}$ are reduced, and AP duration is prolonged.
• In diabetes, $I_{kr}$ reduction contributes to QT interval prolongation. hyperglycemia depresses $I_{kr}$ whereas insulin therapy restores $I_{kr}$ function and shortens QT intervals.
• A high propensity for drug-induced block and acquired long QT syndrome is associated with KCNH2 mutation. $I_{kr}$ currents are susceptible to drug-induced block particularly in individuals with pre-existing repolarization defects (e.g., patients with LQTS or diabetes).
**Slowly activating delayed rectifier $I_{ks}$**

- Kv7.1, encoded by *KCNQ1*, is the $\alpha$-subunit of the channel responsible for $I_{ks}$.
  - Co-expression of *KCNQ1* with minK (Minimal potassium channel protein) encoding *KCNE1* yields currents that resemble $I_{ks}$: a K$^+$ current that activates slowly upon depolarization, displays no inactivation, and deactivates slowly during repolarization.
- $I_{ks}$ is markedly enhanced by $\beta$-adrenergic stimulation through channel phosphorylation by protein kinase A (requiring A-kinase anchoring proteins [AKAPs]) and protein kinase C (requiring minK).
- $I_{ks}$ contributes to repolarization, especially when $\beta$-adrenergic stimulation is present.
- *KCNQ1* and *KCNE1* are also expressed in the inner ear, where they enable endolymph secretion.
- MinK, a protein, acts as a function altering beta subunit of KCNQ1. Mink modifies KCNQ1 gating and pharmacology.
- Mutation in *KCNE1* and *KCNQ1* causes congenital long QT syndrome (LQTS).
- *KCNQ1* mutation resulting in MinK suppression leads to inner ear abnormalities and deafness, as seen in Jarvell and Lange–Nielson (JLN) syndrome. Heterozygous mutations in both *KCNQ1* and *KCNE1* cause JLN, which tends to be more lethal than LQT1 or LQT5.
- Reduced activity of $I_{ks}$ in M cells prolongs APD.
- Bradycardia and class III drugs, which reduce $I_{ks}$ in M cells, prolong APD and predispose to arrhythmias.
- Slow deactivation of $I_{ks}$ is important for rate-dependent shortening of AP. As heart rate increases $I_{ks}$ has less time to deactivate during shortened diastole, it accumulates in open state and contributes to faster repolarization.
- Increase in intracellular magnesium decreases and increase in intracellular calcium increases $I_{ks}$.
- Indapamide (diuretic), thiopental, propofol (anesthetics) benzodiazepines and chromanol block $I_{ks}$.
- Increase cAMP either by $\beta$-adrenergic stimulation or by phosphodiesterase inhibitors increases $I_{ks}$.
- Activation of protein kinase C increases $I_{ks}$.
- Loss-of-function mutations in in *KCNQ1* (LQT1) or *KCNE2* (LQT5) results in long QT syndrome. Gain-of-function mutations in *KCNQ1* are associated with short QT syndrome 2 (SQTS2).

**$I_{ks}$ mutation and inherited diseases**

- LQTS, type 1 (LQT1), is caused by loss-of-function mutations in *KCNQ1*. The resulting $I_{ks}$ reduction is responsible for prolonged AP durations and QT intervals.
- Arrhythmia usually occurs during exercise or emotional stress, because mutant $I_{ks}$ does not increase sufficiently during $\beta$-adrenergic stimulation.
- $\beta$-adrenergic blocking drugs suppress arrhythmic events in LQT1.
- LQTS type 5 is a result of loss-of-function mutations in *KCNE1* and displays a similar phenotype as LQT1 patients.
• Mutation of AKAP9, encoding Yotiao (AKAP9), results in LQTS11. Mutation inhibits the β-adrenergic response of \( I_{Ks} \) by disrupting the interaction between Yotiao and Kv7.1. Yotiao mediates phosphorylation of Kv7.1 by protein kinase A upon β-adrenergic stimulation.

• Loss-of-function mutations in both alleles of KCNQ1 or KCNE1 cause Jervell and Lange-Nielsen syndrome (JLNS) type 1 or 2, respectively.

• It is characterized by prolonged QT interval, arrhythmia and congenital deafness, the latter due to deficient endolymph secretion.

• KCNQ1 gain-of-function mutations cause short QT syndrome (type 2).

• KCNQ1 gain-of-function mutations may cause familial AF by shortening atrial AP duration and facilitating reentry.

I\(_{Ks}\) expression in acquired cardiac diseases

• Contradictory reports of KCNQ1 mutation causing familial AF by increasing \( I_{Ks} \) and KCNE1 polymorphisms increasing AF risk by decreasing \( I_{Ks} \) suggest that multiple mechanisms underlie AF.

• Heart failure reduces \( I_{Ks} \) in atrial, ventricular, and SA node.

\( I_{Kur} \) (ultrarapid) current

• KCNA5 encodes the α-subunit (Kv1.5) of the channel carrying \( I_{Kur} \).

• Kv1.5 is mainly expressed in the atria, and \( I_{Kur} \) is detected only in atrial myocytes. It plays a role in atrial repolarization.

• It activates rapidly upon depolarization but displays very slow inactivation.

• \( I_{Kur} \) is sensitive to 4-aminopyridine and is completely blocked by small concentrations.

• It is responsible for atrial repolarization. It is a potassium selective outwardly rectifying current. Short APD of the atria is due to \( I_{Kur} \).

• \( I_{Kur} \) is also found in intercalated disks.

• \( I_{Kur} \) is absent from human ventricular myocardium.

• It is enhanced by β adrenergic agonists and is inhibited by α-adrenergic agonists.

• Drugs inhibiting \( I_{Ks} \) (amiodarone, ambasilide) or \( I_{Kur} \) (ambasilide) will be therapeutically superior.

• Presence of \( I_{Kur} \) in human atrium makes atrial repolarization relatively insensitive to agents that fail to inhibit this current (d sotalol and flecainide). Quinidine and ambasilide block \( I_{Kur} \) in a rate independent fashion.

• \( I_{Kur} \) decreases with increasing heart rate.

• Both β- and α-adrenergic stimulation increase \( I_{Kur} \) by PKA and PKC effects, respectively.

• Hyperthyroidism can lead to transcriptional upregulation while hypothyroidism leads to decreased expression of Kv1.5 channel genes.

• The effects of male sex hormones lead to a reduction in the density of \( I_{Kur} \) and Kv1.5 expression, which may play a role in gender-specific differences in atrial repolarization.

\( I_{Kur} \) mutation and inherited diseases

• KCNA5 mutations may be responsible for familial AF.

• \( I_{Kur} \) loss of function may cause AF through AP prolongation and EAD
**Voltage-regulated inward rectifier $I_{k1}$**

- $I_{k1}$ stabilizes the resting membrane potential of atrial and ventricular myocytes during phase 4 and contributes to the terminal portion of phase 3 repolarization.
- $I_{k1}$ channels are closed during AP phases 1 and 2.
- $I_{k1}$ is absent in SAN and AVN myocytes.
- Its $\alpha$-subunit ($K\text{v}_2.1$) is encoded by $KCNJ2$ and consists of one domain with two transmembrane segments.
- Blocking of $I_{k1}$ results in depolarization of the resting potential and mild AP prolongation.
- $I_{k1}$ rectification allows it to carry substantial current at negative potentials, which maintains resting potential.
- These channels permit inward potassium flux on membrane hyperpolarization but resist outward potassium flux on depolarization. It prevents potassium ion leak during prolong depolarization.
- $I_{k1}$ is responsible for late phase of repolarization (phase 3) of the cardiac action potential and it sets the resting membrane potential (phase 4).
- Chamber-specific differences in $I_{k1}$ are recognized, with a higher density of $I_{k1}$ in ventricular myocytes but very little $I_{k1}$ current in atrial myocytes.
- Native $I_{k1}$ in human ventricular myocytes is reduced by $\beta$-adrenergic receptor stimulation and by the intracellular application of catalytic subunit of PKA.
- Activation of the AT-1 receptors by angiotensin II also appears to downregulate cardiac $I_{k1}$.
- Kir channels are voltage-regulated despite not having the classic voltage-sensing mechanism – namely, the S1 to S4 segments – of the $K\text{v}$ channels.
- The inward rectifier potassium channel family comprises at least seven subfamilies, $K\text{v}_1$ to $K\text{v}_7$ (i.e., $KCNJ$-1 to $KCNJ$-16).
- Three other inward rectifier (weak) potassium channels are present in the myocardium: 1. TWIK-1 background potassium channels ($KCNK1$), which help to set the resting membrane potential; 2. $I_{k,\text{ACh}}$ channels ($KCNJ3$, $KCNJ5$), which regulate heart rate and conduction through the atrioventricular node in response to acetylcholine (ACh); and 3. $I_{k,\text{ATP}}$ channels ($KCNJ11$), which respond to changes in metabolic state.
- Loss-of-function mutation in $KCNJ1$ is associated with Andersen’s syndrome (LQT7), whereas gain-of-function mutations in Kir2.1 ($KCNJ2$) result in short QT syndrome 3 (SQTS3).
- Intracellular magnesium, calcium and polyamines block $I_{k1}$. Increase in intracellular Ph inactivates $I_{k1}$. Increase extracellular potassium depolarizes resting membrane.

**$I_{k1}$ mutation and inherited diseases**

- Loss-of-function mutations in $KCNJ2$ are linked to Andersen–Tawil syndrome, characterized by skeletal developmental abnormalities, periodic paralysis, and usually nonsustained ventricular arrhythmia, often associated with prominent U waves and mild QT interval prolongation LQTS type 7.
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- **KCNJ2** mutations reduce $I_{K1}$ by encoding defective K$_{ir}$2.1 subunits, which generate nonfunctional channels and/or bind to normal subunits to disrupt their function (“dominant-negative effect”).
- $I_{K1}$ reduction may trigger arrhythmia by allowing inward currents, which are no longer counterbalanced by the strong outward $I_{K1'}$, to gradually depolarize the membrane potential during phase 4.
- Membrane depolarization during phase 4 induces arrhythmia by facilitating spontaneous excitability. $I_{K1}$ reduction may trigger arrhythmia by prolonging AP duration and triggering EADs.
- **KCNJ2** gain-of-function mutation, has been linked to short QT syndrome type 3. Increased $I_{K1}$ shorten AP duration and QT interval by accelerating the terminal phase of repolarization.
- **KCNJ2** gain-of-function mutation may cause AF by shortening atrial AP duration

**$I_{K1}$ expression in acquired diseases**
- In chronic AF, $I_{K1}$ is increased and Kir2.1 mRNA and protein levels are elevated.
- Increased $I_{K1}$ corresponds to more negative resting potentials and, together with reduced $I_{Ca,L}$, accounts for AP shortening in AF.
- In heart failure $I_{K1}$ densities are reduced secondary to increased intracellular Ca$^{2+}$ because Ca$^{2+}$ blocks the outward component of $I_{K1}$.
- $I_{K1}$ reduction in heart failure or ischemia may facilitate spontaneous excitability and trigger arrhythmia.

**ATP-sensitive potassium channel ($K_{ATP}$)**
- $K_{ATP}$ channel opens when intracellular ATP level falls and closes when ATP levels rise. ATP produced by glycolytic pathway is preferentially sensed by $K_{ATP}$ channel.
- $I_{K,ATP}$ is a weak inward rectifier but produces a large outward current during depolarization and its activation decreases APD.
- It is responsible for ischemia preconditioning where brief episodes of ischemia protect myocardium from prolonged episodes of ischemia.
- During ischemia intracellular magnesium and sodium levels increase, and extra cellular potassium increases.
- Protons, lactates, oxygen free radicals, and muscarinic receptor stimulation desensitize $K_{ATP}$ channel to the effects of ATP level.
- Sodium and potassium pump and other ATPases degrade ATP.
- Cromakalim, bimakalim, aprikalim, nicorandil, adenosine and protein kinase C open $K_{ATP}$ channel and mimic preconditioning. Sulfonylureas such as glipizide and tolbutamide block $K_{ATP}$ and abolish preconditioning.
- During ischemia there is loss of intracellular potassium and increase in extra cellular potassium resulting in membrane depolarization, slow conduction, and altered refractoriness resulting in reentrant arrhythmias. $K_{ATP}$ counteracts these effects by shortening APD, decreasing workload, promoting inexcitability and increasing potassium conductance during ischemia and hypoxia.