SECOND EDITION

ESSENTIAL CARDIAC ELECTROPHYSIOLOGY

THE SELF-ASSESSMENT APPROACH

Zainul Abedin

WILEY-BLACKWELL

Essential Cardiac Electrophysiology

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

Essential Cardiac Electrophysiology

The Self-Assessment Approach

Second Edition

Zainul Abedin, MD, FRCP, FHRS

Professor of Clinical Medicine
Paul Foster School of Medicine
Texas Tech University Health Sciences Center;
Adjunct Professor of Electrical Engineering and Computer Science
University of Texas at El Paso
El Paso, TX, USA

WILEY-BLACKWELL

A John Wiley & Sons, Ltd., Publication

Contents

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.

<div align="right">

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

</div>

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, 'essentialep@gmail.com'.

Zainul Abedin

Acknowledgements

Abbreviations

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

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_{CaL}	Ca current long acting
ICE	Intracardiac echocardiography
ICD	Implantable cardioverter-defibrillator
I_f	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

M	Muscarinic
MHC	Myosin heavy chain
MDP	Maximum diastolic potential
MI	Myocardial infarction
MinK	Minimal potassium current controlling protein
$MnCl_2$	Manganese chloride
MTR	Maximum tracking rate
MVT	Monomorphic VT
Na	Sodium
NAPA	*N*-acetylprocainamide
NAT	*N*-acetyltransferase
NCX	Sodium and calcium exchange
NCC	Noncoronary cusp
NSVT	Nonsustained VT
P	Purinergic
PAC	Premature atrial contractions
PAVB	Paroxysmal AV block
PCA	Pulseless cardiac electrical activity
PCCD	Progressive cardiac conduction disease
PES	Programmed electrical stimulation
PG	P glycoprotein
PJRT	Permanent form of junctional reciprocating tachycardia
PKA	Protein kinase A
PPI	Post pacing interval
PVARP	Postventricular atrial refractory period
PVC	Premature ventricular contractions
QT_c	Corrected QT interval
RB	Right bundle
RCC	Right coronary cusp
RCM	Restrictive cardiomyopathy
RF	Radiofrequency
RNA	Ribonucleic acid
RSPV	Right superior pulmonary vein
RVOT	Right ventricular outflow tract
RyR2	Ryanodine receptor
SACT	Sino atrial conduction time
SAECG	Signal average ECG
SAN	Sinoatrial node
SCD	Sudden cardiac death
SCRC	Sarcoplasmic Ca release channel
SND	Sinus node dysfunction
SMVT	Sustained monomorphic VT
SNRT	Sinus node recovery time
SQTS	Short QT syndrome
SR	Sarcoplasmic reticulum
SSS	Sick sinus syndrome

SUR	Sulfonylurea receptor
SVC	Superior vena cava
SVT	Supraventricular tachycardia
TA	Tricuspid annulus
TCL	Tachycardia cycle length
TDP	Torsades de Pointes
TDR	Transmural dispersion of repolarization
TEE	Transesophageal echocardiography
TIA	Transient ischemic attack
TWA	T wave alternans
ULV	Upper limit of vulnerability
VA	Ventriculoatrial
VF	Ventricular fibrillation
VRP	Ventricular refractory period
VT	Ventricular tachycardia
WCT	Wide complex tachycardia
WPW	Wolff–Parkinson–White syndrome

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 Ito 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?
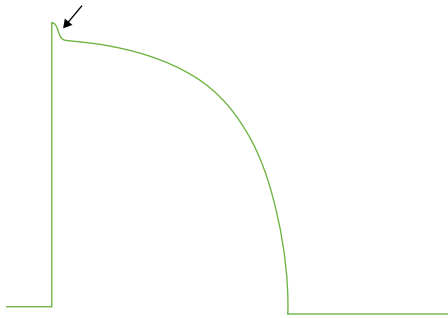
   A I_{to}
   B I_{K1}
   C I_{Na}
   D I_{Ca}

6 Which one of the following genes controls the expression of I_{Kr}?
   A *KCNQ1* (*KvLQT1*)
   B *KCNH2* (*HERG*)
   C *SCN5A*
   D *MinK*

7 Which one of the following actions is likely to activate I_{Katp} current?
   A Rise in intracellular ATP
   B Rise in intracellular calcium
   C Fall of Intracellular ATP
   D Fall of Intracellular calcium

8 How does congestive heart failure affect depolarizing/repolarizing currents?
   A Outward Repolarizing currents are reduced
   B Inward depolarizing currents are reduced
   C Outward repolarizing currents are increased
   D APD is decreased

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

10 Which one of the following is likely to increase the activity of I_{Kr}?
   A Increased extracellular potassium
   B 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 *I*Ca 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 Acidosis
  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^{2+} in SR lumen is bound to the low-affinity calcium-binding protein calsequestrin

C Ca^{2+} signal is generated by Ca^{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[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 α subunits (Figure 1.1). Each α 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_K, 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[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.
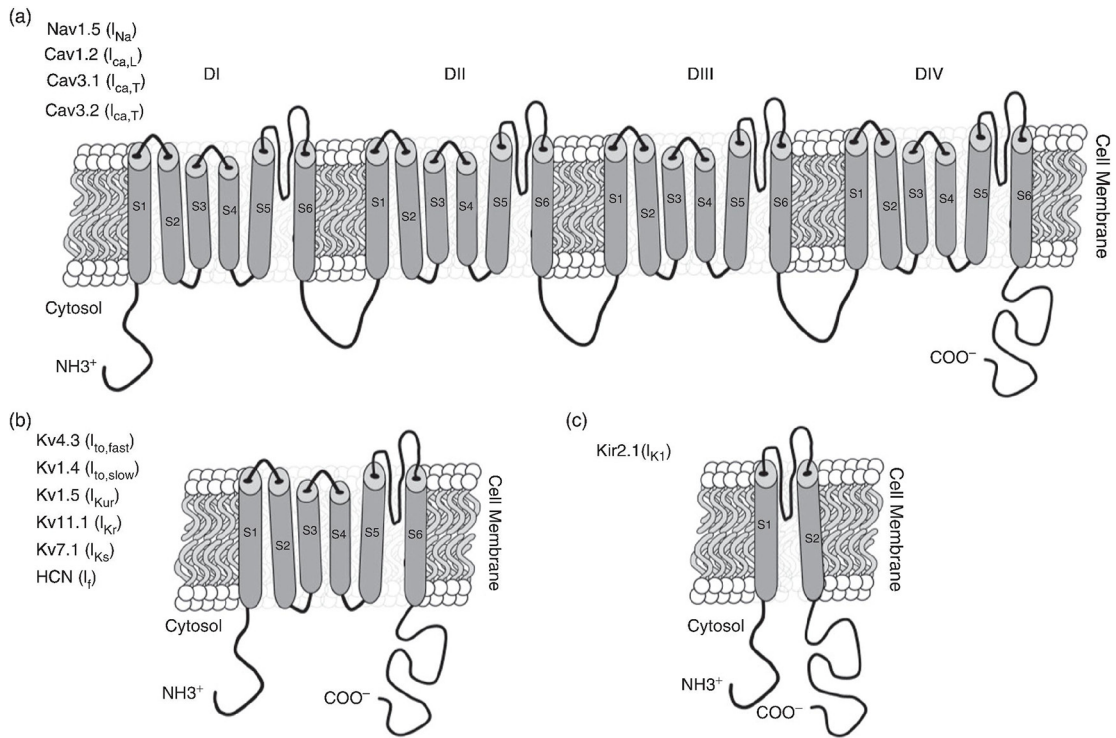
Figure 1.1 α-Subunits of cardiac ion channels. (a) α-Subunits of Na$^+$ and Ca^{2+} channels consists of four serially linked homologous domains (DI–DIV), each containing six transmembrane segments (S1–S6). (b, c) α-Subunits of channels responsible for I_{to}, I_{Kur}, I_{Kr}, I_{Ks}, I_{K1}, and I_f consist of one single domain with six (B) or two (C) (I_{K1}) transmembrane segments. Four subunits (domains) co-assemble to form one functional channel. (Reproduced with permission.)
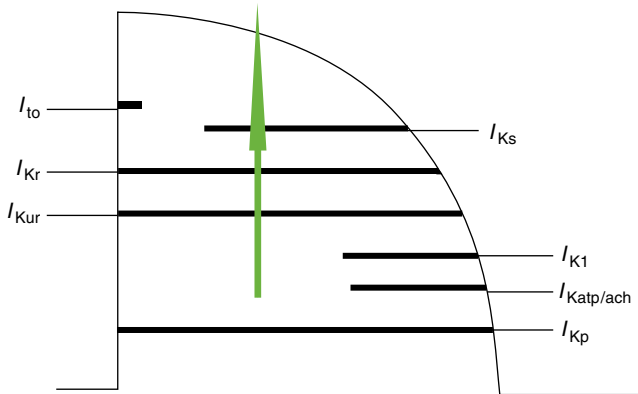
Figure 1.2 Outward currents.

- 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. $I_{to}1$ and $I_{to}2$
- A calcium-activated chloride current ($I_{to}2$) and a classical calcium-independent potassium current ($I_{to}1$) (referred to as I_{to}).
- The calcium-independent I_{to} is of two types: a "rapid" or "fast" $I_{to,f}$ and a slower form, $I_{to,s}$
- $I_{to,s}$ is smaller than $I_{to'f}$
- $I_{to'f}$ recovers rapidly from inactivation, and its α-subunit (Kv4.3) is encoded by *KCND3*. $I_{to,slow}$ recovers slowly from inactivation; its α-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 Kv1.4expression is weak.
- This creates a transmural voltage gradient between epicardium and endocardium.
- $I_{to,f}$ 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.
- $I_{to,f}$ 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 $I_{to,f}$ results in the heterogeneity of action potential, which are responsible for orderly ventricular repolarization.
- Variation in $I_{to,f}$ is responsible for the regional modulation of contractility.
- Electrical heterogeneity associated with the transmural $I_{to,f}$ gradient contributes to synchronization of repolarization and force generation across the ventricular wall.
- The effects of $I_{to,f}$ 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 $I_{to,f}$ levels, controls both the amplitude and the timing of Ca^{2+} release from the SR.
- Reductions in the $I_{to,f}$ and the loss of the notch lead to a slowing of SR Ca^{2+} release.
- The distribution of $I_{to,f}$ in the ventricle synchronizes the timing of force generation between different regions of the ventricle, thereby enhancing mechanical efficiency.
- Generalized downregulation of $I_{to,f}$ occurs in heart failure, slowing the time course of force generation, resulting in reduced myocardial performance.
- Chronic exposure of ventricular myocytes to α-adrenergic agonists (such as phenylephrine) reduces $I_{to,f}$. It also decreased $K_V4.2$, $K_V4.3$, and KChIP2 expression.
- α-adrenergic agonists increase $I_{to,s}$ and $K_V1.4$ expression
- Angiotensin II (AT-II) type 1 (AT-1) receptors stimulation reduces $I_{to,f}$.
- Hypothyroidism prolongs action potential duration reduces $I_{to,f}$ and decreases $K_V4.2$ expression, whereas hyperthyroidism has the reverse effect.
- Aldosterone, induces downregulation of $I_{to,f}$.
- Electrical remodeling in heart disease involves downregulation of $I_{to,f}$ and reductions in $K_V4.2$, $K_V4.3$, and KChIP2, This has been linked to the hypertrophy through the activation of the calcineurin–nuclear factor of activated T cells (NFAT) pathway.
- I_{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 $I_{to}1$. 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 dephosphory-lating 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 α-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 deacti-vates (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_{Kr} 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. hypergly-cemia 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 withKCNH2 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 α-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 β-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 β-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).
- KCNE1 mutation resulting in MinK suppression leads to inner ear abnormalities and deafness, as seen in Jarvell and Lange–Nielsen (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 β-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 IKs 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 β-adrenergic stimulation.
- β-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 K_v1.5 channel genes.
- The effects of male sex hormones lead to a reduction in the density of I_{Kur} and K_v1.5 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 α-subunit ($K_{ir}2.1$) 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 β-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_V channels.
- The inward rectifier potassium channel family comprises at least seven subfamilies, $K_{ir}1$ to $K_{ir}7$ (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. $I_{K,ACh}$ channels (*KCNJ3*, *KCNJ5*), which regulate heart rate and conduction through the atrioventricular node in response to acetylcholine (ACh); and 3. $I_{K,ATP}$ 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[3]

- 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.

- *KNCJ2* 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.