

CONTENTS

Preface	ix
Foreword	xi
Acknowledgement	xiii

1. Electrocardiography in Preclinical Safety 1

Introduction	1
Regulatory Guidance versus Good Science versus Rationale	
Drug Development	1
What To Do When?	1
Safety Pharmacology versus Toxicology	2
Safety Pharmacology Studies: Core-Battery and Second-Tier	
Testing for Cardiotoxicity	3
Why Study Electrocardiography Preclinically?	3
Typical Cardiovascular Safety Pharmacology Designs	5
Cardiotoxicity Endpoints in Toxicology	6
Regarding ECGs	7
Serum Enzymes	7
Postmortem Evaluations	7
The ECG and Drug Safety	8

2. Principles of Electrocardiography 9

Recording the ECG	9
Cardiac Conduction and Waveform Genesis	10
Evaluation of the Electrocardiogram	11
Transmembrane Action Potentials	11
Evaluation of Waveforms	12
Mean Electrical Axis	15
Equipment Considerations	15
Cardiac Effects of Systemic Potassium and Calcium	
Abnormalities	15
Hypokalemia	15
Hyperkalemia	16
Hypocalcemia	17
Hypercalcemia	17

3. Canine Electrocardiography 19

Introduction	19
Etiology, Pathophysiology, and Gross Pathology	19
Rhythm Diagnosis	20
Normal Sinus Rhythm	20
Sinus Tachycardia	23
Sinus Bradycardia	23
Respiratory Sinus Arrhythmia	23
Premature Atrial Complexes	27
Atrial Tachycardia (AT)	29
Atrial Fibrillation	31

Premature Ventricular Complexes	33
Accelerated Idioventricular Rhythm	37
Ventricular Tachycardia	39
Ventricular Flutter, Ventricular Fibrillation	41
Ventricular Asystole	41
Atrioventricular Block	41
Atrial Standstill (Silent Atrium)	55
Sinus Node Dysfunction (Sick Sinus Syndrome, Bradycardia-Tachycardia Syndrome)	57

4. Handling and Restraint of Nonhuman Primates 59

Cynomolgus and Rhesus	59
Manual Restraint	59
Physical Restraint	59
Machine Setup and Configuration	60
Lead Placement	60
Obtaining the Tracing	60
Chemical Restraint	60
Tracing Handling and Storage	60

5. Electrocardiography of Nonhuman Primates 63

Fundamental Principles of Electrocardiography	63
Basic Electrocardiographic Physiology	63
Cardiac Conduction System and the Electrocardiogram	63
Electrocardiography of Cynomolgus and Rhesus Monkeys	65
Introduction	65
Normal Sinus Rhythm	65
Normal Variants	65
Cardiac Arrhythmias	67
Sinoatrial Arrhythmias	67
Supraventricular Arrhythmias	67
Ventricular Arrhythmias	73
Abnormalities of Impulse Conduction	79
Miscellaneous Disturbances	85

5.1. Chimpanzee Electrocardiography 87

Introduction	87
Normal Chimpanzee ECG	87
Sinus Rhythms	87
Abnormal Chimpanzee ECG	87
Supraventricular Arrhythmias	89
Ventricular Arrhythmias	91
Conduction Disturbances	93
Chamber Enlargement	93
Antiarrhythmic Therapy	93
Drug Classes	94

6. Electrocardiography of Minipigs	95	Ventricular Tachycardia	105
Normal Values	95	Torsades de Pointes	105
Normal Variants in Order of Occurrence (Commonality)	95	Ventricular Fibrillation	105
Lead Placement	95	Ventricular Preexcitation	105
Fundamental Principles of Electrocardiography	95	Abnormalities of Impulse Conduction	107
Basic Electrocardiographic Physiology	95	Sinoatrial Standstill	107
Cardiac Conduction System and the Electrocardiogram	96	First-Degree Atrioventricular Block	107
Electrocardiography of Minipigs (<i>Sus scrofa</i>)	96	Second-Degree Atrioventricular Block	107
Introduction	96	Third-Degree Atrioventricular Block	107
Normal Sinus Rhythm	96	Atrioventricular Dissociation	107
Cardiac Arrhythmias	96	Bundle Branch Blocks	107
Sinoatrial Arrhythmias	96	Miscellaneous Disturbances	109
Abnormalities of Impulse Formation	97	Normal Variants	111
Abnormalities of Impulse Conduction	97		
Normal Sinus Rhythm	97	7. Telemetry in Preclinical Safety Studies	113
Sinoatrial Arrhythmias	97		
Sinus Tachycardia	97	8. PR (PQ), QRS, QT, and Other Issues	115
Sinus Arrhythmia	99	The PR (PQ) Interval	115
Sinoatrial Block and Sinus Arrest	99	QRS Complex Duration	115
Wandering Pacemaker	99	QT Interval Duration	115
Sinus Bradycardia	99		
Supraventricular Arrhythmias	101	9. Self-Test	117
Atrial Premature Complexes	101	Canine ECG Examples	117
Atrial Tachycardia	101	Answers	120
Atrial Flutter	101		
Atrial Fibrillation	101	References	125
Junctional Premature Contraction	101	Index	127
Junctional Tachycardia	101		
Ventricular Arrhythmias	103		
Ventricular Premature Complexes (VPCs)	103		