

Contents

1 General Principles of Animal Selection and Normal Physiological Values	1
Special Requirement Considerations.....	2
Normal Physiological Data	3
2 Preanesthesia, Anesthesia, Chemical Restraint, and the Recognition and Treatment of Pain and Distress	17
General Principles of Pain Recognition in Animals.....	17
The Use of Anti-Cholinergic Drugs for Preanesthesia.....	21
General Comments on Preanesthetic Agents	22
Preanesthesia and Anesthesia in Rats and Mice.....	22
Chemical Restraint (Sedation) in Rats and Mice	23
Pain and Distress Recognition in Rats and Mice	23
Treatment of Pain in Rats and Mice	26
Local Anesthetic Agents.....	26
Nonsteroidal Anti-Inflammatory Drugs	26
Narcotics.....	26
Preanesthesia and Anesthesia in Rabbits.....	28
Chemical Restraint (Sedation) in Rabbits	29
Pain Recognition in Rabbits	29
Treatment of Pain in Rabbits.....	29
Local Anesthetics	29
Nonsteroidal Anti-Inflammatory Drugs (NSAIDs).....	30
Narcotics.....	30
Alpha-Agonists	30
Preanesthesia and Anesthesia in Dogs	30
Chemical Restraint (Sedation) in Dogs.....	32
Pain Recognition in Dogs.....	33
Treatment of Pain in Dogs.....	34
Local Anesthetics	34
NSAIDs	34
Narcotics.....	34
Alpha-Agonists.....	35

Preanesthesia and Anesthesia in Cats.....	35
Chemical Restraint (Sedation) in Cats	36
Pain Recognition in Cats	37
Treatment of Pain in Cats	37
Local Anesthetics	37
NSAIDs	37
Narcotics.....	37
Alpha-Agonists.....	38
Preanesthesia and Anesthesia in Guinea Pigs	38
Chemical Restraint (Sedation) in Guinea Pigs	38
Pain Recognition in Guinea Pigs.....	38
Treatment of Pain in Guinea Pigs.....	39
Local Anesthetic Agents.....	39
NSAIDs	39
Narcotics.....	39
Alpha-Agonists.....	39
Preanesthesia and Anesthesia in Pigs	39
Chemical Restraint (Sedation) in Pigs	41
Pain Recognition in Pigs	41
Treatment of Pain in Pigs	41
Local Anesthetic Agents.....	41
NSAIDs	42
Narcotics.....	42
Alpha-Agonists.....	42
Preanesthesia and Anesthesia in Calves, Sheep, and Goats.....	42
Chemical Restraint (Sedation) in Small Ruminants.....	43
Recognition of Pain in Small Ruminants	43
Treatment of Pain in Small Ruminants	44
Local Anesthetic Agents.....	44
NSAIDs	44
Narcotics.....	44
Alpha-Agonists.....	44
Preanesthesia and Anesthesia in Rhesus Monkeys	45
Chemical Restraint (Sedation) in Rhesus Monkeys	45
Pain Recognition in Rhesus Monkeys.....	45
Treatment of Pain in Rhesus Monkeys.....	46
Local Anesthetics	46
NSAIDs	46
Narcotics.....	46
Conclusions	47
3 Normal Cardiac Function Parameters.....	55

4 Measuring Cardiac Function	65
The Pressure–Volume Relationship.....	67
Another Measure of Ventricular Elasticity.....	68
Measurement of Electrical Activity	68
Measurement of Pressure	69
Echocardiography.....	70
History	70
Physics of Echo Technology.....	72
Doppler Flow Velocity and Tissue Doppler Imaging.....	74
History	74
Physics of Doppler Technology.....	75
Tissue Doppler Imaging	76
Examples of Ultrasound Data Reported Using	
<20-MHz Transducers.....	77
Examples of Ultrasound Data Reported Using 20-MHz	
(or Greater) Transducers.....	78
Summary of Information Needed to Ascertain	
the Reliability of Ultrasound Data.....	80
Techniques for Measuring Ventricular Volumes	80
Radiographic.....	80
Echocardiography and Tissue Doppler Imaging	81
Sonomicrometry	81
Radionuclide Ventriculography	81
Magnetic Resonance Imaging and Computer-Assisted	
Tomography Scan.....	82
Conductance-Derived Volume Measurements	82
Other Measures of Myocardial Physical Properties	84
Myocardial Resistivity.....	85
Tissue Characterization	85
Measuring Diastolic Dysfunction.....	86
5 Measuring Vascular Function and Ventricular/	
Arterial Coupling Dynamics	93
History	93
Quantification of Arterial Compliance	94
Force-Displacement Measurements	95
Pulse Wave Velocity	97
Modeling Techniques for Estimating Vascular Mechanical Behavior	99
Ventricular/Vascular Coupling	101
Ventricular/Vascular Coupling Determined Using	
the Input Impedance	101
Ventricular/Vascular Coupling Determined Using	
the Ratio of Ventricular End-Systolic Pressure	
and Stroke Volume (P_{es}/SV) Designated E_a	102

Diastolic Ventricular/Vascular Coupling	104
MRI Imaging for Detection of Ventricular/Vascular Coupling	104
Tissue Doppler Imaging and Elasticity Imaging	104
6 Isolated Heart Preparations, Problems, and Pitfalls	109
Development of the Isolated Heart Preparation	109
Retrograde Perfusion Preparations (The Langendorff Preparation).....	112
Choosing between the Pressure-Regulated or Flow-Regulated	
Langendorff-Type Preparation	114
The Isolated, Working, In Situ Heart-Lung Preparation	114
The Isolated Working Left Heart Preparation	114
The Langendorff-Type Perfused Working Left Heart Preparation.....	115
The Biventricular Isolated Working Heart Preparation.....	117
The Biventricular, Retrograde-Perfused,	
Working Heart Preparation.....	119
Perfusion Solutions	120
Support Animals.....	122
Washed Red Blood Cell Addition to the Perfusate	122
Problems and Pitfalls.....	123
Exclusion Criteria.....	123
Problems Common to Crystalloid Perfusion.....	124
Contamination	124
Temperature	125
Metabolic “Poisoning”	125
Pacing vs. Spontaneously Beating Preparations.....	125
Frequency Response Testing of Ventricular Pressure	
Recording Systems	126
Heterotopic Transplants.....	126
7 Cardiovascular Effects of Anesthetics, Sedatives,	
Postoperative Analgesic Agents, and Other Pharmaceuticals	131
Barbiturates	131
Propofol.....	132
α -Chloralose.....	133
Urethane	134
α -Chloralose + Urethane.....	134
Steroid Anesthetic Agents	134
Inhalation Anesthetic Agents	135
General	135
Halothane.....	136
Isoflurane	137
Desflurane.....	138
Sevoflurane	139
Ether	140
Nitrous Oxide	140

Trichloroethylene.....	140
The Opioids	141
Morphine	141
Meperidine (Demerol)	144
Methadone	144
Levomethadone.....	145
Pentazocine.....	145
Fentanyl	145
Butorphanol	147
Buprenorphine	147
Oxymorphone	148
Naloxone.....	148
Other Synthetic Opioids	149
Dissociative Anesthetic Agents.....	150
Ketamine.....	150
Tiletamine.....	151
Imidazole and Other Hypnotic, Amnesiac, Anxiolytic, or Antipsychotic Compounds.....	152
Etomidate.....	152
Metomidate.....	153
Benzodiazepines	153
Rilmenidine	155
α -2 Adrenergic Receptor Agonists.....	156
Medetomidine and Dexmedetomidine.....	156
Clonidine	157
β -2-Adrenergic Receptor Agonists	157
Clenbuterol	157
KUR-1246	158
Fenoterol.....	158
Rauwolfia Derivatives	158
Reserpine	158
Phenothiazine Derivatives	160
Chlorpromazine and Promazine	160
Acetylpromazine (Acepromazine).....	162
Other Phenothiazine Derivatives	163
Triflupromazine, Levomepromazine, Prochlorperazine (thioridazine), Cyamemazine	163
Butyrophenones.....	164
Droperidol.....	164
Haloperidol	165
Azaperone.....	166
Other Antipsychotic/Anxiolytic/Antidepressant (Tranquilizer) Drugs.....	166
Tricyclic Antidepressants	167
Selective Serotonin Uptake Inhibitors	167

Atypical Antipsychotics	169
Sertindole.....	169
Pimozide	169
Clozapine	169
Risperidone.....	170
Amisulpride	170
Minaprine	171
Atypical Antipsychotics	171
Aripiprazole.....	171
Fezolamine	171
Olanzapine.....	171
Lortalamine.....	171
Xylazine.....	172
Drugs in Combination Providing Neurolept Analgesia/Anesthesia.....	172
Metomidate + Azaperone	172
Medetomidine + Butorphanol.....	173
Medetomidine + Butorphanol + Midazolam	173
Medetomidine + Buprenorphine + Ketamine.....	173
Medetomidine + Midazolam	174
Medetomidine + Hydromorphone	174
Dexmedetomidine + Butorphanol	174
Medetomidine + Ketamine	174
Medetomidine + Ketamine + Midazolam.....	175
Dexmedetomidine + Ketamine	175
Ketamine in Combination with Tranquilizers	175
Ketamine + Acepromazine	175
Ketamine + Xylazine	176
Ketamine + Xylazine + Guaifenesin	178
Ketamine + Xylazine + Buprenorphine.....	178
Ketamine + Diazepam	178
Midazolam + Butorphanol.....	179
Midazolam + Fentanyl + Fluanisone.....	179
Midazolam + Methadone + Propofol + Isoflurane + Continuous Infusion of Propofol and Fentanyl.....	179
Acepromazine + Meperidine	179
Fentanyl + Droperidol (Innovar-Vet®).....	180
Azaperone + Metomidate	180
Acepromazine + Etorphine.....	180
Fentanyl + Morphine	180
Fentanyl + Propofol.....	181
Xylazine + Morphine.....	181
Oxymorphone + Bupivacaine	181
Tiletamine + Zolazepam (Telazol®, Zoletil®).....	181
Local Anesthetic Agents	182
Non-steroidal Anti-inflammatory Agents.....	183

Contents	xix
Neuromuscular Blocking Agents	185
Aminoglycoside, Fluoroquinolone, and Anthracycline Antibiotics	187
8 Naturally Occurring and Iatrogenic Animal Models of Valvular, Infectious, and Arrhythmic Cardiovascular Disease.....	203
Congenital Cardiac Defects, General Information	203
Genetically Engineered Models, General Information.....	204
Naturally Occurring Models of Valvular Disease	205
Iatrogenic Models of Valvular Disease	207
Infectious Cardiovascular Disease	208
Bartonella sp.....	208
Borrelia sp	208
Coxsackievirus sp.....	209
Diphtheritic Myocarditis	209
Encephalomyocarditis Virus.....	210
Autoimmune Myocarditis	210
Infectious Complications Following Burn Injury.....	210
Arrhythmic Cardiovascular Disease.....	211
Naturally Occurring Cardiac Arrhythmias	211
Iatrogenic Cardiac Arrhythmias	211
9 Iatrogenic Models of Ischemic Heart Disease.....	219
Global Ischemia	219
Regional Ischemia.....	221
10 Iatrogenic, Transgenic, and Naturally Occurring Models of Cardiomyopathy and Heart Failure	231
Naturally Occurring Models of Cardiomyopathy	232
Heritable HCM in Cats	232
DCM in Dogs	233
Cattle with Cardiomyopathy and Woolly Hair Coat Syndrome.....	234
Primates.....	235
Whales.....	235
Iatrogenic Models of Cardiomyopathy and Heart Failure	235
Ventricular Arrhythmia	235
Increasing the Ventricular Workload.....	236
Rapid Cardiac Pacing.....	236
Pressure Overload	236
Volume Overload	237
Valvular Stenoses or Insufficiencies	237

Other Iatrogenic Models of Cardiomyopathy and Heart Failure	237
Anthracycline-Induced Cardiomyopathy	237
Diabetic and Lipid-Toxic Models of Cardiomyopathy	238
Chronic Myocardial Ischemia Models of Cardiomyopathy.....	238
Toxicosis and Mineral-Deficient Models of Cardiomyopathy.....	239
Autoimmune Models of Cardiomyopathy	239
Hyperthyroid and Hyper-Adrenergic Models of Cardiomyopathy	240
Chronic Hypoxia Models of Cardiomyopathy.....	240
Liver Cirrhosis Models of Cardiomyopathy	240
Murine Cysticercosis Model of Cardiomyopathy	240
Commercially Available Inbred-Rat Models of Cardiomyopathy and Heart Failure	240
Transgenic Models of Cardiomyopathy and Heart Failure.....	241
Mouse and Rat Models of Familial Hypertrophic Cardiomyopathy and HCM.....	241
Mouse and Rat Models of DCM.....	242
Overexpression Models.....	245
11 Iatrogenic, Congenic, and Transgenic Models of Hypertension	259
Renovascular Hypertension	260
2K1C and 1K1C Renovascular Hypertension in Rats	261
2K1C and 1K1C Renovascular Hypertension Models in Mice	263
Renovascular Hypertension Models in Rabbits.....	264
1K1C Renovascular Hypertension in Dogs	265
Renovascular Hypertension in Pigs	265
Genetic Models of Hypertension	266
Spontaneously Hypertensive Rat	266
Stroke-Prone SHR.....	269
Dahl Salt-Sensitive and Insensitive Rats.....	270
Other Salt-Sensitive (Salt-Induced) Models of Hypertension	272
Angiotensin-II-Induced Hypertension	273
DOCA-Induced Hypertension	276
NO-Synthesis Blockade Hypertension	278
Glucocorticoid-Induced Hypertension.....	280
Intrauterine Growth-Restricted Induced Hypertension.....	281
Other Transgenic and Congenic Models of Hypertension.....	283
The mRen-2 Model.....	283
ATR-1 Models.....	283
Angio-II Overexpression Models.....	284
G-Protein Models.....	284
eNOS Models	285
Endothelin Models	285
Chromogranin-A Models	286
PPAR- α Models	286

Bradykinin-2 Models	286
Estrogen Models	287
Corin Models	287
Vitamin D Receptor Models	287
Glucocorticoid Receptor Models	287
Smoothelin Models	288
Adiponectin Models.....	288
Aryl Hydrocarbon Models	288
Parathyroid Hormone Type 1 Receptor Models.....	289
Profilin Models.....	289
Oligodeoxynucleotide Models.....	289
Multiple Transgenic Models	290
Congenetic Models	290
Other Models of Systemic Hypertension.....	291
Pulmonary Hypertension	292
Hypoxia-Induced Pulmonary Hypertension	292
Monocrotaline-Induced Pulmonary Hypertension.....	293
Transgenic Models of Pulmonary Hypertension	294
12 Naturally Occurring, Iatrogenic and Transgenic Models of Atherosclerotic Disease	307
Characteristics of Plaque Rupture and Resulting Thrombosis	309
Implication of New “Players” in the Pathogenesis of Atherosclerotic Disease	309
Animal Models.....	310
Naturally Occurring Animal Models of Atherosclerosis	311
Primate Models of Atherosclerosis.....	311
Swine Models of Atherosclerosis	312
Dog and Cat Models	312
Rabbit Models	313
Transgenic Rabbit Models	314
Rat Models	315
Transgenic Rat Models	317
Mouse Models.....	317
Mice Models of Glucose Intolerance	317
Graft Vasculopathy.....	323
Hamsters	324
Sand Rats	324
13 Animal Models for the Study of Neurohumeral and Central Neural Control of the Cardiovascular System.....	331
The Autonomic Nervous System in Blood Pressure Homeostasis and Cardiorespiratory Reflex Responses	333
Rostal and Caudal Ventrolateral Medulla	334

Nucleus Tractus Solitarius	337
Hypothalamic Paraventricular Nucleus.....	339
Periaqueductal Gray	340
Anterior and Posterior Hypothalamic Areas	342
Median Preoptic Nucleus.....	342
Nucleus Cuneatus.....	342
Lateral Parabrachial Nucleus and the Dorsal Raphe Nucleus.....	343
Caudal Vestibular Nucleus	343
Gender Effects on Central Control of Cardiovascular Responses	343
Neurohumeral Control	344
Renin-Angiotensin System	344
Serotonin	344
Vasopressin	345
Endogenous Ouabain-Like Substance	345
Opioids.....	345
Tyrosine Hydroxylase and Phenylethanolamine N-Methyltransferase.....	346
Neuropeptide Y.....	346
Leptin	346
Dopamine- β -Hydroxylase.....	346
11- β -Hydroxylase and Aldosterone Synthase	347
Orexin	347
Urotensin-II.....	347
Cholecystokinin	348
14 Other Transgenic Animal Models Used in Cardiovascular Studies	355
Sex-Related Responses	356
Kinases.....	357
Oxidases and Oxygenases.....	358
Adenosine and Adrenergic Receptors.....	359
Nitric Oxide Synthase.....	360
Metabolic Syndrome.....	361
Xenotransplantation	362
Na ⁺ /Ca ²⁺ and Na ⁺ /H ⁺ Exchangers.....	364
Inflammatory Cytokines.....	365
Peroxisome Proliferator-Activated Receptor	366
Renin-Angiotensin System	366
Bradykinin-2 Receptor.....	367
Apolipoprotein-E and Low-Density Lipoprotein Knockout Models.....	367
Toll-Like Receptors.....	368
Caveolin-1 (Cav-1).....	368
Long QT Syndrome	369

Nuclear Factor Kappa-B	369
Orphan Nuclear Receptors	370
Troponin	370
Chromogranin A	371
Lectin-Like Oxidized Low-Density Lipoprotein Receptor	371
Junctin	371
Connexin	372
Phospholamban	372
Fas Ligand	373
Proteases, Metalloproteinases, and ATPases	373
Binary Calsequestrin/P2Xr-Purinergic Receptor (CSQ/P2X4R) Transgenics	374
pro-ANP Gene Disrupted Mouse	375
Macrophage Colony-Stimulating Factor	375
Endothelin-1	375
Elastin	376
α -2-Antiplasmin	376
cAMP Response Element Binding Protein	376
Fatty Acid Transport Protein: CD36	376
Clotting Factor XIII	377
Apelin	377
T-Box Transcription Factor	377
Thrombospondin-1 and Its Receptor CD47	377
Polyomavirus Middle T Antigen	378
Thrombopoietin Receptor	378
Vascular Endothelial Growth Factor	378
Osteopontin	378
ATP-Binding Membrane Cassette Transporter-A1	379
The K ⁺ /Cl ⁻ Cotransporter KCC3	379
Aldosterone Synthase Overexpression	379
Cysteine and Glycine-Rich Protein-2 (CSRP-2)	379
Parathyroid Hormone Type-1 Receptor and PTH/PTH-Related Protein	380
Vitamin D Receptor	380
Thromboxane Receptor (Tp)	380
T and B Cells	380
Vanilloid Type-1 Receptors (TRPV-1)	381
Serotonin Transporter (SERT)	381
CC Chemokine Receptor-2 (CCR-2)	381
Thymosin β -4	381
Index	393