

PREFACE

Issues related to arterial vascular injury are central to the cardiovascular practitioner and research scientist alike. Whether acute (i.e., mechanically induced) or chronic (i.e., hypertension, atherosclerosis, and immune-mediated), vascular injury and the responses it elicits are leading causes of disease today, producing such acute ischemic syndromes as transient ischemic attacks, stroke, unstable angina pectoris, and acute myocardial infarction, as well as restenosis following percutaneous angioplasty or revascularization surgeries. The development of effective cardiovascular therapeutics to treat or prevent atherosclerosis and restenosis relies on preclinical research—both cell biological studies and observations and findings from animal models.

We have found that no one resource is available for a comprehensive presentation of animal models related to vascular disease. We hope that *Vascular Disease and Injury: Preclinical Research* will provide such a medium by presenting topics related to vascular injury in an organized and comprehensive fashion. Our approach is to present issues related to vascular disease and injury in five major areas: acute mechanical injury and vascular repair, models of arterial thrombosis, chronic atherosclerotic models, vascular disease in transplanted vessels, and vascular disease in models of systemic and pulmonary arterial hypertension. We have aimed to provide a “how-to” guide and have, therefore, worked to ensure that each chapter is highly practical by including equipment lists, current sources for animals, diet and reagents, schematic diagrams and, when pertinent, photomicrographs of sample histology.

In Part I of the book, Acute Mechanical Injury and Vascular Repair, Drs. Welt and Rogers review the widely used rabbit iliac artery models of balloon- and stent-induced angioplasty. Dr. Schwartz follows with a comprehensive presentation of the classic porcine overstretch stent model, emphasizing the relationship he has characterized between the degree of vascular injury and resultant neointimal thickening that follows. Dr. Carter extends this model into an atherosclerotic milieu. Drs. Nedelman and Rogers then apply central elements of these lower animal models to nonhuman primate experimental angioplasty and stenting, a burgeoning field suited to evaluation of human-targeted biologics. Since venous conduits are used extensively with high failure rates in coronary and peripheral bypass procedures, Dr. Dzau’s group provides a chapter on pathologic responses in experimental models of arterial-venous grafting. Murine systems allow cardiovascular researchers to take advantage of key transgenic and knockout strains. Therefore, we have provided extensive material on recently described models of

acute and chronic vascular injury in mice. Dr. Lindner, who pioneered the use of mice in this field, discusses wire denudation and ligation models of neointimal thickening. Drs. Chen, Rogers, and Simon then describe a recently published model of arterial dilation and endothelial denudation that is accompanied by inflammatory cell recruitment and neointimal thickening. Drs. Eitzman and Westrick present a very interesting vascular photochemical model that has components of thrombosis, as well as neointimal thickening. Finally, Dr. Collier's group discusses their approach using a femoral wire injury model, a modification of the carotid wire denudation resulting in increased neointimal thickening.

In Part II, two chapters will focus on Models of Arterial Thrombosis. In the first, Drs. Fay, Parker, and Zhu use perivascular ferric chloride to induce arterial injury and thrombosis in the mouse carotid. These investigators have exploited this model to investigate the importance of plasminogen activator inhibitor-1 in modulating endogenous fibrinolysis. Finally, Dr. Folts provides a comprehensive overview of his animal preparation for studying *in vivo* platelet activity and platelet interactions with damaged arterial walls. This model has been instrumental in the clinical development of therapeutics for acute ischemic syndromes and percutaneous coronary interventions.

Part III focuses on Chronic Atherosclerotic Models. Drs. Palinski, Napoli, and Reaven provide an in-depth overview of mouse models of atherosclerosis, in particular the apolipoprotein E (ApoE) and low density lipoprotein (LDL) receptor knockouts. Drs. Aikawa and Libby then present their work regarding progression and regression of atherosclerosis using the classic hypercholesterolemic rabbit model. Finally, Drs. Nicolosi and Kritchevsky present the use of higher animals, including nonhuman primates, for preclinical research in atherosclerosis.

Part IV of the book concentrates on Vascular Disease in Transplanted Vessels. Drs. Shi and Hoover discuss the use of a murine carotid loop model of transplant disease that has been helpful in elucidating the important role of proteases, such as plasminogen, in transplant-related vascular disease. Dr. Mitchell then follows with an overview of heterotopic heart transplantation in the mouse. His group has used this model to study the role of cytokines and immune co-stimulatory molecules in parenchymal rejection and accelerated graft arteriosclerosis. The concluding chapter in this section by Drs. Chen and Adams presents exciting material regarding hyperacute vascular rejection in pig-to-primate xenotransplantation.

The next set of chapters in Part V concentrates on Vascular Disease in Models of Arterial Hypertension. Dr. Baumbach examines methods for investigating cerebrovascular disease in experimental systemic hypertension. Two chapters are devoted to pulmonary hypertension. In the first, Dr. Rabinovitch provides an in-depth discussion of monocrotaline-induced pulmonary hypertension. She focuses on the cellular and molecular biology of pulmonary vasculopathy, integrating dynamic interactions between smooth muscle cells, extracellular matrix, and the

endothelium. This leads into the chapter by Drs. Meyrick and Tchekneva on chronic pulmonary hypertension in the hypoxic rat and in the sheep following continuous air embolization.

The final section, Part VI, provides an essential foundation in Animal Care and Tissue Processing and analysis. Dr. Marini discusses veterinary issues and anesthesia options, addressing all species covered elsewhere in the book, from mice to nonhuman primates. Key points regarding survival surgery, choice of anesthetic, and analgesia are included. Histopathologic methods are then discussed by Drs. Seifert, Rogers, and Edelman. This chapter provides the “basics” for tissue harvesting and fixation, and histology methods for routine immunology and electron microscopy.

The topics we have chosen to include in *Vascular Disease and Injury: Pre-clinical Research* are not meant to be all inclusive and, undoubtedly, a few areas have not been covered. We have simply tried to show the range and breadth of animal models that have been useful in translational cardiovascular research. It is important to end this discussion on a cautionary note. The track record of animal models of vascular repair after injury, as predictors of human responses, is poor. Myriad agents have been proven effective in one or another model, only to fail clinical scrutiny. This fact means that for each experimental approach, by any of the models described in this book, the purpose of research must be to further mechanistic understanding, not to recapitulate human disease in an experimental animal.

In closing, we must acknowledge the tremendous efforts of our administrative assistant, Paula McColgan, the series editor, Dr. Christopher Cannon, and the staff of Humana Press. We are indebted to Drs. Eugene Braunwald, Victor J. Dzau, Thomas W. Smith, and Peter Libby for encouraging and supporting our clinician-scientist careers. Dr. Rogers would like to thank most deeply his mentors in the study of vascular injury and repair, Drs. Morris Karnovsky and Elazer Edelman, and to dedicate this book to his wife Nathalie and three children, Camille, Genevieve, and Charles. Dr. Simon would like to honor his mentor in life and medicine, Dr. Norman M. Simon, and to dedicate this book to his wife Dr. Marcy Schwartz and three children Benjamin, Maxwell, and Aaron.

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