The Coronary Circulation in Health and Disease

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ORONARY CIRCULATION IN HEALTH AND DISEASE

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Notice

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PREFACE

Coronary heart disease is the predominant cardiovascular affliction in the industrialized world. Because of the prevalence and severity of coronary disease, many physicians and scientists have focused their attention to this area.

The evaluation and treatment of patients with heart disease must be founded upon a thorough understanding of the function of the coronary circulation in normal and pathological states. In 1950, Donald Gregg published *The Coronary Circulation in Health and Disease*, a classic treatise on coronary physiology that has continued to serve as a major reference text in this field.* Although other volumes on the coronary circulation have been published subsequent to Dr. Gregg's book, a comprehensive text written by a single author has not been published since 1950. Contributed texts are almost always plagued by fragmentation, gaps, and inconsistencies. The present monograph provides the reader with an integrated, comprehensive summary of the present state of knowledge concerning the regulation of the coronary circulation in health and disease. It is directed toward physicians involved in the care of patients with heart disease (internists, cardiologists, radiologists, cardiac surgeons, anesthesiologists) and basic scientists (physiologists, pharmacologists, bioengineers, anatomists, etc.) interested in problems that involve the coronary circulation.

The volume is divided into six parts. Parts 1 and 2 contain one chapter each on coronary anatomy and methods of measuring coronary blood flow. The anatomic description of the coronary vasculature is closely linked to the functional capacity of the circulation. Part 2, on methods of measuring coronary blood flow, focuses on approaches in current use. Part 3 deals with basic mechanisms that regulate coronary flow under normal conditions. Throughout the six chapters in Part 3 I have emphasized the critical role these basic regulatory mechanisms play in determining the clinical manifestations of disease processes that affect the coronary circulation. Part 4, which is comprised of seven chapters, centers on the manner in which specific disease processes (coronary occlusion, coronary spasm, coronary stenosis, etc.) disturb the functional capacity of the coronary circulation. Part 5 calls attention to significant differences in the regulation of blood flow to the right

*Dr. Gregg kindly allowed me to use this title for the present book.

and left ventricles. The six chapters in Part 6 describe the manner in which various medical and surgical therapies alter the functional characteristics of the coronary circulation.

The roots of this book stem from my years in medical school at the University of Wisconsin where three individuals—Richard Wasserberger, Professor of Medicine; George G. Rowe, Professor of Medicine; and Thomas C. Meyer, Professor of Pediatrics—provoked my initial interest in cardiology. My training in cardiovascular research began under the tutelage of Stephen E. Epstein, Chief of the Cardiology Branch at the National Institutes of Health. My interest in the coronary circulation was fostered by François M. Abboud, Chairman of the Department of Medicine and Director of the Cardiovascular Center at the University of Iowa. Dr. Abboud provided my colleagues and me with superb laboratory facilities, generous financial support, constant guidance, and a stimulating, challenging atmosphere in which we have been able to pursue a wide range of studies concerning the regulation of the coronary circulation. The information contained in this volume is a reflection of the work I have done and the knowledge I have gained at the Cardiovascular Center at the University of Iowa.

Although a monograph supposedly represents the efforts of an individual, many people often contribute to such works. *The Coronary Circulation in Health and Disease* was immensely improved as a result of the efforts of four reviewers: Julien I.E. Hoffman, Professor of Pediatrics, University of California, San Francisco; Joseph C. Greenfield, James Duke Professor of Medicine and Chief of the Cardiology Division at Duke University; Donald E. Heistad, Professor of Medicine, University of Iowa; and Richard E. Kerber, Professor of Medicine, University of Iowa and Associate Director of the Cardiology Division. Each of these colleagues reviewed the entire volume and made numerous suggestions for additions, deletions, and revisions which were incorporated into the final manuscript.

For over a decade I have learned a great deal about the coronary circulation by studying the published works of Drs. Julien I.E. Hoffman and Joseph C. Greenfield and their coworkers. In addition, numerous formal and informal meetings with these two outstanding coronary physiologists have played a major role in shaping my views concerning a host of basic concepts that relate to the regulation of the coronary circulation. In the course of reviewing this monograph, Dr. Hoffman and Dr. Greenfield encouraged me to reexamine my views in many areas relevant to this field. In so doing, they have contributed even further to this work.

Drs. Donald E. Heistad and Richard E. Kerber have been close colleagues and collaborators since I came to the University of Iowa in 1973, and I have come to place great value on their criticism. Hence, I deeply appreciate the time and effort they devoted to reviewing the manuscript. Their many suggestions significantly improved the book.

I have received valuable criticism concerning selected chapters from James Willerson, Professor of Medicine and Chief of the Cardiology Division, Southwestern Medical School; Lewis Becker, Associate Professor of Medicine at Johns Hopkins Medical School; Paul Cannon, Associate Professor of Medicine at Columbia Medical School; Carl White, Associate Professor of Medicine, University

of Iowa; Robert Bache, Professor of Medicine, University of Minnesota; and William C. Chilian, Assistant Research Scientist, University of Iowa.

During the past decade I have been privileged to participate in the education of many young investigators and senior research associates who came to the Cardiovascular Center to study the regulation of the coronary circulation. These young people have been a constant source of stimulation to me. In many instances they have significantly influenced my views on many controversial areas that relate to the coronary circulation. In this regard, I am particularly thankful to Thomas Mueller, James Martins, Sidney Klopfenstein, Joseph Gascho, Charles Eastham, David Harrsion, Roger Wangler, Kevin Peters, Samon Koyanagi, Tesuji Inou, John Rumberger, Natsea Pandian, David Gutterman, Andrew Feiring, Tarek Husayni, and William Chilian.

I want to thank Dr. Allyn Mark, Professor of Medicine and Chief of the Cardiology Division at the University of Iowa for arranging to decrease my clinical assignments so I would have sufficient time to complete this book.

I am also grateful to Linda Godfrey, Director of Medical Graphics, University of Iowa, who designed the illustrations for the book, and to my secretaries, Beverly Layton and Maureen Kent who assisted me in preparing the manuscript.

Finally, it has been a pleasure to work with McGraw-Hill Book Company. Special thanks should be given to Robert P. McGraw, Richard Laufer, and Maggie Schwarz. They provided me with excellent counsel regarding many aspects of this project, and assigned a superb copyeditor, Irene Curran, to assist me. Irene worked diligently to enhance the accuracy and clarity of the presentation.

Many talented individuals have made significant contributions to this volume. I am indebted to all of them and deeply appreciate their unselfish efforts on my behalf.

Melvin L. Marcus

CONTENTS

PREFACE

PART 1 CORONARY ANATOMY

1 Anatomy of the Coronary Vasculature 3

PART 2 METHODS OF MEASURING CORONARY BLOOD FLOW

2 Methods of Measuring Coronary Blood Flow 25

PART 3 BASIC REGULATORY MECHANISMS IN THE CORONARY CIRCULATION

3 Metabolic Regulation of Coronary Blood Flow 65
4 Autoregulation in the Coronary Circulation 93
5 Transmural Distribution of Myocardial Perfusion 113
6 Neural Control of the Coronary Circulation 129
7 Myogenic Regulation of Coronary Blood Flow 147
8 Humoral Control of the Coronary Circulation 155

PART 4 EFFECTS OF DISEASE PROCESSES ON THE CORONARY CIRCULATION

9 Effects of Coronary Occlusion on Myocardial Perfusion 191
10 The Coronary Collateral Circulation 221
11 Physiological Effects of a Coronary Stenosis 242

	12	Effects of Coronary Spasm on the Coronary Circulation	270
	13	Effects of Cardiac Hypertrophy on the Coronary Circulation	285
	14	Effects of Anemia and Polycythemia on the Coronary Circulation	307
	15	Rare Diseases of the Coronary Vasculature Which Can Impair Myocardial Perfusion	320
PART	**5**	**DIFFERENCES IN THE CORONARY CIRCULATION OF THE RIGHT AND LEFT VENTRICLES**	
	16	Differences in the Regulation of Coronary Perfusion to the Right and Left Ventricles	337
PART	**6**	**MEDICAL AND SURGICAL INTERVENTIONS THAT MODIFY THE CORONARY CIRCULATION**	
	17	Coronary Bypass Grafts	351
	18	Cardiopulmonary Bypass with Cold Chemical Cardioplegia	377
	19	Intraaortic Balloon Counterpulsation	390
	20	Coronary Angioplasty	400
	21	Intracoronary Thrombolysis	408
	22	Pharmacologic Agents	416
		INDEX	453

PART ONE

CORONARY ANATOMY

CHAPTER 1

ANATOMY OF THE CORONARY VASCULATURE

GENERAL FUNCTIONS OF THE VASCULATURE
- Conduit Function
- Resistance Function
- Capacitance Function
- Function as Semipermeable Membranes
- Function as Metabolic Units

EPICARDIAL CORONARY VESSELS
- Distribution
- Histology
- Species Differences
- Interdigitation of Perfusion Fields
- Specific Functions of the Epicardial Coronary Vessels

INTRAMURAL CORONARY VESSELS
- Distribution
- Species Differences
- Special Functions

THE PRECAPILLARY SPHINCTERS
- Histology
- Specific Functions

CAPILLARIES
- Distribution
- Histology
- Specific Functions

CORONARY COLLATERAL VESSELS

CORONARY VEINS
- Distribution
- Specific Functions

BLOOD VOLUME OF THE CORONARY VASCULATURE

Each segment in the coronary vasculature has specific anatomic characteristics which enable the vascular segment to perform its functional role. The various individual vascular components act in concert to permit the coronary circulation to respond effectively to a wide variety of physiologic stimuli.

GENERAL FUNCTIONS OF THE VASCULATURE

All segments of the coronary vasculature (epicardial vessels, capillaries, venules, etc.) act as conduits, metabolic units, and semipermeable membranes, but only selected vascular segments contribute significantly to the resistance and capacitance of the vasculature. For example, the epicardial coronary arteries contribute importantly to coronary capacitance, but under most conditions they have only a small effect on total coronary vascular resistance. In contrast, the small transmural coronary arterial vessels (100 μm in diameter) play a dominant role in regulating total coronary vascular resistance. Before describing the anatomic characteristics of various vascular segments in the coronary tree, I will briefly review the specific functions of various segments of the vasculature.

Conduit Function

All vessels in the body act as conduits; that is, they facilitate the transport of blood. Synthetic conduits have fixed configurations and are relatively unresponsive to external stimuli. Vessels are much more versatile. Besides maintaining the blood within a confined space, blood vessels can dilate and constrict, change permeability, and grow or degenerate in response to a myriad of stimuli.

Resistance Function

Under normal conditions in the human left ventricle, a 90 mmHg pressure head will drive 90 to 180 ml of blood per minute through the coronary vasculature. This ratio (driving pressure/coronary blood flow = coronary vascular resistance) can be altered markedly in either direction. Powerful coronary vasoconstrictors such as angiotensin [1], vasopressin [2], and thromboxane A_2 [3] can increase coronary vascular resistance substantially. Potent coronary dilators such as adenosine [4] can decrease coronary vascular resistance to as little as one-sixth of the usual resting value. These alterations in coronary vascular resistance can occur within seconds. Although changes in the caliber of large epicardial coronary vessels contribute to these alterations in total coronary vascular resistance [5], major changes in resistance are mediated primarily by intramural coronary vessels 10 to 140 μm in diameter [6,6a].

Capacitance Function

When the left ventricle contracts, blood in the venules is moved toward the coronary sinus [7] and blood in the intramural coronary arteries is forced retro-

grade into the large epicardial coronary vessels [8,9]. Because blood flow in the proximal epicardial coronary arteries is usually anterograde throughout systole [7], the retrograde flow must be masked by dilation of large epicardial coronary vessels. These vessels store energy and blood, and thus act as a functional capacitance during systole.

Function as Semipermeable Membranes

Vessels may be thought of as having semipermeable membranes at two levels. First, the endothelium is a semipermeable membrane between the blood column and the vessel wall. Substances such as lipids, glucose and oxygen gain access to the wall of the blood vessel by passing from the vascular space through the endothelium into the vessel wall. A major theory of atherogenesis [10], the insudation theory, depends on the assumption that lipids carried in the blood enter the vascular wall. Second, there is a semipermeable membrane at the capillary level that links the vascular and interstitial spaces. Although some exchange between the vascular and interstitial space occurs in larger vessels [11], the bulk of the exchange processes occur in capillaries and perhaps venules. Oxygen, electrolytes, and nutrients leave the vessels and enter the interstitial space of the myocardium, while CO_2 and metabolites leave the interstitium and enter the vascular space from the interstitium. The exchange of substances through the plasma membrane and endothelial clefts of capillaries is accomplished by both passive diffusion and vesicular transport [12,13].

Function as Metabolic Units

All vascular segments act as metabolic units. Coronary vessels can grow and repair damaged components [14], synthesize and degrade numerous molecules, some of which are vasoactive [15], maintain the functional integrity of their cellular components and respond to pathologic challenges. Thus, the vascular wall is a microcosm of metabolic activity.

The following sections of this chapter will describe the anatomic characteristics of specific vascular segments in the coronary hierarchy.

EPICARDIAL CORONARY VESSELS

Distribution

The epicardial coronary arteries originate from ostia in the left and right sinuses of Valsalva (Figure 1-1). In adult humans, the main left coronary artery is 2 to 5.5 mm in diameter (mean ~ 4 to 4.7 mm) and varies in length from 2 to 40 mm (mean = 13 mm) [16–20]. The major branch vessels of the left main are the left anterior descending artery and the circumflex coronary artery. A large intermediate or obtuse marginal vessel occasionally arises from the main left coronary artery; more often, this branch originates from the proximal circumflex. The left anterior descending coronary artery in humans has many septal perforating branches

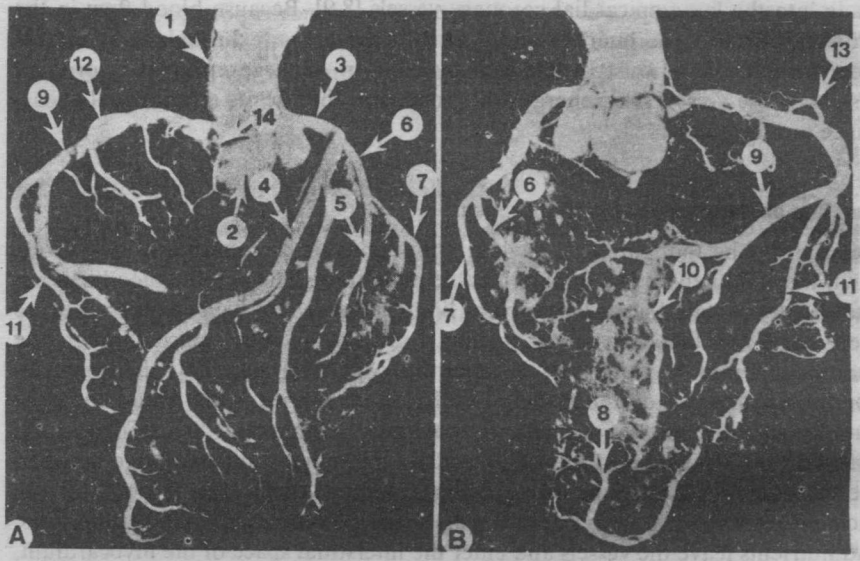

FIGURE 1-1
Extramural coronary arteries. Plastic cast of the coronary arteries (male, 15 years) injected with Geon under low pressure in order to fill only the extramural arterial vessels. *(a)* Anterior surface of the heart. *(b)* Posterior surface of the heart. 1. Aorta. 2. Aortic valve. 3. Left main coronary artery. 4. Left anterior descending branch (LADB). 5. Left diagonal branch. 6. Left circumflex branch. 7. Left marginal branch, ascending portion of the LADB. 9. Right coronary artery. 10. Posterior descending branch. 11. Right marginal branch. 12. Anterior branch of the right coronary artery. 13. Main atrial branch. 14. Third coronary atery. (*From G Baroldi and G Scomazzoni* [*16*].)

(mean = 13: range 16 to 23) [16–20] which perfuse the interventricular septum. In addition, the left anterior descending artery and its diagonal branches usually supply a larger mass of the left ventricular myocardium than the circumflex or the right coronary arteries [16–20].

The right coronary artery in adult humans is 1.5 to 5.5 mm in diameter (mean = 3.2 to 4.1 mm) at its origin [16–20]. In 86 percent of people, the inferior wall of the left ventricle is perfused by a posterior descending branch which arises from the right coronary artery. Numerous variations in the distribution of the large epicardial coronary arteries have been carefully described [16–25a]. Congenital abnormalities in the coronary arteries will be discussed in Chapter 15.

Histology

The wall of the epicardial and large intramural coronary vessels is composed of three coats: tunica intima, tunica media, and tunica adventitia. The *tunica intima*

is several cell layers thick. The innermost layer of this coat is the vascular endothelium. The tunica intima and tunica media are separated by a continuous internal elastic membrane. The *tunica media* makes up the bulk of the arterial wall and is composed of alternating lamellae of smooth muscle cells and elastic tissue which are disposed circularly around the vessel. The outermost portion of the media is perfused by a separate vascular network, the vasa vasorum [7,26]. Recent studies of vasa vasorum in the thoracic aorta [26] indicate that this vascular bed responds to neural and humoral stimulation and is altered by disease processes. It is possible that the vasa vasorum in the large coronary vessels play some role in the pathenogenesis of coronary atherosclerosis. The *tunica adventitia*, an outer layer, is composed of areolar tissue mixed with collagenous tissue, fat, and elastic fibers. The tunica adventitia contains lymphatic channels and nerve fibers in route to the smooth muscle cells in the tunica media.

The architecture of large epicardial coronary arteries differs significantly from that of similar-sized vessels that serve skeletal muscle. In large epicardial coronary arteries, the wall-to-lumen ratio is 1:15; in vessels of similar external diameter that perfuse skeletal muscle, i.e., posterior tibial artery, the wall-to-lumen ratio is 1:6 [26a]. This difference in architecture may help to explain why vasoconstrictor responses of large coronary vessels to several stimuli, such as adrenergic stimulation, are less prominent than those observed in vessels that serve skeletal muscle (see Figure 6-3). In addition, age, sex, and ethnic background affect the architectural characteristics of large epicardial coronary arteries in humans [26b,26c].

Species Differences

Dog In the dog, the circumflex coronary artery supplies the largest mass of cardiac muscle. Average values of the mass of the ventricle perfused by major coronary vessels are circumflex 39 percent, left anterior descending 32 percent, and the right coronary artery 17 percent [27]. In addition, in the dog, the first septal perforator arises very proximally and supplies 12 percent of left ventricular mass [27]. The posterior descending coronary artery in the dog invariably arises from the circumflex [18].

Pig The distribution of the major epicardial coronary arteries is similar to the most common pattern (right dominant system) observed in humans [28]. However, in the pig, the septum is mainly supplied by a single large septal perforating branch.

Rat In the rat, the left anterior descending artery and its main branches supply the largest portion of the left ventricle. Also, within a short distance from the left coronary artery the major conduit vessels become subepicardial.

Monkey The pattern of the coronary vasculature in nonhuman primates is similar to that observed in humans.

Interdigitation of Perfusion Fields

The perfusion fields of large epicardial coronary vessels interdigitate with each other to a great extent. This is dramatically illustrated in Figure 1-2. This macroscopic interdigitation is of great concern in studies of experimental myocardial infarction. Unless special techniques are employed to outline the perfusion field or "risk area" of the coronary artery to be occluded, it is nearly impossible to determine if a given intervention alters infarct size (see Chapter 9). In addition to macroscopic interdigitation, recent studies suggest that capillary loops from adjacent vascular beds interdigitate and may provide dual circulatory support to single myocardial cells [29].

Specific Functions of the Epicardial Coronary Vessels

Like all vessels, epicardial arteries act as conduits, semipermeable membranes, and metabolic units. The large surface coronary vessels also contribute to total resistance and capacitance of the coronary vasculature. These arteries slightly decrease total coronary artery resistance by dilating in response to nitroglycerin [5,30,31,31a] and other stimuli (see Figure 1-3). Epicardial coronary vessels can modestly increase total coronary vascular resistance by constricting in response to alpha-adrenergic stimulation [5,31,32] (see Figure 1-4) and ergonovine [33]. Although small changes in the diameter of large coronary arteries are of limited importance in normal coronary vessels, active constriction or dilation of these vessels in the presence of superimposed atherosclerosis can importantly modify the physiological significance of obstructive lesions (see Chapter 11). The large quantity of elastic fibers in the epicardial coronary vessels permits them to contribute to coronary capacitance. During early systole, the epicardial coronary vessels expand and store blood and energy (Figures 1-3 and 1-4).

INTRAMURAL CORONARY VESSELS

Distribution

Intramural coronary vessels penetrate perpendicularly into the myocardium from the epicardial vessels. In humans the longest intramyocardial vessels (4 to 6 cm) originate from the left anterior descending coronary artery and perfuse the anterior two-thirds of the interventricular septum [16–20]. Usually one of the proximal two or three septal perforators of the left anterior descending artery is particularly large (0.5 to 1.2 mm proximal diameter). The perforating branches of the posterior descending coronary artery which perfuse the posterior one-third of the interventricular septum are also relatively long. All other perforating branches are relatively short (0.8 to 1.4 cm), as they course directly down to the subendocardium.

The intramural coronary arteries form a dense vascular network in the wall of the left ventricle (see Figure 1-5). In humans, these penetrating branches form

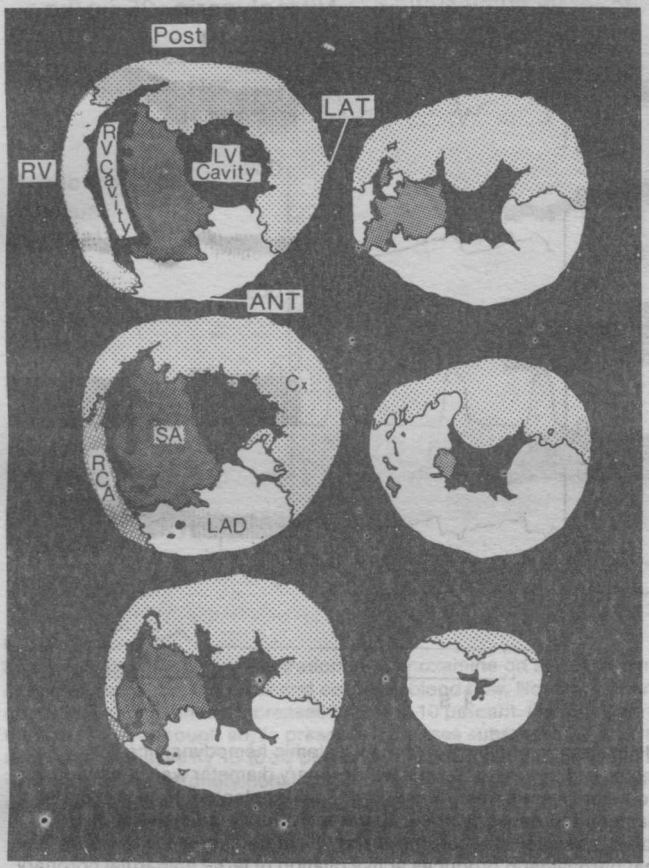

FIGURE 1-2
Perfusion fields of the four major coronary vessels. RCA = right coronary artery; SA = sepal artery; Cx = circumflex coronary artery; LAD = left anterior descending coronary artery. The six contiguous heart slices are from the ventricles of a dog. The top left slice is from the base of the heart. The bottom right slice is from the apex. The vascular fields were outlined by perfusing all four vessels simultaneously at 100 mmHg with four different colored batches of Microphil [27]. The irregularity and interdigitation of the vascular perfusion fields is obvious. The exact pattern varies considerably in different dogs. RV = right ventricle: ANT = anterior; POST = posterior; LAT = lateral; RV cavity = right ventricular cavity; LV = left ventricular cavity. (*Courtesy of C Scheel, Professor of Physiology, Osteopathic School of Medicine, Kirksville, Missouri.*)