Cardiac Pharmacology

Edited by

R. DOUGLAS WILKERSON

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Department of Pharmacology and Therapeutics
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Preface

This volume "Cardiac Pharmacology" is intended to interface basic and clinical knowledge of those interventions used or being studied for use in the treatment of heart disease. The volume is divided into four major sections which address intrinsic and neural control of cardiac function, pharmacologic modification of cardiac contractility and cardiac output, the genesis and control of cardiac arrhythmias, and pharmacologic manipulation of myocardial oxygen supply and demand. A somewhat unique feature of this volume is that each of the last three sections contains a chapter describing the most up-to-date techniques employed in the study of that particular aspect of cardiac function and its alterations by pharmacologic interventions. Further, each section contains a blend of basic and clinical material written in such a way as to be useful to both the scientist in the laboratory and the clinician at the bedside. Although no single volume dealing with a topic as complex as the actions of drugs upon the heart can be all things to all people, this volume will be of value to anyone interested in the area of cardiovascular medicine. Undoubtedly, the greatest asset to this volume is the outstanding group of authors who have contributed. In addition to many established investigators whose names are readily recognizable, this group also includes a number of younger scientists and clinicians who are rapidly making a place for themselves in the areas of cardiac pharmacology, physiology, or cardiology.

I would like to express my gratitude to all of the individuals who have helped in the preparation of this book. Special thanks go to the secretarial staff of the Department of Pharmacology and Therapeutics at the Medical College of Ohio for their patient typing and retyping of many parts of the text and to my wife, Dottie, for invaluable assistance in indexing this volume.

R. Douglas Wilkerson

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I

Intrinsic and Neural Control of Cardiac Function

1

Regulation of Myocardial Contractility

DOUGLAS F. MUNCH and JAMES M. DOWNEY

The regulation of cardiac contractility covers a very broad area of physiologic knowledge. Since volumes have been written about individual regulatory mechanisms, an overview is all that we can hope to accomplish in these few pages. No introductory chapter on the regulation of myocardial contractility would be complete without first defining the meaning of the term "contractility." A theoretical definition will be presented here to facilitate the discussion of the factors involved in the regulation of contractility.

The regulation of myocardial contractility will be presented in three primary areas. First, the action of the sympathetic and parasympathetic autonomic nervous system, their neural transmitters, and the influence of physiologic receptor reflexes (baroreceptors and chemoreceptors) will be reviewed in the section concerning neural regulation of contractility. Second, humoral agents such as epinephrine and cortisol may play an important role in the regulation of cardiac performance. A model that describes the interactions of these agents with heart performance will be developed. Finally, intrinsic autoregulatory mechanisms that

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may play a role in control of the heart's response to increases in afterload (the Anrep effect) and heart rate (the Bowditch effect) will be presented.

I. CONTRACTILITY DEFINED

Since Starling's statement of "the law of the heart" in 1918, great interest and energy has been directed toward evaluating and measuring the performance of cardiac muscle. Classically, Starling's law states that the energy output during contraction of heart muscle increases as the initial muscle length increases (Starling, 1918). Factors that are not related to changes in initial length can also vary the force generation of cardiac muscle. Though many factors have been identified, they all appear to act by changing the functional interaction between the actin and the myosin molecules. This has led investigators to seek a common index that will evaluate the functional state of these molecules at any given moment, the so-called "contractility." The difficulty arises in finding an index that separates the contribution due to initial length changes from those related to the "contractile state."

Contractility indices may be sensitive to either the absolute contractile state of a given heart or merely to changes in contractility, the latter task being considerably simpler than the former. All of our present methods for assessing contractility involve measuring one or more of the mechanical properties of the heart muscle. According to Sonnenblick (1965), there are four critical parameters which must be taken into account. These include the force of contraction, the velocity of contraction, the length of the muscle, and the time course of these variables during the activation period. When pooled together, the individual relationships between velocity, length (or volume), and load (or pressure) generate a surface as shown in Fig. 1. Activation of the contractile elements begins at point A, which represents the end of diastole.

Isovolumetric pressure generation continues through the peak of the active state, B, to the beginning of ejection at C, where the aortic valve opens. The ventricular ejection phase of the cardiac cycle continues to point D where the aortic valve closes, and ventricular volume is at a minimum. Finally, isovolumetric relaxation occurs from point D to E. Any change in the ionic or chemical environment will alter the interaction between myosin and actin, and therefore the contractility changes. Such a change in contractility would alter the relationships between the velocity–length, velocity–load, and length–load relationships, and a new surface would result (Sonnenblick, 1965).

Although the three-dimensional representation of the contractility surface appears to be an elegant method for measuring contractility, it is not presently possible to obtain all of the necessary data to construct such a surface in either the clinical setting or in the animal laboratory. Fortunately, however, certain

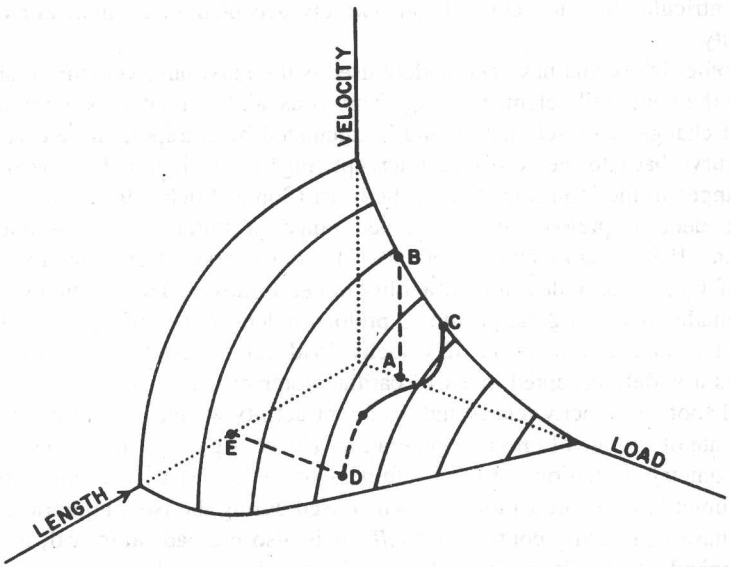

Fig. 1. The relationship among the parameters of velocity–muscle length–load forms a three-dimensional surface upon which the sequence of the cardiac cycle may be traced. Systole begins at point A. The velocity of the isovolumetric contraction increases to point B where velocity of the contraction declines while force continues to build. Ejection starts at point C, continues along the surface and ends at D. The path from D to E represents isovolumetric relaxation. (Modified from Sonnenblick, 1965, *Fed. Proc., Fed. Am. Soc. Exp. Biol.* **24,** 1396–1409.)

portions of these curves contain information concerning the contractile state and do lend themselves to laboratory measurement.

One of the earliest attempts at a practical index of contractility was to describe the relationship between stroke volume or cardiac output and ventricular volume (Patterson *et al.*, 1914). This technique takes advantage of the fact that stroke volume is a function of the contractile state. Since the influence of initial length is defined by the curve, any shift in the curve should denote a change in contractility. Unfortunately, stroke volume and cardiac output are not solely a function of the contractile state and ventricular filling, as they are affected by heart rate and ventricular afterload. Because stroke volume and afterload are inversely related, Sarnoff (1955) suggested that a better index of contractility could be derived by using stroke work (stroke volume × afterload). The product of stroke volume and afterload is relatively constant for any intropic state and was less influenced by heart rate yet is responsive to changes in contractility induced by inotropic agents (Sarnoff *et al.*, 1964), and coronary ischemia (Sarnoff, 1955). However, the ventricular function curve described by Sarnoff is also sensitive to changes in afterload (Sagawa, 1967). Recognizing this afterload dependence,