Nervous Control of Cardiovascular Function

Edited by

Walter C. Randall, Ph.D.

Nervous Control of Cardiovascular Function

Edited by

Walter C. Randall, Ph.D.
PROFESSOR OF PHYSIOLOGY
LOYOLA UNIVERSITY STRITCH SCHOOL OF MEDICINE

New York Oxford
OXFORD UNIVERSITY PRESS
1984

Library of Congress Cataloging in Publication Data
Main entry under title:

Nervous control of cardiovascular function.

Bibliography: p.
Includes index.
1. Heart—Innervation. 2. Nervous system, Vasomotor. 3. Heart—Diseases. I. Randall, Walter C.
[DNLM: 1. Autonomic nervous system—Physiology. 2. Cardiovascular system—Innervation. 3. Heart—Physiology. 4. Heart conduction system. WG 202 N456]
QP113.4.N47 1984 612'.17 83-23619
ISBN 0-19-503390-6

Printed in the United States of America

Printing (last digit): 9 8 7 6 5 4 3 2 1

Preface

Just 20 years ago I was deeply involved in organizing a symposium on The Nervous Control of the Heart to be presented at the annual meeting of the American Physiological Society. A volume carrying the same title [3] and describing the papers presented at the meeting was dedicated to Dr. Carl J. Wiggers who was deeply interested in the topic but could not attend because of serious illness. He died less than two weeks later on April 29, 1963. This volume represents the continuing influence and inspiration of this giant among cardiovascular teachers and investigators.

The impetus for the 1963 symposium was the awakening of interest in central nervous control of the circulation, as discussed in Washington, D.C. in 1959, when the National Academy of Sciences brought together a small group of investigators in either cardiovascular *or* neurophysiological research. At the time, very few considered the circulation from *both* perspectives. Approximately one-hundred interested researchers and specialists were invited to attend the sessions, and discussions were open to the entire group. Relatively few new data were actually revealed at the meeting, but there was recognition of how amazingly little was known about the relationship between the brain and the heart. This recognition encouraged laboratories all over the world to actively pursue research in the field, funding became available, and recent history has seen an almost explosive development of new information and understanding about cardiovascular and neurophysiological control mechanisms. The interrelations between the two systems progressively became dramatically emphasized.

It is important to realize from our present perspective in 1983 that no more than 20% of the knowledge and technical know-how now available to the patient with serious cardiovascular disease was known at the time of the Washington meeting only 20 years ago. Intensive research in virtually every area of cardiovascular physiology has expanded knowledge of the many ways in which the nervous system regulates the heart and circulation.

Levy (2) recently illustrated this deficit in understanding of the circulation in describing the development of insight into clinical abilities to recognize and treat hypertension (in 1948) at the time of the organization of the National Institutes of Health. Very little research was being done, and the main therapeutic alternative was the rice diet. It was not clear whether hypertension was a disease, a symptom of a disease, or a possibly beneficial circulatory adaptation to aging. In fact, a popular theory at the time held that hypertension was essential to maintain critical perfusion pressure in areas like the brain, and there was concern that harm might be done if the blood pressure were lowered. The intervening generation of research has revealed much about the complexities of this disease. The involvement of the central and autonomic nervous systems in control of blood pressure, the role of kallikreins and kinins, prostaglandins, renin and angiotensin, the vessel wall and its intrinsic reactivity, the role of the heart and kidneys, and the importance of nutrition and salt and water balance have all been elaborated. There is penetrating (but still incomplete) insight into the importance of psychological and sociological factors. By selective pharmacological treatment, deaths due to clinically associated cerebrovascular disease, strokes, heart, and renal failure, have been reduced by 30 to 40%. Still, despite all that has been learned about the complexities of hypertension, its cause remains unknown in more than 95% of patients suffering from the disease.

Before 1950, cardiovascular research was confined almost exclusively to experimental animals. Following the genesis of new excitement and insights of both basic and clinical scientists, findings from the experimental laboratory were promptly tested and introduced into the practice of human medicine. Indeed, many of the new observations were made by physicians upon patients admitted to superbly instrumented hospital critical care units. The modern, well-equipped coronary care unit was born during this period and under this research emphasis. Cardiac catheterization was first conceptualized, tested, and applied. New information from "invasive" studies was translated into advanced diagnosis and treatment so soon after the original research that it was sometimes difficult to separate research from clinical application. The NIH sponsored the development and testing of such direct applications of research information to the patient through use of hospital-based concentrations of highly specialized personnel and instrumentation in dramatically new installations such as the myocardial infarction research unit (MIRU). Spectacular improvements in the management of cardiovascular disease resulted in an incredibly short period of time, and deaths from these diseases declined remarkably. Cardiovascular mortality rates in the United States fell 25% in the decade ending in 1979, and the decline continues. However, 30 million Americans still suffer from heart and vessel diseases. The cost of cardiac care was estimated at 28.5 billion dollars in 1978. This is a huge, continuing burden of disability and suffering, as well as a staggering strain upon the American economy. More than 650,000 died of coronary heart disease in 1979. Explanations for the decline in cardiovascular disease mortality include better fundamental knowledge of underlying cardiovascular mechanisms; advances in diagnosis and treatment; improvement in preventive measures; and changes in life-style such as improving one's diet,

quitting smoking, and exercising regularly (1). Perhaps even more important, the quality of life that patients can expect has improved, and the productivity of literally thousands of previously doomed individuals has been greatly extended. I do not hesitate to assert that virtually *all* of these dramatically optimistic statistics stem from cardiovascular research. Therefore, it is hard to understand the current curtailment of health-related research emphasis and funding by the responsible government authorities. Given the firm information that cardiovascular diseases kill more people, many in their most productive years, than all other causes of death combined, it is difficult to rationalize decisions to cut back on the very research that has had such spectacular success during the past 20 years. Such research would appear to offer the best bargain available for tax dollar expended.

Perhaps the reader will indulge me in a brief personal expression of appreciation for this research. At the present writing I am recuperating from a recent quadruple aorto-coronary arterial bypass operation. As I sustained the unique experiences of the cardiac catheterization laboratory, a few recollections may be of interest. During the procedure, it occurred to me that I had known Drs. Andre Cournand and Dickinson Richards who initially conceived of and implemented cardiac catheterization in 1941, and that Dr. Mason Sones, who actually applied the technology to the diagnosis of human cardiac disease in the late 1950s, was a colleague and close friend on an NIH Program-project Committee for many years. The cardiologist in charge of my catheterization was among his early trainees at the Cleveland Clinic. Also, as he "cut down" to insert the Schwann-Ganz catheter, I recalled that I had participated in the NIH Site Visit to evaluate and ultimately to fund the original experiments designed to develop and test this instrument. Similarly, when I awakened from the anesthesia of the bypass surgery, I became aware of a pair of tiny lead wires protruding through my chest wall, and realized that the original use of direct pick-up electrodes (also available for direct cardiac pacing) was the product of a close friend's research, and they were first employed clinically only five or six years ago. They were vividly reminiscent of similar leads emerging from the chronic dog models employed in my own current experimental protocols. Thus, procedures now routinely employed in the modern cardiology-thoracic surgery suite, would have been considered "pie-in-the-sky" only a few years ago.

Following the catheterization, I told Dr. Gunnar, my cardiologist, that I thought I had noted evidence on the oscilloscopic monitor of relatively rich collateralization of the ventricles. He informed me that I certainly had, and that I was undoubtedly "dependent upon such collaterals since my conduit arteries were substantially occluded." My commitment to regular exercise (vigorous walking for 2–4 miles per day) for the past twelve years, following an earlier episode of myocardial ischemia, flashed through my mind. It also piqued my interest because we have not successfully demonstrated such collateral development in experimental animals whose anterior descendens are experimentally tied off while they undergo a regimen of treadmill exercise. Thus, it is abundantly clear to me that while dramatic progress has been made through research in my time, much remains to be learned. To quote from one of Dr. Cournand's

classic articles, *"Knowledge is proud that it has learned so much, Wisdom is humble that it knows no more."*

In 1977, a second volume, entitled *Neural Regulation of the Heart* (4), updated the first with information derived from cardiovascular research between 1963 and 1977, the fourteen chapters detailing new approaches and new conclusions. Many chapters in this book still stand as current understanding in their field, and there has been no attempt or intention to detract from their authoritative positions. Thus, it is not our intention to prepare a second edition of that volume. We wish, rather, to approach the research of the past several years differently, and to examine many different areas in which newly discovered facts have bearing on the neural regulation of the cardiovascular system. Examination of the table of contents reveals that the majority of chapters concern topics that were not explored previously, which now appear to represent areas in which real breakthroughs in knowledge have been, or are about to be achieved. We feel also that new insights will offer great challenges to current researchers, and hold even greater potential for direct contributions to understanding cardiovascular disease. All of the authors stand as authorities in their fields, and each has personally participated in experiments at the cutting edge of rapidly expanding cardiovascular research. The resulting chapters in this book represent up-to-the minute statements of new facts and their implications for existing concepts of neurophysiological regulation of the heart and vascular system. Each author also elaborates how, in his judgment, the new data will enhance our understanding and treatment of disease.

I wish to acknowledge the contribution of Dr. David C. Randall who read the page proofs and developed the index. Finally, I wish to thank Mrs. Bette Kalina for her secretarial assistance.

Maywood, Illinois W.C.R.

REFERENCES

1. Kannel, W. B., Meaning of the downward trend in cardiovascular mortality. *JAMA 247:* 877–80, 1982.
2. Levy, R. I., The National Heart, Lung, and Blood Institute Overview, 1980. The Director's Report to the NHLBI Advisory Council, *Circulation 65:* 217–25, 1982.
3. Randall, W. C., ed., *Nervous Control of the Heart,* Williams and Wilkins, Baltimore, Maryland, 1965.
4. Randall, W. C., ed., *Neural Regulation of the Heart,* Oxford University Press, New York, 1977.

Contents

CONTRIBUTORS

J. ANDREW ARMOUR, M.D., Ph.D., Associate Professor, Physiology and Biophysics, Dalhousie University Faculty of Medicine, Halifax, Nova Scotia, Canada

SUSAN M. BARMAN, Ph.D., Assistant Professor, Pharmacology and Toxicology, Michigan State University, East Lansing, Michigan

ROBERT D. FOREMAN, Ph.D., Associate Professor, Physiology and Biophysics, University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma

GERARD L. GEBBER, Ph.D., Professor of Pharmacology and Toxicology, Michigan State University, East Lansing, Michigan

ROLF M. GUNNAR, M.D., Professor and Chairman of Internal Medicine and Professor of Cardiology, Loyola University Stritch Schooi of Medicine, Maywood, Illinois

DAVID A. HOPKINS, Ph.D., Professor of Anatomy, Faculty of Medicine, Dalhousie University, Halifax, Nova Scotia, Canada

THOMAS N. JAMES, M.D., Mary Gertrude Waters Professor of Cardiology and Distinguished Professor of Medicine, University of Alabama School of Medicine, Birmingham, Alabama

CARL E. JONES, Ph.D., Professor and Chairman of Physiology, Texas College of Osteopathic Medicine, Fort Worth, Texas

STEPHEN B. JONES, Ph.D., Associate Professor of Physiology, Loyola University Stritch School of Medicine, Maywood, Illinois

MICHAEL P. KAYE, M.S., M.D., Professor and Director, Cardiovascular Research in Surgery, Mayo Clinic Foundation and Mayo Graduate School of Medicine, Rochester, Minnesota

ROBERT J. LEFKOWITZ, M.D., Professor of Medicine, Duke University Medical Center, Durham, North Carolina

MATTHEW N. LEVY, M.D., Chief, Investigative Medicine, Mt. Sinai Hospital, and Professor of Physiology, Case-Western Reserve University School of Medicine, Cleveland, Ohio

STEPHEN L. LIPSIUS, Ph.D., Associate Professor of Physiology, Loyola University Stritch School of Medicine, Maywood, Illinois

PAUL MARTIN, Ph.D., Head, Bioengineering Section, Department of Investigative Medicine, Mt. Sinai Hospital, and Professor of Physiology, Case-Western Reserve University School of Medicine, Cleveland, Ohio

DAVID C. RANDALL, Ph.D., Associate Professor of Physiology, University of Kentucky School of Medicine, Lexington, Kentucky

WALTER C. RANDALL, Ph.D., Professor of Physiology, Loyola University Stritch School of Medicine, Maywood, Illinois

GEORGE J. ROZANSKI, Ph D., Research Scientist, Masonic Medical Research Laboratory, Utica, New York

PETER J. SCHWARTZ, M.D., Associate Professor of Medicine, Centro per lo Studio della ritmie e Fisiologia Clinica, Istituto di Clinica Medica IV, Universita di Milano, CNR, Ospedale Maggiore, Milan, Italy

ORVILLE A. SMITH, Ph.D., Professor of Physiology and Director, Primate Center, University of Washington School of Medicine, Seattle, Washington

JOHN X. THOMAS, JR., Ph.D., Assistant Professor of Physiology, Loyola University Stritch School of Medicine, Maywood, Illinois

STEPHEN F. VATNER, M.D., Associate Professor of Medicine, Harvard University Medical School and Peter Bent Brigham Hospital, Boston, Massachusetts

AUGUST M. WATANABE, M.D., Professor of Medicine and Pharmacology, Indiana University School of Medicine, Indianapolis, Indiana

WILLIAM H. WEHRMACHER, M.D., Adjunct Professor of Physiology and Clinical Professor of Medicine, Loyola University Stritch School of Medicine, Maywood, Illinois

JARL E.S. WIKBERG, M.D., Assistant Professor of Medicine, Duke University Medical Center, Durham, North Carolina

ROBERT D. WURSTER, Ph.D., Professor of Physiology, Loyola University Stritch School of Medicine, Maywood, Illinois

1

Regulation of the Heart in Health and Disease

WILLIAM H. WEHRMACHER and WALTER C. RANDALL

Recognition of the complex, interrelated physiological mechanisms responsible for preservation of the "milieu interne," and their dependence on the heart and vascular system requires a constantly renewing perspective for both practicing physician and basic scientist in keeping pace with the ever increasing body of fundamental knowledge. In considering cardiovascular adjustments to changing external and internal stresses, lines of distinction between a wide variety of causes and effects tend to become blurred. Emphases shift from one to the other, particularly in clinical practice where the clinical syndrome becomes the specific target for diagnostic and/or therapeutic attention. The cardiovascular system ordinarily maintains appropriate performance for the circumstances, but the response may have limits beyond which its integrity breaks down or decompensates. Although the heart appears to function independently when isolated from the body, it is actually balanced among powerful neural, humoral, and hydrostatic forces. Disturbance of critical balance impairs functional integrity [20], but appropriate interactions provide for finely tuned cardiac response throughout a lifetime of complex challenges. Those mechanisms that preserve overall integrity, as well as those that may fail and lead to life-threatening decompensations must be fully appreciated. It is a primary objective of this book to assist both the practicing physician and the cardiovascular investigator in comprehending these interrelated mechanisms and to update his understanding of recent research in neural regulation of the cardiovascular system.

The healthy heart pumps 3.5 liters of blood per square meter of body surface at rest, with heart rates varying between 60 and 100 beats per minute. Untrained subjects can increase this volume of ejection to 12 liters, and athletes to about 20 liters during exercise, with heart rates between 160 and 190 beats per minute. Such broad changes in capacity with the common challenge of

The data reported were derived from experiments supported by Grant HL 08682, The James R. DePauw Fund, Chicago Illinois, and the Bane Charitable Trust Fund, Chicago Illinois.

exercise demonstrate the remarkable adaptability of the unique cardiac pump. Adaptations to internal derangements produced by congenital abnormalities, shunts, plugs within branches of the system, injury, inflammation, and neoplastic disease are not only astonishing but absolutely essential for preservation of life. Life expectancy was 49 years in 1900 and now approaches 73 years. It should be expected to extend still further if the spectacularly successful research of this century continues. Special recognition of Federal support of health-related research through such agencies as the National Institutes of Health, National Science Foundation, and the Veterans Administration Hospital System during the period from 1950 to the present should be continued and augmented by properly stimulated private philanthropy.

Adaptation to external forces has extended to nonterrestrial environments within the past twenty years. Consider the incredibly effective adaptations which have been elaborated in the conquest of extremes of heat, cold, wet, dry, wakefulness, fatigue, anxiety, excitement, aggression, fear, frustration, sorrow, aversion, love, and delight—a remarkable range of stresses requiring unique physiologic adjustments for maintenance of the overall system. Most current operational knowledge of the cardiovascular system was totally unknown a score of years ago, and much of this will be summarized and updated by the contributors to this volume.

Looking back over the 19th century for mileposts of progress in understanding cardiovascular adaptive mechanisms, I. P. Pavlov [12] in his M.D. thesis (1883) drew attention to the four functions of the "centrifugal nerves of the heart": (1) those which inhibit (slow) the heart, (2) those which weaken its contraction, both via the vagus, (3) those which accelerate contractions, and (4) those which augment them. In 1929, Cannon [2] published a book on his concept of "fight or flight," emphasizing sympathetic reactions to stress characterized by tachycardia and hypertension. In 1957, Richter [16] extended Cannon's view of the sympathetic mechanism to stress to include a fatal parasympathetic reaction: "A phenomenon of sudden death in man, rats, and other animals, apparently resulting from hopelessness, seems to involve overactivity of the parasympathetic system." His experimental model (dewhiskered swimming wild rats) showed that the animal, hopeless because of loss of sensory clues to guide behavior, simply sank to the bottom of the vessel and died (before drowning) with bradycardia. The heart stopped in diastole—a vagal death—unless atropine was given previously, which substantially increased survival. Sudden death of captured wild animals may represent a similar phenomenon. In 1972, attention was focused on highly localized alterations in cardiac function that can be induced by excitation of small branches of the vagosympathetic nerves [13]. This recognition made the remarkably localized adaptations of the heart clear for the first time, and accounted for essential moment-to-moment adjustments in cardiac functions which could not previously be explained from classical concepts of generalized autonomic regulation.

More recently, parasympathetic reactions to stress have received attention as part of the aversion reaction with vagal components of bradycardia or even of cardiac arrest, hypotension, faintness, and vomiting. It is unlikely that these

autonomic reactions occur entirely independently or in pure form, but rather appear in combinations depending on the stressor and the responsiveness of the subject to stress. Either predominant dysautonomia may prove fatal in the extreme case: sympathetic excess terminating in ventricular fibrillation and parasympathetic excess terminating in asystole.

In health, reaction to stress results in an appropriate balance among a variety of cardiocirculatory adjustments, often with overall feelings of invigoration and enthusiasm. People exercise with pleasure, seek excitement, and promote love and affection as they enter into interpersonal activities and competition. Some avoid competition because they experience symptoms of decompensation when they attempt to compete. Are they as healthy? Should one conclude that competition and athletics make one healthy or that one is able to compete because of good health? Can one expect to cure the ill person who avoids competition by forcing him to change his way of life?

The competitive choice may be one way to look at the Type A personality described by Friedman and Rosenman [15], a personality type or behavior pattern sometimes considered to be coronary disease-prone. This is the personality characterized by an intense, chronic struggle to achieve more and more in less and less time, and may be associated with exaggerated hostile reactions to others. Type-B behavior personalities lack these behavioral components. Radically different responses can be expected when stress acts upon these different types of people. Thus it is not only the stressor but also the receptivity of the stressed that must be considered in determining the response. Even those who are healthy may decompensate if stressed beyond their ability to adjust; the unhealthy decompensate with still less stress. The physician must recognize the reserves available, and be prepared to exploit these reserves but not overwhelm the system.

EXERCISE

Energy requirements for physical work are maintained by large volumes of blood flow delivered by the cardiovascular system, adequacy of pulmonary ventilation, and diffusion capacity of the lungs. Physical work increases metabolic rate, initially elevating metabolites, decreasing oxygen tension in the immediate vicinity of the working muscle, and causing local vasodilatation through autoregulation. Local receptors and central activation of autonomic activity improve the adjustments.

At the onset of physical exercise, catabolism of high-energy phosphates (ATP and creatine phosphate) utilizes oxygen stored in the blood and myoglobin, aerobically, to produce the necessary energy. Thereafter, anaerobic glycogenolysis and glycolysis produce energy with the formation of lactic acid. As oxygen is supplied, lactates are metabolized and energy stores are repleted. Cardiac output is increased by increased stroke volume and heart rate; systolic blood pressure is increased to supply the microcirculation with increased perfusion pressure throughout both systemic and pulmonary systems. Regional blood flow increases by recruitment of capillary beds not perfused at rest. Diffusion dis-

tances are shortened. Increased hydrostatic pressures and diminished reabsorption contribute to elevated extracellular fluid volume, plasma protein concentration, and colloidal osmotic pressure—a hemoconcentration. This, in turn, results in reabsorption from tissues other than the active muscles, adjustments within the venous system, and contraction of capacitance vessels consequent to sympathetic stimulation. All these combine to improve venous return to the heart and facilitate its performance.

Perhaps the circulatory system is the weakest link in any prolonged demand for aerobic transformation of energy required by vigorous muscular activity. Therefore, it is likely to show the first signs of decompensation if exercise becomes excessive. This furnishes a basis for use of exercise stress testing in noninvasive cardiovascular studies. Unless significant lung disease is present, neither the ventilatory nor diffusion capacity of the lung are likely to be limiting factors except at high altitude or in circumstances which limit oxygen intake. Actually, maximal ventilatory volumes and the transfer coefficients for oxygen transport across alveolar membranes are remarkably similar in sedentary subjects and in olympic athletes. Not so for the circulatory system; the well-trained subject adjusts his cardiac output much more quickly than does the untrained.

HYPERBARIC CONDITIONS (SUBMERSION UNDER WATER)

Barometric pressure increases as one dives beneath the water at sea level, increasing one atmosphere for each 10 meter descent. The most significant effect of the increased pressure is not on oxygen saturation of the blood or on cardiovascular function, but rather on gases trapped within the body, especially in the lung, middle ear, paranasal sinuses, and bowel. Circulatory adjustments come not with increasing compression but rather with release of the compressing force (dysbarsim) as the subject returns to normal atmospheric conditions. Equilibration of gases, and particularly nitrogen, which is only slowly removed as the pressure is reduced, may not occur smoothly and produce small bubbles, particularly in joints, to become painful (bends) or in the pulmonary circulation to disturb function (chokes). If bubbles form in the brain, severe nervous system dysfunction may evolve. Rapid ascent from hyperbaric conditions to increased altitude is particularly hazardous.

HYPOBARIC CONDITIONS (HIGH ALTITUDES)

Barometric pressure decreases approximately exponentially with distance from the earth's surface; at 18,000 ft, it is about half ordinary sea-level pressure of 760 mm Hg. Thus the oxygen pressure of moist imspired air is only 80 mm Hg at 18,000 ft in comparison to 160 mm Hg at sea level (each minus water vapor 47 mm Hg for moist air reaching the lungs). Although newcomers complain of headache, dizziness, dyspnea, palpitation, nausea, and insomnia on arrival at high altitude, this acute mountain sickness is usually dissipated promptly. Some long-term residents fail to maintain tolerance and develop chronic mountain sickness (Monge's disease), complaining of fatigue and reduced exercise toler-

ance associated with hypoxemia and polycythemia. The acute syndrome probably results from hypocapnia of hyperventilation associated with the hypoxemia incident with lowered atmospheric pressure. Acclimatization results from hyperventilation, polycythemia, and shift to the right in the oxygen dissociation curve. The adjustment is hampered by tendencies to pulmonary vasoconstriction, and may be complicated by high-altitude pulmonary edema, which may become life threatening. Residents at very high altitudes, as in the Peruvian Andes, make remarkable adjustments over a period of time, permitting excellent work capacity and development of astonishing athletic prowess.

STRESS OF AMBIENT TEMPERATURE

Body tempreature is ordinarily well maintained between 98 and 100° F (36.7–37.8° C) in spite of wide shifts in environmental temperature. The nude body in dry, quiet air will tolerate variations between 60 and 130° F (16–54° C) ambient temperature. Normal individuals respond to sensations of cold and heat by altering temperature of the surroundings and air flow or clothing to maintain temperature homeostasis. When compensatory mechanisms are exhausted, severe impairment may result. Heat exchanges are maintained by physical processes of radiation, conduction, convection, and vaporization (sweating). The natural insulators of the body, supplemented by clothing, contribute to heat conservation. Both the integrity and critical responsiveness of the heart and circulatory system are essential for adaptation to excessive heat. Loss of plasma volume through profuse sweating requires extensive adjustments, including altered cardiac output, splanchnic constriction, and response to decreased venous return. Decompensation is heralded by falling cardiac output, decreasing central blood volume, and cessation of sweating. Facial color changes from pink to ashen grey as core temperature rises. With acclimatization, three critical adjustments prevent decompensation: increased maximal cardiac output, decreased peak heart rate, and increased stroke volume. Oxygen delivery to muscle is increased through training; myoglobin content may increase; the density of mitochondria per unit muscle mass also increases. Thus, energy utilization is improved and heat production per unit amount of work is less in trained, acclimatized man.

Facilitating the sweating mechanism requires simultaneous cardiovascular increments in blood flow to the skin and to the exercising muscle. More blood, greatly warmed by metabolic processes, is brought to the body surface to facilitate heat loss. High ambient temperatures alone make strenuous demands upon the circulation. In dry, moderately hot environments, increased cutaneous flow is accomplished by reduction in peripheral vascular resistance. This may be accompanied by falling blood pressure with relatively little augmentation in cardiac output. Greater environmental stress, particularly when the increased temperature is accompanied by high humidity, requires greater increments in cardiac output; central venous pressure rises and the heart may be seriously challenged to maintain compensation. This is an especially challenging stress for patients with damaged cardiac compensatory reserves. The subject may