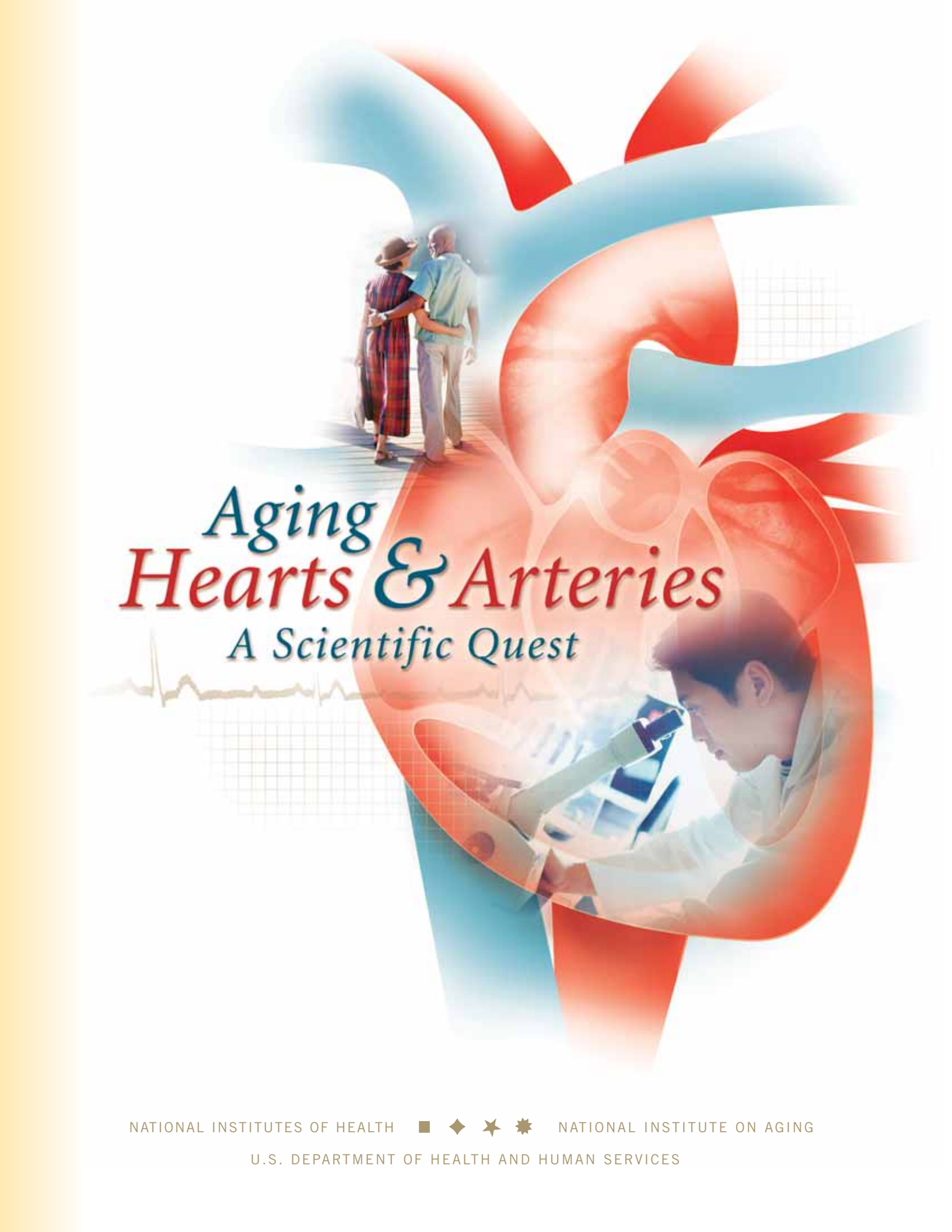


Aging Hearts & Arteries

A Scientific Quest

NATIONAL INSTITUTES OF HEALTH ■ ✦ ✶ ✸ NATIONAL INSTITUTE ON AGING

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

THE MISSION OF THE NATIONAL INSTITUTE ON AGING

"...the conduct and support of biomedical, social and behavioral research, training, health information dissemination, and other programs with respect to the aging process and the diseases and other special problems and needs of the aged."

RESEARCH ON AGING ACT OF 1974, AS AMENDED IN 1990 BY P.L. 101-557

TABLE OF CONTENTS

✦ INFORMATIONAL GRAPHIC ★ INFORMATIONAL SIDEBAR

INTRODUCTION

Age is the major risk factor for cardiovascular disease. Heart disease and stroke incidence rises steeply after age 65, accounting for more than 40 percent of all deaths among people age 65 to 74 and almost 60 percent at age 85 and above. People age 65 and older are much more likely than younger people to suffer a heart attack, to have a stroke, or to develop coronary heart disease and high blood pressure leading to heart failure. Cardiovascular disease is also a major cause of disability, limiting the activity and eroding the quality of life of millions of older people each year. The cost of these diseases to the Nation is in the billions of dollars.

To understand why aging is so closely linked to cardiovascular disease, and ultimately to understand the causes and develop cures for this group of diseases, it is essential to understand what is happening in the heart and arteries during normal aging—aging in the absence of disease. This understanding has moved forward dramatically in the past 30 years. The purpose of this booklet is to tell the story of this progress, describe some of the most important findings, and give a sense of what may lie ahead.

While we know a great deal about cardiovascular disease and its risk factors, new areas of research are beginning to shed further light on the link between aging and the development and course of the disease. For instance, scientists at the National Institute on Aging (NIA) are paying special attention to certain age-related changes that occur in the arteries and their influence on cardiac function. Many of these changes, once considered a normal part of aging, may put people at increased risk for cardiovascular disease.

This and other compelling research on the aging heart and blood vessels takes place at many different research centers. A great deal of the work is being done by researchers in the Laboratory of Cardiovascular Science at the NIA or by NIA-funded scientists at other institutions. Others have worked at or been funded by the National Heart, Lung, and Blood Institute (NHLBI). NIA and NHLBI are two of 27 research institutes and centers at the National Institutes of Health, and their work is complementary. NIA research focuses on the effects of aging on the heart, blood vessels, and other parts of the body, while NHLBI works to understand the diseases and risk factors that affect the heart and blood vessels.

Both perspectives are bringing us closer to the possibility that heart disease and stroke will someday be defeated. Research on the basic biology of the aging cardiovascular system nurtures hope that we as a Nation need not accept the high rates of death and disability and the enormous health care costs imposed by cardiovascular disease among older people in our society.

RICHARD J. HODES, MD, DIRECTOR, NATIONAL INSTITUTE ON AGING

A *Host* OF INTERCONNECTIONS

The heart is purest theater…throbbing in its cage palpably as any nightingale.

RICHARD SELZER, MD, AMERICAN SURGEON AND AUTHOR

It is scarcely as big as the palm of your hand yet it sustains life, pumping up to 5 quarts or more of blood per minute to the body's organs, tissues, and cells. In a typical day, it beats 100,000 times. And in a lifetime, it beats more than 2.5 billion times. Even as you rest, your heart is working twice as hard as your leg muscles would if you were running at full speed.

Little wonder then that from earliest mythology to modern medicine, the heart has fascinated and perplexed us. Fortunately, today we know far more about the heart and the blood vessels than was known even a decade ago. Yet for all scientists have learned, there is still much more to unravel. Investigators, for instance, now know that the cardiovascular system undergoes significant changes as we age, and the heart and arteries that we are born with are surprisingly different in later life.

But how and why do these changes occur? What influence do these changes have on our risk of developing heart disease and other cardiovascular disorders as we get older? Are there any underlying signs—even in people who appear to have healthy hearts—that precede and predict who will develop severe cardiovascular disease and who won't?

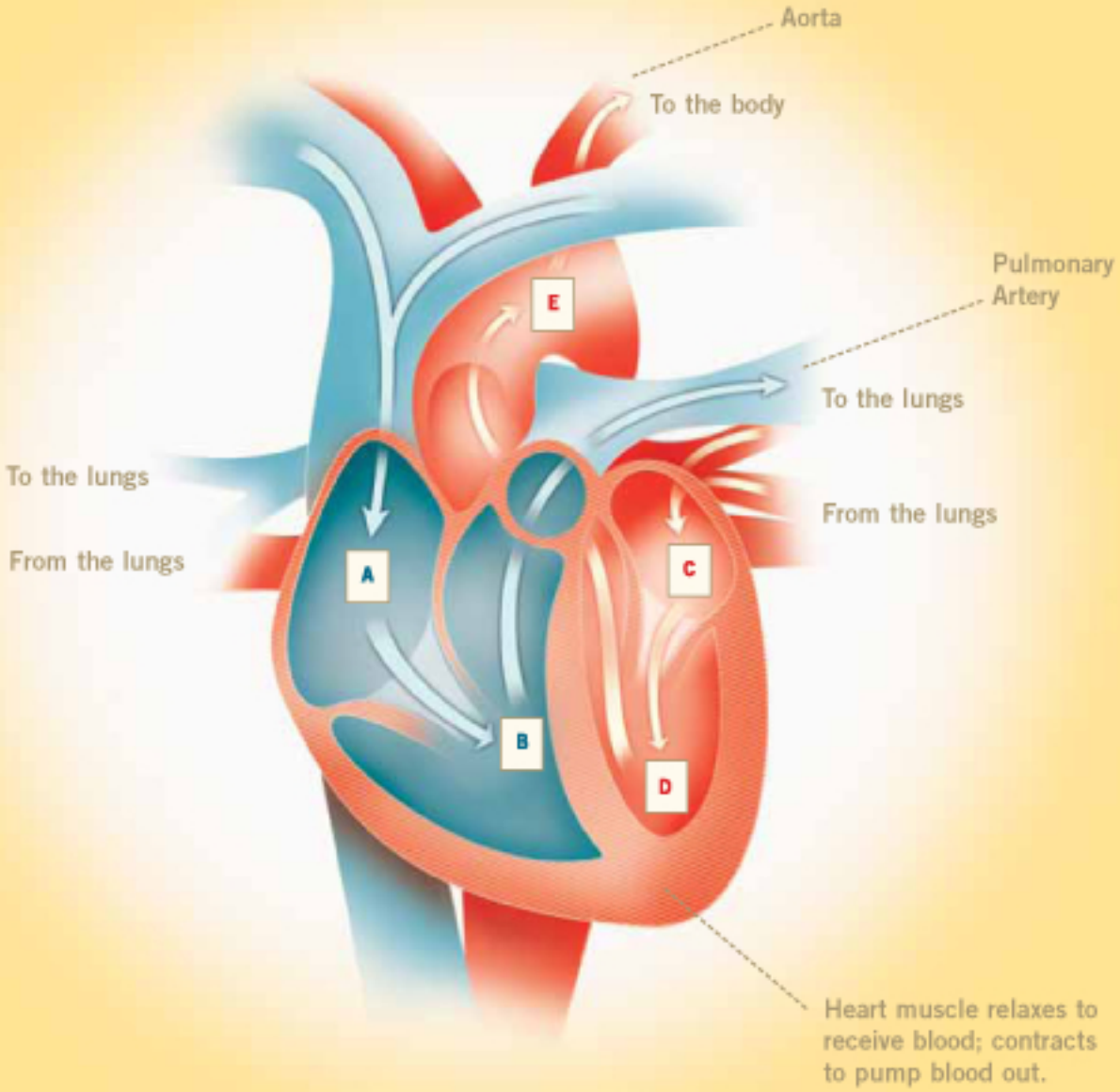
Scientists called gerontologists, who study aging, are seeking to answer these and other questions. As a result of this probing, some old ideas about the aging cardiovascular system are giving way to new theories. In other cases, gerontologists are just beginning to explore some questions, and the heart and arteries are yielding their secrets grudgingly.

But to truly understand what is emerging and what remains mysterious, we'll need to start where these gerontologists began: in the normal, healthy heart.

The Intricate Pump

The heart is a marvel of coordination and timing. Almost completely composed of muscle called myocardium, it is well-equipped for its life-long marathon of ceaseless beating. It is essentially two pumps in one. The right side pumps blood to the lungs to load up on oxygen and dispose of carbon dioxide. The left side pumps oxygen-rich blood to the body.

To accomplish these tasks, the heart depends on a precise sequence of contractions involving its two upper chambers—the right and left atria—and its two lower ones, the right and left ventricles. Between these chambers are two valves, each with



Anatomy of the Heart

A

RIGHT ATRIUM
receives blood from veins depleted of oxygen.

B

RIGHT VENTRICLE
pumps blood to lungs to pick up oxygen.

C

LEFT ATRIUM
receives blood from lungs with fresh oxygen.

D

LEFT VENTRICLE
pumps blood into the aorta.

E

AORTA
largest artery in the body; carries blood away from the heart, branching into smaller arteries that carry blood to the rest of the body.

two or three flaps, also known as cusps. The tricuspid valve separates the right atrium and the right ventricle. Its counterpart, separating the left atrium and the left ventricle, is called the mitral valve. The pulmonic valve controls blood flow out of the right ventricle to the lungs where it picks up oxygen. The aortic valve controls the flow of oxygenated blood out of the left ventricle into the body. Normally these valves let blood flow in just one direction.

The heart beats in two synchronized stages. First, the right and left atria contract at the same time pumping blood into the right and left ventricles. Then the mitral and tricuspid valves close. A split second later, the ventricles contract (beat) simultaneously to pump blood out of the heart. Together, these coordinated contractions produce the familiar "lub-dub" sound of a heart beat—slightly faster than once a second. After contracting, the heart muscles momentarily relax, allowing blood to refill the heart.

To picture how this all works, imagine that as the heart relaxes dark red blood returning from the body flows into the right atrium. This blood carries little oxygen and is laden with carbon dioxide, which is produced by body tissues. When the right atrium contracts, it propels oxygen-poor blood through the tricuspid valve into the right ventricle. In turn, the right ventricle pumps blood into the pulmonary artery. From there, it flows into the lungs where it picks up oxygen and returns to the left atrium. When it contracts, the left atrium pumps the now bright red oxygenated blood through the mitral valve into the left ventricle, which pumps it into the aorta, from which it is distributed to other arteries to nourish your cells, tissues, and organs. Then the cycle begins again.

This cardiac cycle is regulated by nerve impulses, generated by the heart's internal pacemaker called the sinoatrial node (SA node), a small bundle of specialized cells located in the right atrium. These impulses cause the heart to beat. Once generated by the SA node, the impulses spread in a coordinated fashion across the heart muscle in less than a quarter of a second. As they travel, the impulses are relayed through switching stations at precise intervals, eventually causing millions of interlocked cells to contract in near unison.

Age, Change, and Adaptation

The major sequences in this ever-moving picture of the heart beat have been known for nearly 400 years. But gerontologists are uncovering another influence on this chain of events—age—and the picture appears to be even more complex. Aging, it turns out, brings not a simple slowing down of heart function, as one might expect, but a set of intricate alterations: a slowing here, an enhancement there, a minor adjustment elsewhere. The result of these numerous small alterations is adaptation. In various ingenious, important ways, the heart at age 65 has adapted to meet the needs of the 65-year-old body.

However, these refinements have a downside. In recent years, gerontologists have learned that some changes in the structure and function of the aging cardiovascular system, even in a healthy older person without any diagnosed medical condition, can actually greatly increase the risk of developing cardiovascular diseases, including high blood pressure, atherosclerosis, and heart failure. In fact, these changes can create the nearly perfect setting for the onset of severe cardiovascular disease in some healthy older people.

Gerontologists seeking to reconcile these two conflicting pictures of cardiovascular aging are intensely studying the fundamental underpinnings of the age-associated changes in the heart and arteries in hopes of discovering new ways to effectively prevent and treat cardiovascular disease in older people. This quest—from the impact of the smallest molecule to the influence of diet and exercise—is radically changing how scientists think about the cardiovascular system.

The notion, for instance, that heart cells can't replicate themselves is being reconsidered. Gerontologists now know far more about how

aging affects blood vessels and how this process influences the development of atherosclerosis. They are learning much more about how physical activity, diet, and other lifestyle factors influence the "rate of aging" in the healthy older heart and arteries.

In the Beginning

Untangling the effects of age from those of disease and lifestyle is a theme that appears again and again in modern studies of aging. It wasn't always so. In the 1940s and 50s, clinical gerontologists had to conduct most of their studies in chronic care hospitals or nursing homes. The people they studied lived sedentary lives, and many may have had undetected heart disease or other illnesses. From this perspective, it appeared as if virtually all bodily functions, including the cardiovascular system, deteriorated markedly with age.

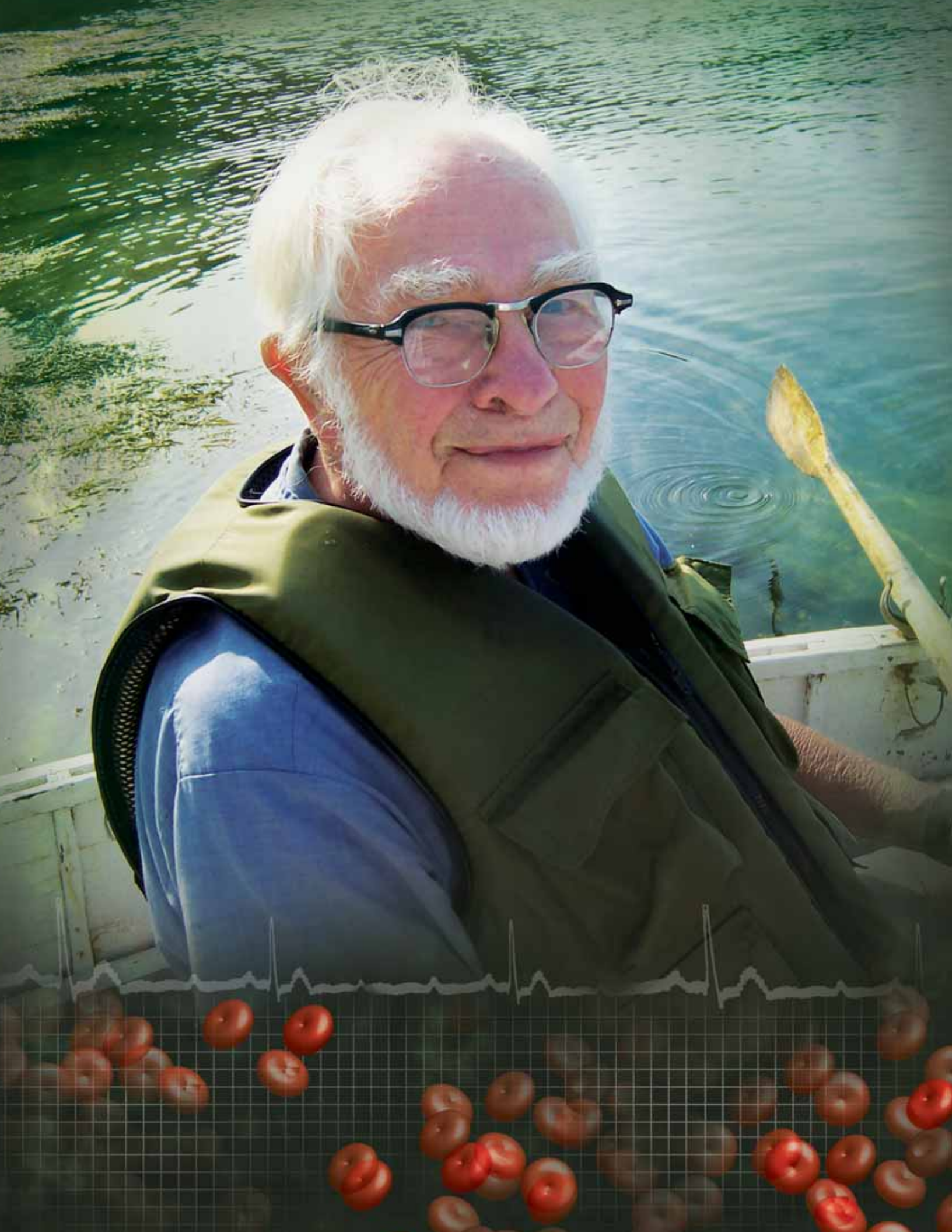
Then, in 1958, the National Institutes of Health (NIH) launched the Baltimore Longitudinal Study of Aging (BLSA). This ongoing investigation, now part of the National Institute on Aging (NIA), has tracked the lives of more than 3,000 people from age 20 to 90 and older in an effort to document the normal or usual physiological changes that occur in a stable population of people who live in the community rather than institutions. BLSA data have been valuable to scientists searching for different ways in which aging, lifestyle, and disease affect the heart and blood vessels.

The modern era of heart research has also depended heavily on the development of powerful, non-invasive technologies, such as echocardiography, magnetic resonance imaging, and radionuclide imaging, which have allowed investigators to easily see valves, walls, and chambers of the heart and the flow of blood through these chambers. Two techniques, thallium scintigraphy, a highly sensitive radionuclide stress test that can detect hidden coronary artery disease, and stress electrocardiogram (ECG), a measurement of the electrical activity of the heart, are particularly useful. In combination, these two tests allow researchers to differentiate between the effects of age and the effects of coronary disease that is so prevalent among older people—effects that were once entangled and indistinguishable.

The Next Steps

As you explore this booklet, you will find that scientists have learned a tremendous amount about aging. Today, more than ever, they understand what causes your blood vessels and heart to age and know a lot about how this process interacts with cardiovascular disease-related changes. In addition, they have even pinpointed risk factors that increase the odds a person will develop cardiovascular disease as well as other illnesses. And while many mysteries of the aging heart and arteries remain unsolved, gerontologists have discovered much about how to prevent or postpone heart disease in later life.

Scientists have been fascinated with the heart for centuries. Left: This 1523 woodcut by Jacopo Berengario da Carpi was sophisticated for its time. Right: Today, researchers use magnetic resonance imaging (MRI) and other high-tech tools to study the living heart.



THE *Aging* HEART

The heart is a tough organ: a marvelous mechanism that, mostly without repairs, will give valiant pumping service up to a hundred years.

WILLIS JOHN POTTS, MD, AMERICAN SURGEON, 1895-1968

For 92-year-old John Bicknell, this is the best of times. A long-retired English professor, he remains mentally and physically active. In addition to singing in community choirs and performing in local musical theater productions, he continues to mow his own large yard and often walks up to a mile or two a day around his island home in Maine.

As he walks around his property, Bicknell sometimes gathers small twigs and branches for kindling, and makes a mental note of larger deadfall so he and his son-in-law can return later to cut it up and haul it back to the house in a truck. An avid boater, he frequently motors between the island and the mainland. In the summer, he enjoys swimming with his grandchildren in the brisk, but invigorating waters of a nearby cove.

After a recent trip to England and France, he returned home to a brewing winter storm. The next morning, he shoveled 9-inches of snow off his deck and front porch.

He looks healthy; his muscles are strong; he has no excess fat. And while gerontologists now know that John Bicknell's 92-year-old heart is not quite the same as it was when he was 22, it continues to serve him extraordinarily well.

On one level, it's not surprising that an older person who exercises regularly is more physically fit and better able to care for himself than most other people his age. But below the surface of that assumption lie intriguing questions that scientists are just beginning to answer. "We know that older people who exercise regularly can do more aerobic work, meaning they are more physically fit," says Edward Lakatta, MD, who is chief of the Laboratory of Cardiovascular Science at the NIA. "But for decades gerontologists have wanted to know what changes in the aging heart and arteries allow this to happen. Fortunately, in the past few years, we have uncovered some remarkable new clues that have clarified how and why these changes occur. At the same time, however, we have detected some intriguing evidence that transforms much of what we once thought of as normal cardiovascular aging."

John Bicknell

Many of these adjustments are remarkably efficient, helping the older heart work as well as possible. But some ultimately may be detrimental. In particular, some gerontologists suspect several of these age-related changes may lower the heart's resistance to disease and compromise its ability to respond to increased demands for blood and oxygen during stress.

"Fortunately, in the past few years, we have uncovered some remarkable new clues that have clarified how and why these changes occur. At the same time, however, we have detected some intriguing evidence that transforms much of what we once thought of as normal cardiovascular aging."

EDWARD LAKATTA, MD, CHIEF OF THE LABORATORY OF CARDIOVASCULAR SCIENCE, NIA

The Effects of Normal Aging

The emerging methods of studying the heart have led to the growing realization that the many factors influencing the aging heart and blood vessels are interdependent. At least six major factors affect how the heart fills with blood and pumps it out. When scientists first discovered these factors, they thought they operated independently. But as investigators more closely examined these factors, they discovered that these six factors influence each other in various direct and indirect ways.

The diagram on the facing page illustrating their interdependence is deceptively simple. It shows only the six broad categories, but each of these terms encompasses a host of related factors. Many of these factors are the focus of rigorous research, including structural changes in the normal aging heart.

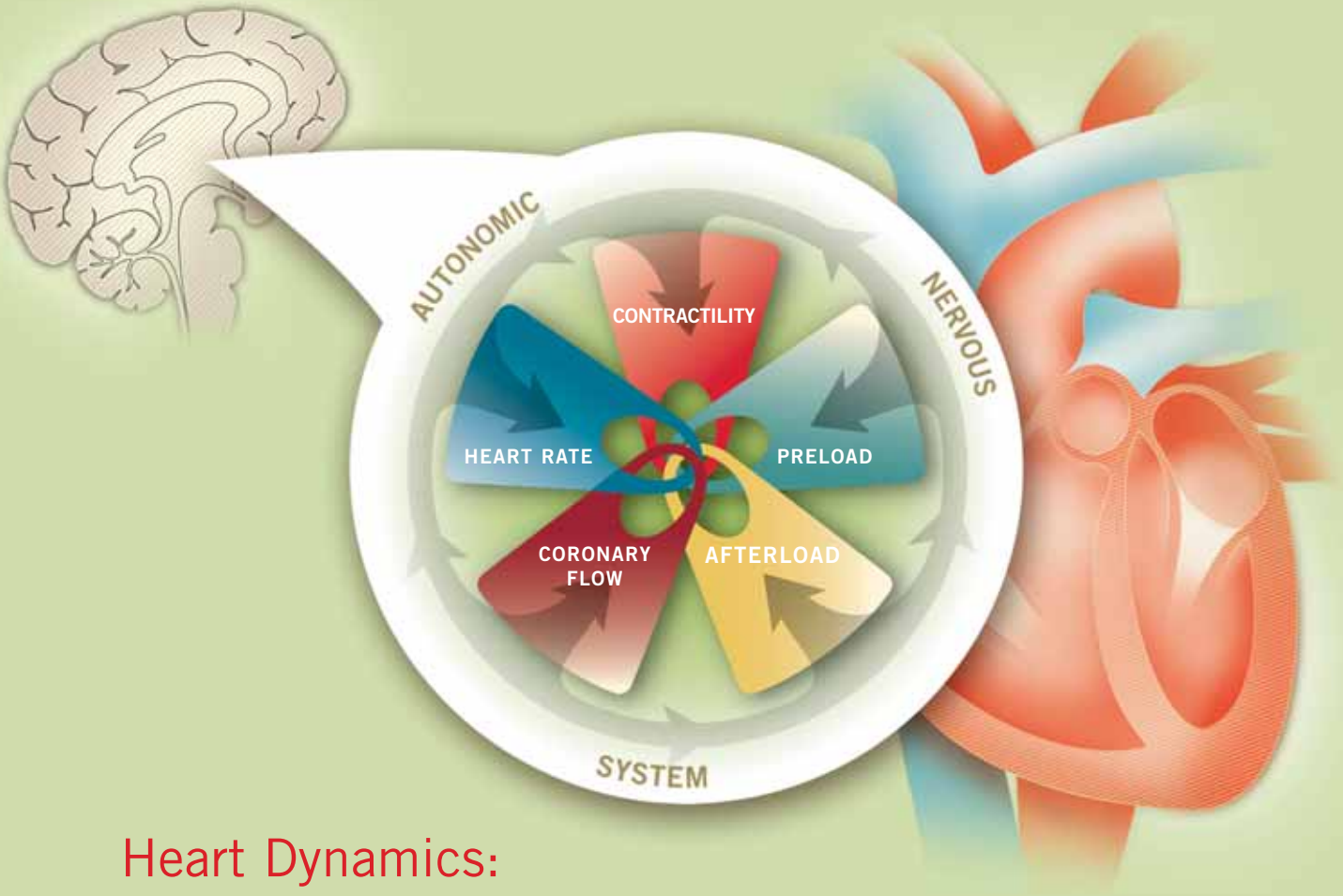
Structural Changes

The NIA's studies of normal aging have revealed a series of fine-tuned adjustments that allow the heart to meet the needs of the aging body. This picture is radically different from the one that prevailed several decades ago when marked declines in overall heart function were thought to be the norm. The revolution in perspective began in the 1970s when researchers came upon their first surprise: The walls of the left ventricle, as it ages, grow thicker.

Up until then, gerontologists thought that the heart shrank with age. One reason was that early researchers knew about the older heart mainly through chest x-rays and autopsy studies of people who were institutionalized, often with chronic illnesses. These people's hearts, which were affected by disease or extremely sedentary lives, often were smaller than those of younger, healthier people.

Then, in the late 1950s, gerontologists began to study healthy volunteers, such as those who participate in the BLSA. Soon afterward, scientists devised new technologies like echocardiography and radionuclide imaging. While x-rays provide a static, shadowy silhouette, echocardiography and other imaging techniques clearly show thickness, diameter, volume, and in some cases, shape of the heart and how these change with time during a given heart beat. Recently, gerontologists have begun using magnetic resonance imaging (MRI) to get a better look at the aging heart. MRI is a type of body scan that uses magnets and computers to provide high-quality images based on varying characteristics of the body's tissues. The technology allows physicians to noninvasively study the beating heart's overall structure and function continuously in three dimensions.

The thicker left ventricular walls supplied the first clue that the heart might be adjusting rather than simply declining with age. Scientists think that the increased thickness allows the walls to compensate for the extra stress they bear with age (stress imposed by pumping blood into stiffer blood vessels, for instance). When walls thicken, stress is spread out over a larger area of heart muscle.



Heart Dynamics:
Autonomic Nervous System

Six broad factors determine how much blood the heart pumps per minute (cardiac output). All six are highly interdependent. The following definitions include just a few examples of their interconnections.

HEART RATE — **the number of beats per minute; it affects the amount of blood getting to every organ in the body. It is regulated by the autonomic nervous system.**

CONTRACTILITY — **the ability of the heart muscle cells to contract in response to an increase in calcium in their cytosol.**

PRELOAD — **stretch on the heart cells prior to excitation; it is affected by the amount of blood in the left pumping chamber, or ventricle, before contraction.**

AFTERLOAD — **the forces that resist contraction once it begins; these forces include resistance by the arteries to pulsing and steady blood flow, which depends partly on the "tightness" or stiffness of arteries. This tightness depends, in part, on the contractility of vascular smooth cells with the arteries.**

CORONARY FLOW — **the flow of blood through the coronary arteries to the heart muscle itself. Since the coronary flow determines how much oxygen reaches the heart muscle cells, it helps determine their contractility, which affects all other factors.**

AUTONOMIC NERVOUS SYSTEM DISCHARGES NEUROTRANSMITTERS — **part of the nervous system that controls involuntary muscles such as the heart; it modulates the other five factors in many ways.**

In a Heart Beat

1

Heart muscle relaxes and valves open (early diastole)

2

Valves float nearly shut and ventricles fill with blood

3

Electrical impulse begins in sinoatrial node (the heart's pacemaker); Atria contract, adding more blood to ventricles (late diastole)

Heart Filling

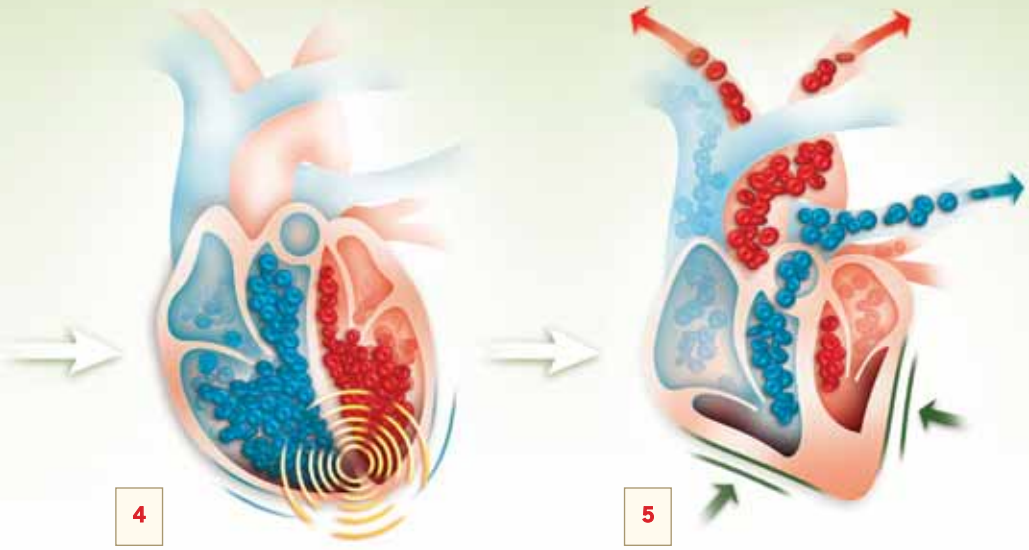
Other findings about the left side of the heart soon followed. While at the NIA, Gary Gerstenblith, MD, and his colleagues studied the left ventricle and the left atrium, the receiving chamber into which blood flows from the lungs before passing into the ventricle. Their echocardiograms with BLSA volunteers showed that in addition to the left ventricular wall growing thicker, the cavity of the left atrium increased.

This study also yielded one other finding, a curious one: The mitral valve—the gateway between the left atrium and ventricle—appeared to close more slowly in older people. As the ventricle fills, the two flaps of the mitral valve—like a trap door with two separate panels—float up on the rising pool of blood and come together to close the passage. If this valve were closing more slowly in older people, as the echocardiograms indicated, then perhaps the ventricle was filling more slowly.

Gary Gerstenblith, MD

To figure out why this occurs and if it makes any difference, investigators turned their attention to the fraction of a second between heart beats. During this momentary lull, called the diastole, the heart relaxes, fills with blood, and readies for the next contraction or systole.

Heart researchers divide the moments of diastole into even shorter periods. There is the early filling phase when blood from the left atrium pushes the mitral valve open, flows rapidly into the left ventricle, and floats the valve shut. This early diastolic filling is the phase that takes longer as people grow older, according to the Gerstenblith study. Then comes the late filling phase, when the left atrium contracts, forces open the mitral valve a second time, and delivers a last surge of blood to the ventricle, just before it too contracts.



4

Electrical impulse spreads to ventricles via atrioventricular node

5

Ventricles contract, aortic valve opens, blood is ejected from the heart (systole)

Why should early diastolic filling slow down as people age? Could it be because the ventricle wall was not relaxing between heart beats as quickly as it once had?

This possibility intrigued NIA investigators because it fit neatly with another stray piece to the puzzle. In animal studies several years earlier, Dr. Lakatta had learned that rat hearts studied in the laboratory took longer to relax after a contraction when they were from older rats.

Later imaging studies in humans confirmed the animal studies: Between beats, the aging ventricle fills with blood more slowly because it is relaxing more slowly than it did when young.

But now another piece of the diastolic puzzle needed to be fit into place. If the older left ventricle fills more slowly with blood, does this mean it has less blood pooled at the end of diastole and thus less to send out to the body during the next contraction? The answer is no, and the reason was found in another of the adjustments that the heart makes with age. NIA investigators found that the heart compensates for the slower early filling rate by filling more quickly in the late diastolic period.

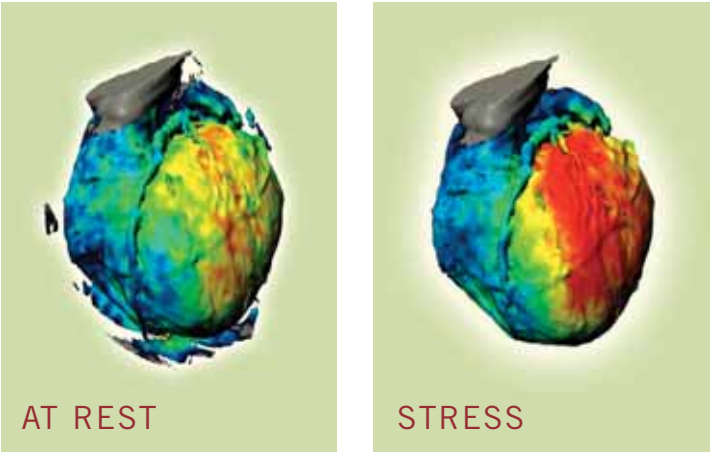
It happens like this: As the mitral valve slowly closes, incoming blood from the lungs pools in the left atrium, which is now larger and holds more blood than when young. In the last moments of the diastole, the SA node—the heart's pacemaker—triggers the first electrical impulse (the action potential), which will lead to contraction. The impulse spreads across the cells of the two atria.

Why should early diastolic filling slow down as people age? Could it be because the ventricle wall was not relaxing between heart beats as quickly as it once had?

The left atrium, stretched with a greater volume of blood in older hearts, contracts harder, pushing open the valves and propelling the blood into the ventricle. The late diastolic surge of blood into the left ventricle from the atrium's contraction occurs at all ages but is stronger in older hearts and delivers a greater volume of blood to the left ventricle. As a result, at the end of diastole, the volume of blood in older hearts is about the same (in women) or slightly greater (in men) than in younger hearts. In younger people, about twice as much blood flows into the ventricle during the early filling period than during late filling. But as we age, this ratio changes so blood flow during early and late filling is about equal.

The next step in this chain of events is contraction or systole, and here the puzzle becomes more complex.

Picture the left ventricle at the end of diastole filled with a volume of blood that is equal to or slightly greater than the volume in younger hearts; this is called end diastolic volume. When the contraction occurs, it forces out a certain amount of blood—the stroke volume. However, not all of the blood in the heart is pumped out at once. A portion remains in the ventricle, and this is called the end systolic volume. The proportion of blood that is pumped out during each beat compared to the amount that remains in the heart at the beginning of the next beat is called the ejection fraction. Doctors frequently use the ejection fraction to estimate how well the heart is pumping.



The heart requires more energy and more blood during exertion or other times of stress. These metabolic images dramatically show the difference in blood flow through the heart at rest and during stress. Red indicates greater blood flow to that portion of the heart.

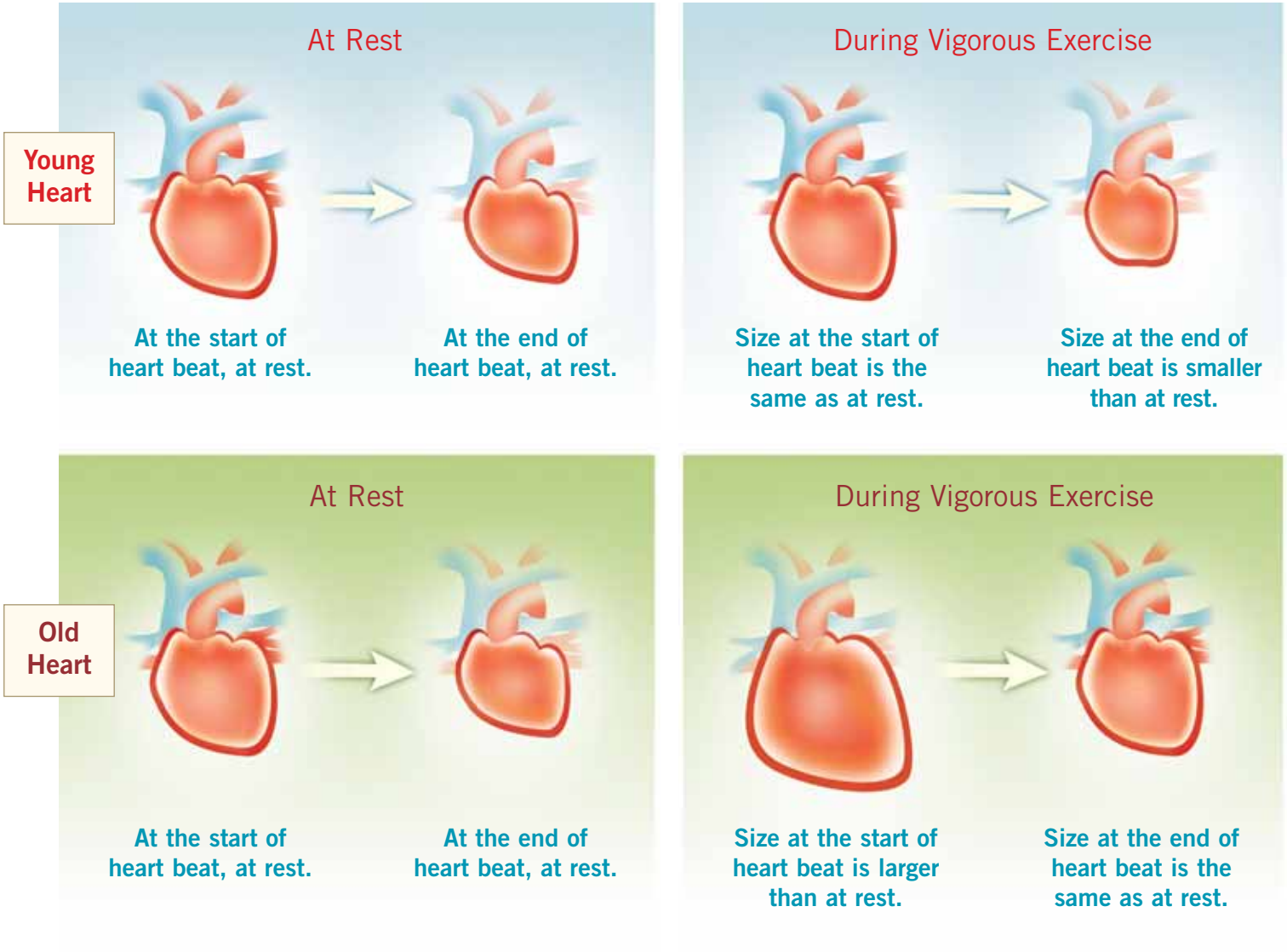
These measurements are important because the links between end diastolic volume, stroke volume, end systolic volume, and ejection fraction make up a complex set of dynamics that researchers had to sort out as they attempted to understand what differences aging makes in the heart's pumping ability. The various cardiac volumes differ according to age, gender, body size and composition, and degree of physical activity. However, keep in mind that the various changes discussed in this section are what occur, on average, in older hearts. As we age, the differences in these measures between one individual and another will vary much more than in younger people. So, for instance, among 65 to 70-year-old women the range of end diastolic volumes and stroke volumes can be quite vast.

Pumping at Rest

When you are sitting in a chair reading a book or watching television, your heart—regardless of age—usually works well below its full capacity. Instead, the heart saves or reserves most of its capacity for times when it is really needed, such as playing tennis or shoveling snow.

In fact, at first glance, healthy young and old hearts don't seem very different—at least when resting. For instance, cardiac output—the amount of blood pumped through the heart each minute—averages 4 to 6 quarts per minute at rest depending on body size and doesn't change much with age. Similarly, while resting, both young and old hearts eject about two-thirds of the blood in the left ventricle during each heart beat.

The Heart: **Young and Old**



But on closer examination, there is at least one important difference between a healthy resting young heart and an older one: heart rate. When we're lying down, the rates of young and old hearts remain about the same. But when we're sitting, heart rate is less in older people compared to younger men and women, in part, because of age-associated changes in the sympathetic nervous system's signals to the heart's pacemaker. As we age, some of the pathways in this system may develop fibrous tissue and fat deposits. The SA node, the heart's natural pacemaker, loses some of its cells.

In men, the heart compensates partly for this decline in two ways. First, the increase in end diastolic volume that comes with age, means there is more blood to pump; and second, the greater volume stretches the ventricular walls and brings into play a peculiar property of muscle cells—the more they are stretched, the more they contract. This phenomenon is called the Frank-Starling mechanism and together with the greater volume of blood to be pumped, it helps to make up for the lower heart rate.