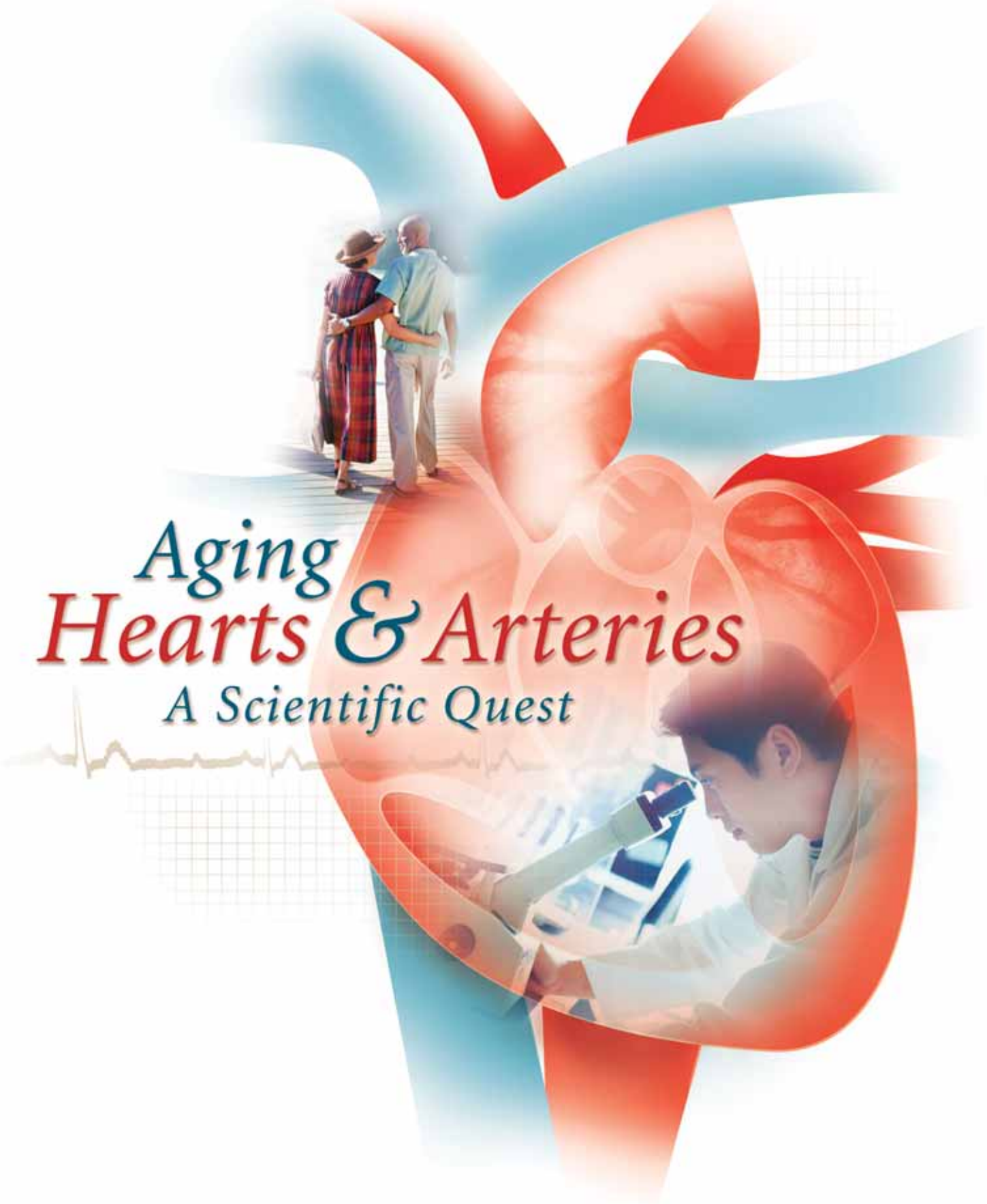

Aging Hearts & Arteries

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

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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?

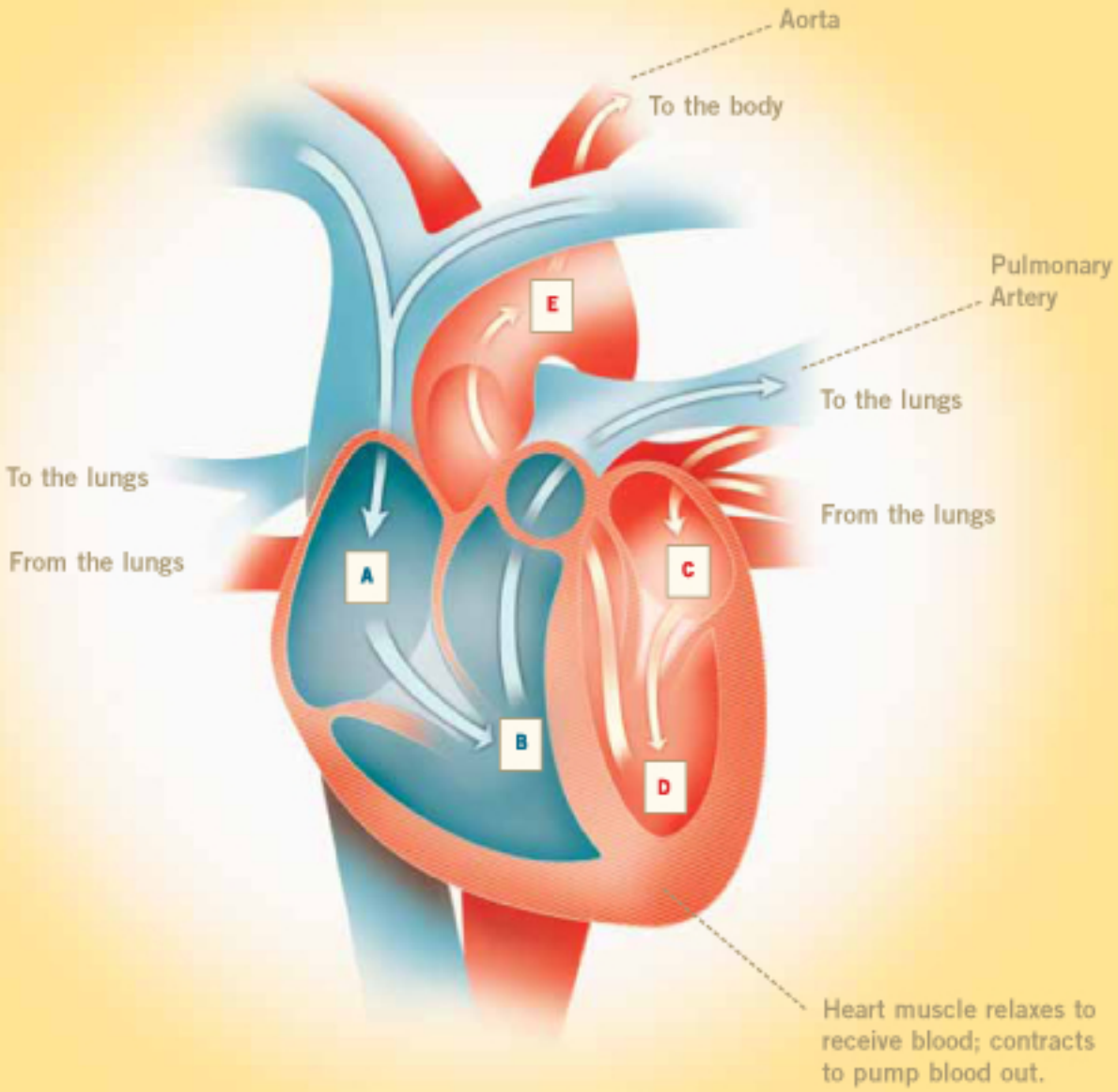
Scientists called gerontologists, who study aging, are seeking to answer these and other questions. As a result of this probing, some old ideas about the aging cardiovascular system are giving way to new theories. In other cases, gerontologists are just beginning to explore some questions, and the heart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

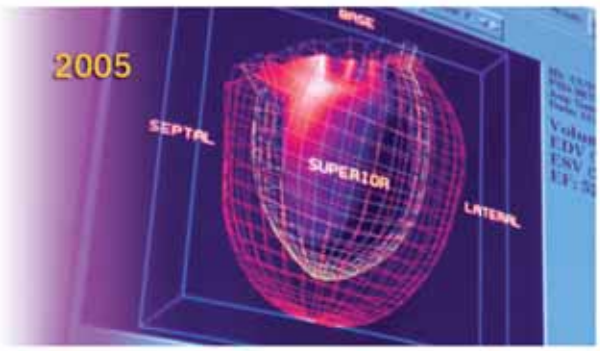
Untangling the effects of age from those of disease and lifestyle is a theme that appears again and again in modern studies of aging. It wasn't always so. In the 1940s and 50s, clinical gerontologists had to conduct most of their studies in chronic care hospitals or nursing homes. The people they studied 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.

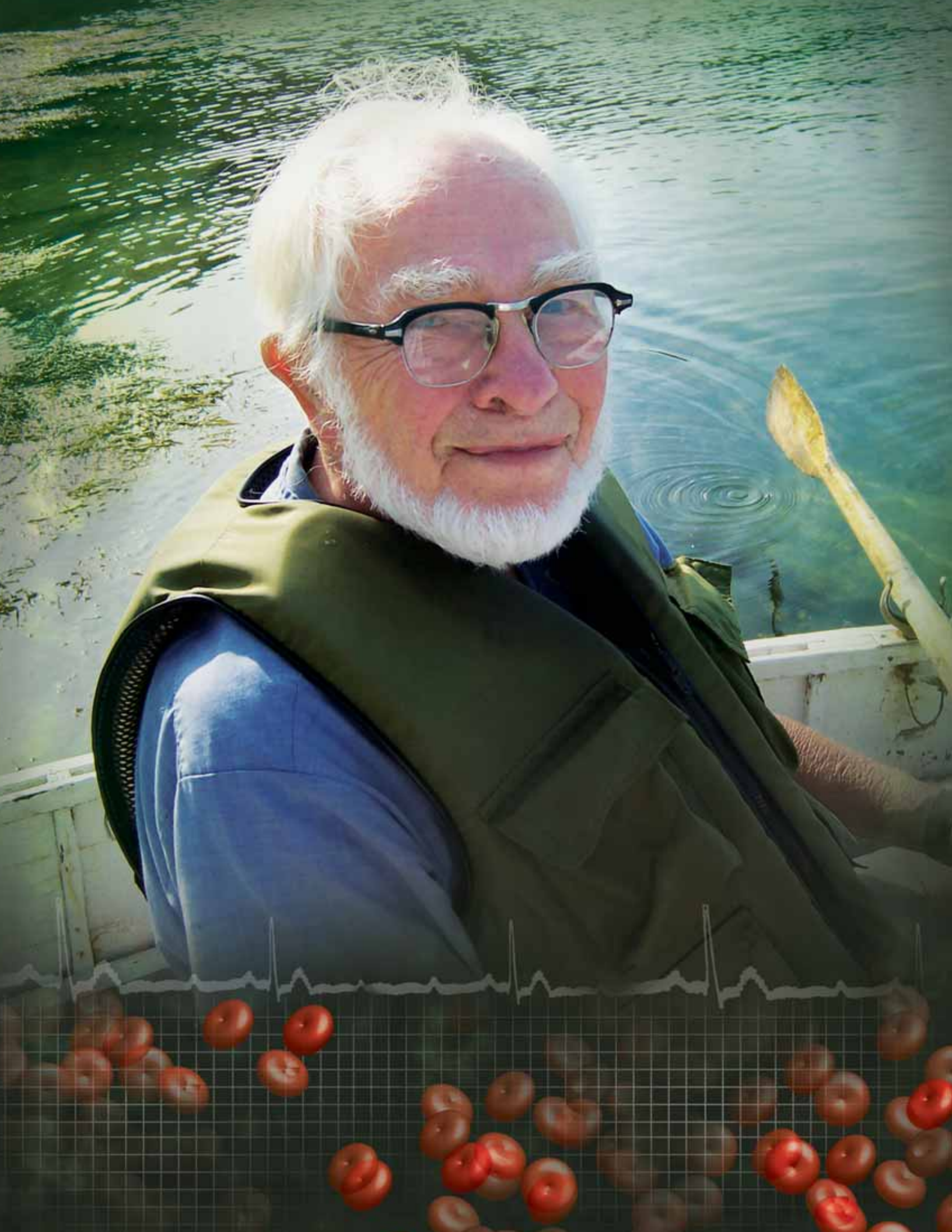
The modern era of heart research has also depended heavily on the development of powerful, non-invasive technologies, such as echocardiography, magnetic resonance imaging, and radionuclide imaging, which have allowed investigators to easily see valves, walls, and chambers of the heart and the flow of 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.

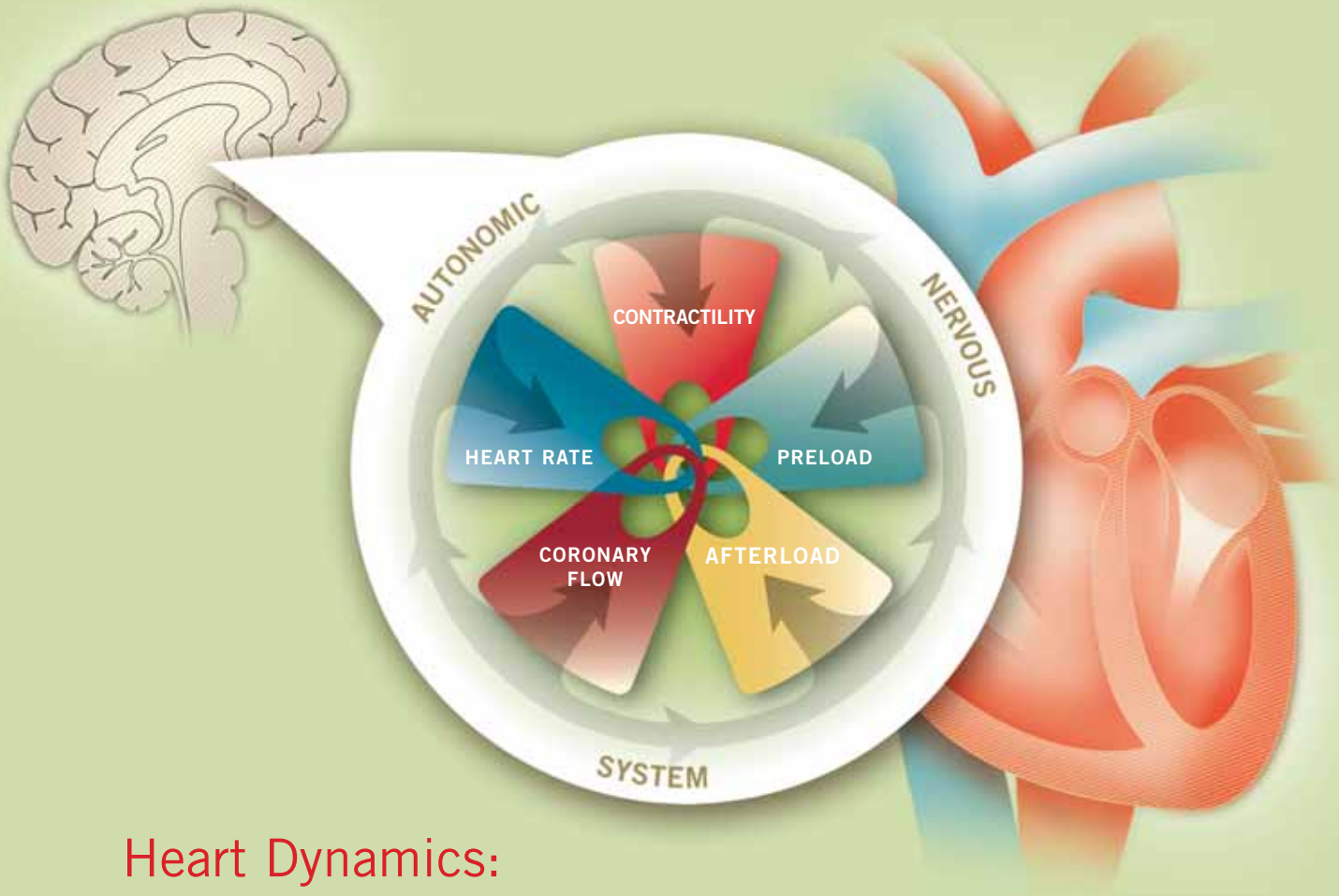
Structural Changes

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

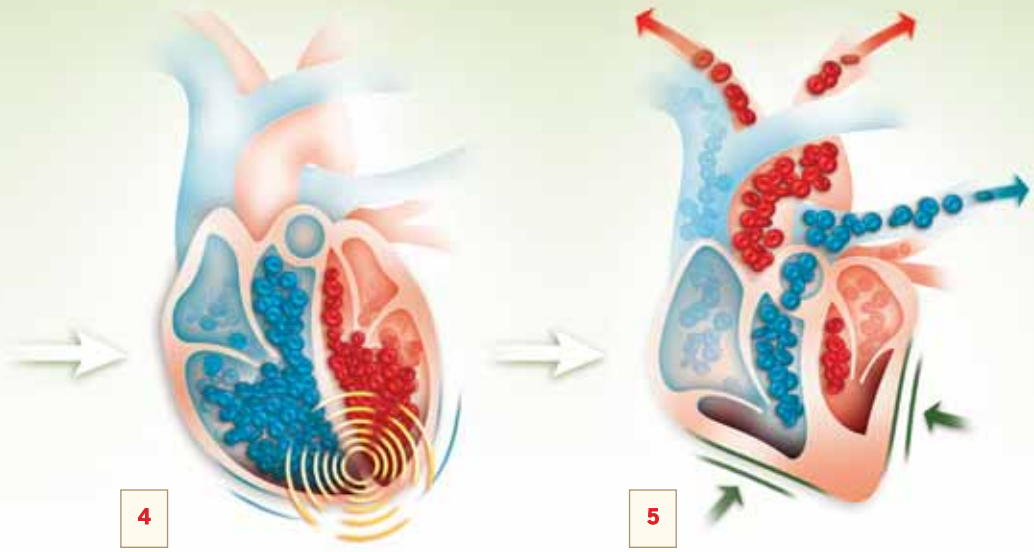
Other findings about the left side of the heart soon followed. While at the NIA, Gary Gerstenblith, MD, and his colleagues studied the left ventricle and the left atrium, the receiving chamber into which blood flows from the lungs before passing into the ventricle. Their echocardiograms with BLSA volunteers 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.

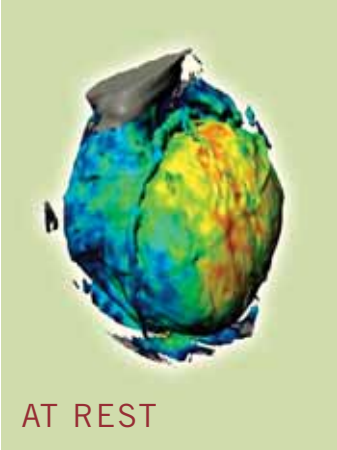
It happens like this: As the mitral valve slowly closes, incoming blood from the lungs pools in the left atrium, which is now larger and holds more blood than when young. In the last moments of the diastole, the SA node—the heart's pacemaker—triggers the first electrical impulse (the action potential),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

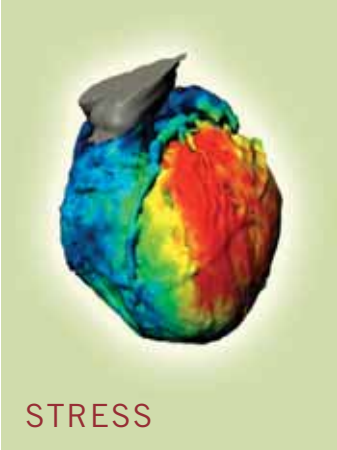
Why should early diastolic filling slow down as people age? Could it be because the ventricle wall was not relaxing between heart beats as quickly as it once had?

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.

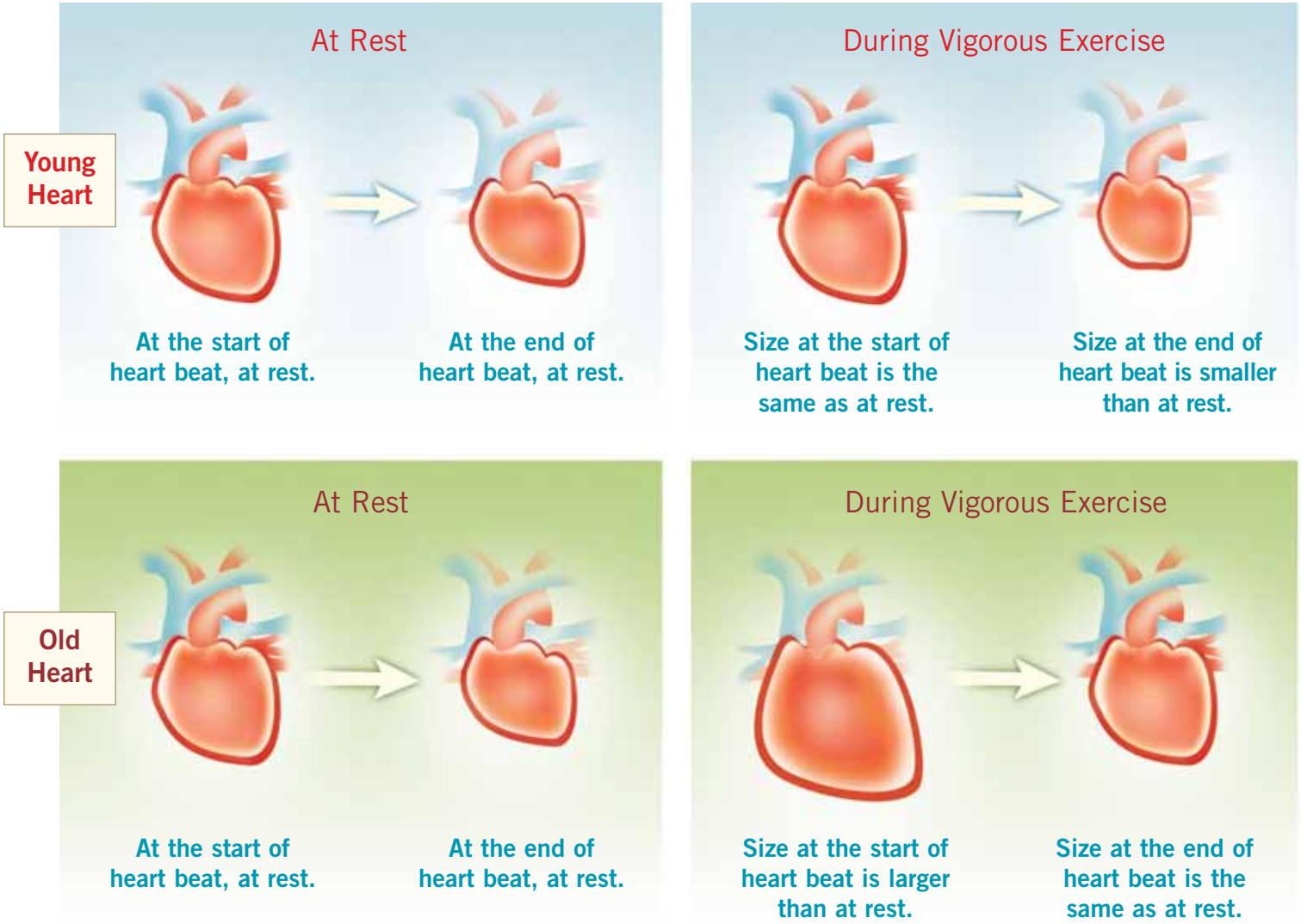
These measurements are important because the links between end diastolic volume, stroke volume, end systolic volume, and ejection fraction make up a complex set of dynamics that researchers had to sort out as they attempted to understand what differences aging makes in the heart's pumping ability. The 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.

...the aging heart must respond to many of the same demands as the younger heart. To do so, it takes advantage of its natural flexibility.

In women, end diastolic volume while sitting does not increase with age, so stroke volume does not increase. The difference between the sexes probably reflects their different needs rather than a difference in their hearts' pumping abilities.

But while the resting older heart can keep pace with its younger counterpart, the older heart—even if in peak condition—is no match for a younger one during exercise or stress.

Pumping During Exercise

It's no secret that the ability to run, swim, and exert ourselves in other ways diminishes as we get older. In fact, the body's capacity to perform vigorous exercise declines by about 50 percent between the ages of 20 and 80. About half of this decline can be attributed to changes in the typical aging heart.

During any kind of activity—even moving from a sitting to a standing position—the heart must pump more blood to the working muscles. In younger people it does this by increasing the heart rate and squeezing harder during contractions, sending more blood with each beat. But age brings changes. Heart rate still rises, but it can no longer rise as high. In your 20s, for instance, your maximum heart rate is typically about 190 to 200 beats per minute; by age 80, this rate has diminished to about 145 beats per minute. A reduced response of heart cells to signals from the brain result in a substantial decline in the peak rate at which the older heart can beat. In addition, force of contraction during vigorous exercise increases, but not as much in older people as in younger ones.

As a result, the heart's cardiovascular reserve diminishes. Put another way, a typical 20-year-old can increase cardiac output during exercise to 3 1/2-4 times over resting levels. In comparison, by age 80, a person can only muster about two times as much cardiac output as at rest.

Yet the aging heart still must respond to many of the same demands as the younger heart. To do so, it takes advantage of its natural flexibility. The heart, which is composed of elastic-like material, can readily alter shape and size depending on the amount of blood within its chambers.

At rest, only a small portion of the body's blood supply is flowing into the heart at any given moment. But with exertion, your body sends out signals that increase blood flow from the veins back to the heart initially stretching and swelling it. This triggers the Frank-Starling mechanism. In response, the young heart pumps harder. Then the brain kicks in, releasing neurotransmitters that elevate heart rate, increase contraction strength, and boost ejection fraction. In addition, the young heart returns to its small, resting size at the start of each beat. All of these reactions help the young heart work more efficiently. (See *When the Brain Talks to the Heart,* page 18)

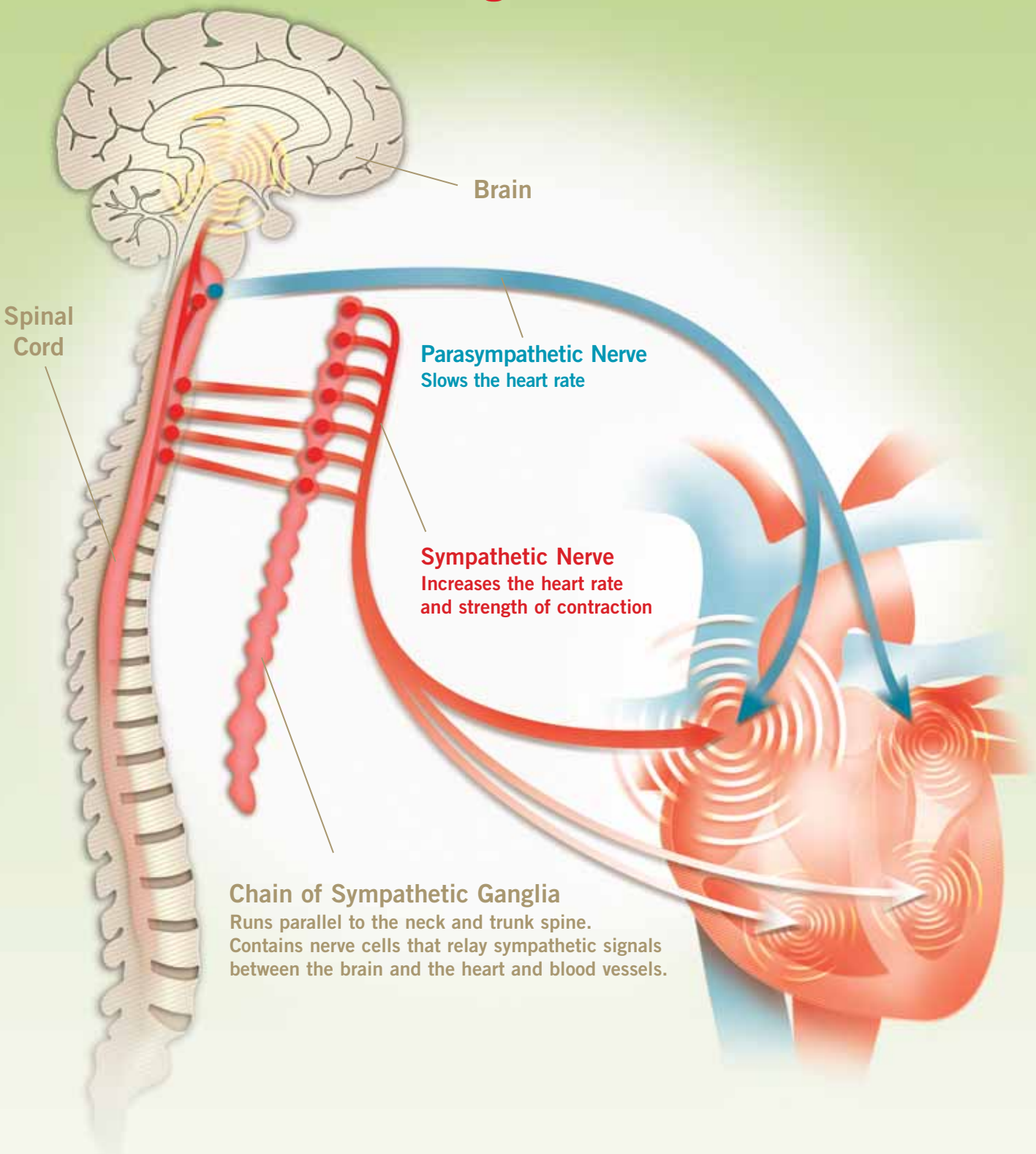
But the older heart doesn't respond in the same way. Although the brain still releases neurotransmitters that stimulate the heart to work harder during vigorous exercise, the older heart is less responsive to these signals than the younger heart. And unlike the young heart, it can't squeeze down to a small size at the end of a heart beat. So its ejection fraction increases only slightly from its resting level of about 65 percent during vigorous exercise. In addition, you might recall that the older heart can't increase its rate as much as the younger heart during exertion. So if it can't beat as fast or squeeze down as hard, then how does the older heart respond to the demands of exercise? The answer is: it adapts.

Because its pumping rate increases less during exercise, the older heart has more time than a younger heart to fill with blood between beats. This additional filling time, combined with a lower ejection fraction, causes the older heart to expand to a larger size during diastole than a young heart. As a result, during exercise the older, bigger heart has more blood in its chambers at the start of each beat than a younger heart. This extra blood volume allows the older heart to pump out just about as much blood with each beat as a younger, smaller heart, even though it has a lower ejection fraction. This represents the Frank-Starling mechanism working at its finest. However during vigorous exercise the older heart is still pumping less blood overall because it can't beat as fast as a young heart.

While this adaptation certainly helps the heart meet the immediate needs of the exercising older body, it does so at a cost. As the older heart dilates between beats, wall tension and pressure within its cavities rises. This increases load on the heart and forces it to work harder. In the long run, persistently elevated pressure promotes thickening and stiffening of the ventricular walls. As a result, the ventricles don't fully relax between beats, and this—combined with a greater filling volume—causes end diastolic left ventricular pressure to increase. When this happens the left atrial pressure increases and this pressure increase is transmitted to the lungs. As pressure rises, oxygenated blood has trouble getting from your lungs into the left side of your heart so it can be pumped out to the body. One outward sign of this scenario within the lungs is that you begin to feel short of breath while exerting yourself. How much exercise you can do before you experience this symptom depends, in part, on how much of the left ventricle's pumping capacity has been eroded. Regular aerobic exercise can help diminish the impact of many of these age-related changes.

Changes in the aging heart result in reduced cardiac output during exertion. However, regular aerobic exercise, such as swimming or water aerobics, can improve fitness and diminish the effects of these age-related changes.

When the Brain Talks to the Heart: Does Age Make a Difference?



Brain-heart communication controls how fast and hard the heart beats.

The brain talks to the heart through the nervous system, using the language of biochemistry. Substances called neurotransmitters travel from nerve cell to heart cell, deliver the brain's messages by binding with special receptors on the membranes of heart cells, and set off a chain of molecular events that ends with a faster beating heart, stronger contractions, and faster relaxation between beats. Or, depending on what neurotransmitter is used, the brain can tell the heart to reverse all of these effects.

This heart-brain dialogue occurs through the autonomic nervous system without you having to think about it. This system automatically regulates all of the body's processes like breathing or digestion that don't require conscious control. But as we age, some of these lines of communication begin to fray, and the heart doesn't respond to the brain's messages as promptly or as well as it once did.

For years, scientists were puzzled by this phenomenon, but they may be getting closer to understanding how and why these messages get muffled. In particular, investigators are looking at the sympathetic nervous system, the part of the autonomic nervous system that signals the heart to speed up. This subsystem helps regulate the heart beat through a series of signals passed from neurotransmitters to receptors on the membranes of heart cells. One of these important signaling cascades starts when neurotransmitters, such as catecholamines, bind to special protein molecules, called beta adrenergic receptors, on the heart cell membrane. Once activated by a neurotransmitter, these beta adrenergic receptors set off a chain of molecular events that allows more calcium to enter heart cells. Increased calcium within these cells can lead to a stronger and more rapid heart beat.

But as we get older, something goes awry in this signaling cascade. As a result, the older heart can't respond to these neurotransmitters, so it doesn't react to stress as well as a younger heart. During exercise, for instance, an older heart is less able than a younger heart to increase its heart rate, augment its contraction strength or boost its cardiac output to meet the needs of the body.

At first, researchers suspected that the diminished supply of catecholamines and other neurotransmitters might be the problem. To test this theory, NIA investigators infused catecholamines into the blood streams of older and younger volunteers to simulate the effects of exercise. As expected, the heart rates of the young men increased. But the older men's rates increased less, even though they received the same supply of catecholamines. So the problem wasn't supply.

Could the problem then be somewhere in the aging cardiovascular system's response to catecholamines? Studies show that this is probably the case. There is a drug called propranolol which blocks the body's response to catecholamines by blocking the beta adrenergic receptors on heart and blood vessel cells. Propranolol and aging have the same effects, according to a number of studies. Older hearts and blood vessels, apparently, have blocked some of these beta adrenergic receptors.

Investigators soon found that with age the number of beta adrenergic receptors on heart cells did diminish. But this reduction was only modest. Instead, studies now suggest that something else about these receptors changes with age: the number of them that are capable of binding with catecholamines, i.e., those in a "high affinity state," seems to decline with age.

The reason for the reduced response could lie anywhere in the cascade of events in heart muscle cells that occurs after catecholamine binds to the receptor. Scientists are finding a host of possible cellular mechanisms that might explain the reduced response. They hope once these mechanisms are better understood, they will be able to find a way to mend the link or prevent it from disrupting messages in the first place. Eventually such findings could lead to new ways to prevent heart failure. •

CELLULAR *Clues*

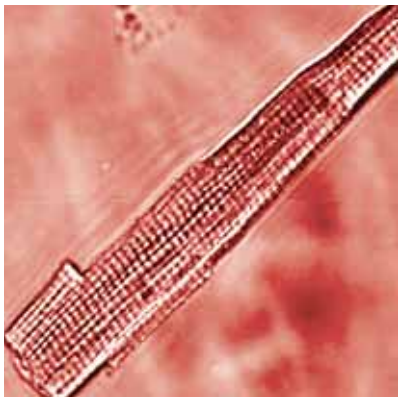
The sustained dependability of a tireless heart relies…on the performance of the trillions of chemical reactions occurring in its aggregate of cells every instant of its function.

SHERWIN NULAND, MD, AUTHOR OF *THE WISDOM OF THE BODY*, 1997

Under a microscope, the true grandeur of the heart reveals itself. Magnified, a rod-shaped heart muscle cell taps out a constant beat. A closer look within the cell reveals a series of thin contractile fibers called myofilaments that are the machinery driving these contractions. In the left ventricle alone, there are nearly 5 billion of these cells beating rhythmically, as if they are all listening to the same snappy tune.

The chemical chain of events that underlies the beating of these cells and of the heart as a whole is truly remarkable. First, there's the electrical impulse along the cell's membrane; then channels open in the cell membrane allowing sodium to flow into the cell. After that, more channels open and calcium enters and binds to a tiny structure near the membrane; then, much more calcium explodes out of that structure into the cell's inner fluid and combines with a myofilament protein called troponin. Troponin then changes shape to allow two other proteins, actin and myosin, to come together. The joined proteins slide past each other in such a way as to shorten the cell, pulling the ends of the cell inward—this is the actual contraction—and then the whole process reverses itself as the heart relaxes in preparation for the next beat.

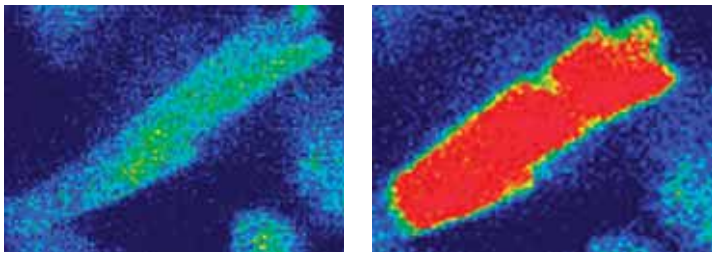
During the past 30 years, scientists have made some intriguing discoveries about the process that changes an electrical impulse into a muscle contraction. These discoveries have led to novel hypotheses about aging and disease. Scientists have found that age-related changes in heart muscle cells (myocytes) help explain alterations in the heart as a whole. For instance, they've learned there are fewer myocytes to do the work as we age and those that remain enlarge, compromising their ability to pump blood efficiently. They've also discovered much about how these changes could interact with disease processes and found clues to how exercise affects the biochemistry of cells. Scientists have begun to question some of the long-held theories about the nature of the aging heart, including whether some myocytes can replicate and what role aging may have in this process. And they've learned a great deal more about the critical role calcium plays in the drama of the aging heart.



Magnified, a rod-shaped heart muscle cell (myocyte) contracts its myofilaments. Billions of these cells contracting in synchronization produce a heart beat.

The Marvelous Calcium Pump

Scientists have long known that calcium—the mineral that helps keep your teeth and bones strong—also has an important job within your heart. Calcium entering the myocyte's inner fluid or cytosol binds with other contractile proteins to bring about contraction. Calcium leaving the cytosol allows the cell to relax. It's this constantly changing ebb and flow of calcium in and out of the cytosol of heart muscle cells that is the essence of the heart beat. (See *How a Myocyte Contracts*, page 23)



Between heart beats, calcium levels (red) diminish in a myocyte's inner fluid or cytosol, allowing it to relax (left). During contraction, a large amount of calcium surges out of a myocyte's sarcoplasmic reticulum, right, triggering tightening or shortening of the cell's muscle fibers (right). This process occurs almost simultaneously in every cell in the heart wall, causing them to contract and pump blood out of the heart.

At the beginning of the calcium cycle—which coincides with the heart filling with blood—calcium in the cytosol and surrounding the contractile filaments of each myocyte is at least 10,000 times lower than calcium levels in your blood and in other fluids between your cells, called the intercellular spaces. As the cycle progresses, pores (or channels) in cell membranes open and close, allowing various salts to flow in and out of the cell. This activity triggers momentary fluctuations in the positive and negative electrical charges across the cell's membrane. When these fluctuations reach a particular threshold, an electrical discharge occurs. This discharge, called the action potential, essentially flips a switch on the myocyte's membrane to open pores that allow a small amount of calcium to enter the cell.

This tiny bit of calcium binds to openings called calcium release channels on the sarcoplasmic reticulum, an organelle (a small cellular "organ") that serves as a storage bin for calcium. In response, the sarcoplasmic reticulum releases a large amount of its stored calcium into the cell. The calcium released from this storage compartment binds to the cell's myofilaments, causing them to tighten or shorten. As the myofilaments tighten, the myocyte compresses (shrinking in length and fattening in width). This process occurs almost simultaneously in every cell in the heart wall, causing them to contract and pump blood out of the heart.

In order for the heart to relax, the cycle winds down and calcium detaches from the myofilaments. A cellular mechanism kicks in and pumps most of the calcium back into the storage bins located in the sarcoplasmic reticulum. Any residual calcium is driven out of the cell through specialized exit calcium carriers located on the cell's membrane. These carriers are proteins that swap calcium inside the cell for sodium outside of it. Then the cycle restarts in preparation for the next heart beat.

If this system fails, and calcium cycling gets out of whack, chaos can ensue. The heart, for instance, can't relax and fill with blood properly and diastolic pressure in the heart increases. In addition, individual cells may fire off rapidly and independently, resulting in arrhythmias—variations from the normal heart beat rhythm—and fibrillation, which is a very rapid twitching of individual muscle fibers. In particular, older hearts are more susceptible to spontaneous calcium oscillations than younger hearts, and it takes fewer oscillations to bring about fibrillation. Fibrillation in the left ventricle leads quickly to acute heart failure and to death if not treated.

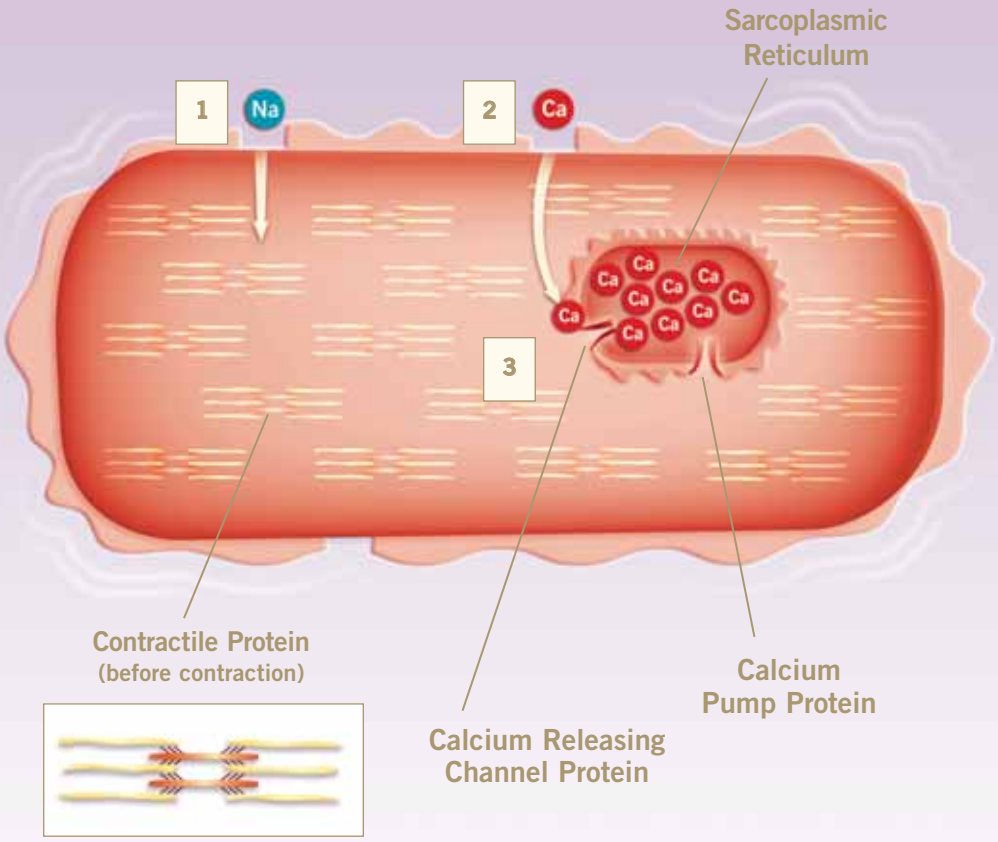
Heart failure occurs when the heart loses its ability to pump enough blood to meet the body's requirements. In particular, heart failure causes the heart to gradually lose its reserve pumping

How a Myocyte Contracts

Relaxed

Action Potential

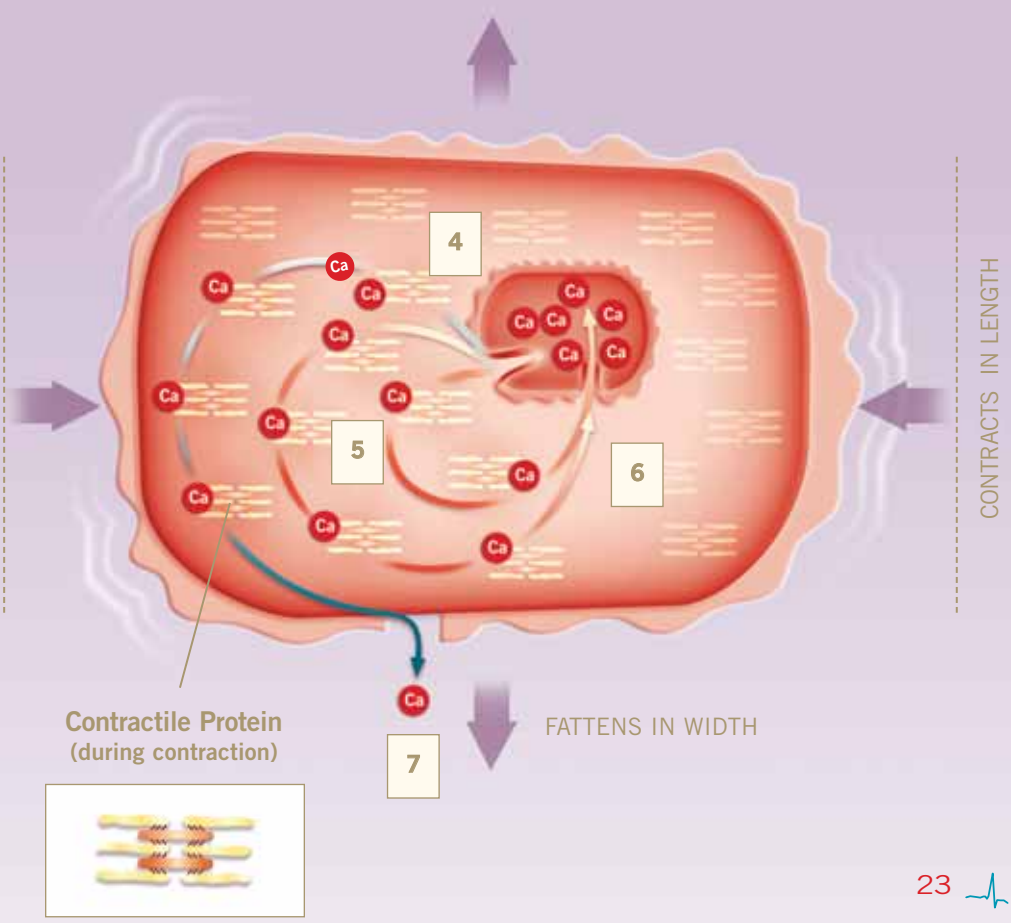
1. Sodium (Na) channels open in membrane causing change in electrical charge.
2. This causes surface membrane Calcium (Ca) channels to open, causing small Ca influx.
3. Calcium binds to calcium releasing channel protein on sarcoplasmic reticulum.



Contracted

4. A large amount of calcium is released from sarcoplasmic reticulum.
5. Calcium activates the contractile proteins. Cell contracts.
6. Calcium disengages from the contractile proteins. Most is pumped back into the sarcoplasmic reticulum.
7. Some calcium leaves the cell.

Cell relaxes and cycle renews.



capacity and work less efficiently. Blood pressure and flow to body organs drops. The kidneys sense this and send out signals prompting retention of body fluid, which contributes to swelling. This can cause a backup of fluid into the lungs and body tissues triggering shortness of breath, swelling of the legs and feet, and other symptoms. As heart failure progresses the effects can become quite severe, and patients often lose the ability to perform even modest physical activity. Eventually, the heart's reduced pumping capacity may interfere with routine tasks, and individuals may become unable to care for themselves. Heart failure rises exponentially with advancing age, and studies of the calcium cycle in heart cells suggest a number of possible reasons.

When a Good Pump Goes Bad

Imagine sitting calmly in a living room chair when the smoke detector goes off. As you scramble to quickly get out of the house, your heart starts beating faster. A few moments later, after you discover it was a false alarm, you return to your comfortable chair, and your heart rate slows again. As this scenario suggests, your heart beat can vary from moment to moment. And your heart's ability to respond to these changes depends a lot on calcium. The more calcium your heart cells release from their intracellular storage bins, the greater the force of the heart's contractions. But how well these mechanisms work depends on how much calcium can be pumped from these storage bins between heart beats. In young hearts, these calcium pumps work quite well, but in older hearts these pumps are much less efficient.

After the heart beat, if you recall, most of the calcium returns to the storage bins in the sarcoplasmic reticulum and then awaits the next signal to do its job again. Scientists began taking a closer look at this mechanism when they learned that muscle from older hearts takes longer to relax than muscle from younger hearts. One of the prime suspects for this phenomenon was calcium. To test this idea, Dr. Lakatta and his colleagues at the NIA used a protein that binds to calcium and gives off a blue light to detect how much calcium is in a cell at any one time. When they injected this calcium-sensing protein into myocytes within heart muscle in laboratory dishes, the blue light showed that calcium levels, after a contraction, fell more slowly in older myocytes. Or, putting it in biologists' terms, the cytosolic calcium transit was longer. But why? Could the calcium be spending longer in the inner fluid because the sarcoplasmic reticulum wasn't removing it as quickly in older cells?

The answer was yes. In experiments, NIA scientists isolated the sarcoplasmic reticulum from the rest of the heart cell, placed it in a test tube, and then added calcium. The sarcoplasmic reticulum took up the calcium more slowly in samples from older animals than those from younger ones.

Subsequent studies confirmed that the sarcoplasmic reticulum—or more precisely, a protein on this organelle—removes calcium more slowly in older hearts. Researchers have found that older cells have lower amounts of this particular protein, often called the calcium pump protein because it removes the calcium in a series of repeated movements. In essence, the sarcoplasmic reticulum removes calcium from the inner fluid more slowly in older hearts because there are fewer pumps, and those that remain don't work as well because of communication breakdowns between the brain and the heart.

Like other changes, the longer calcium transient appears to be one way that the heart adjusts to age, or more specifically to the stiffer arteries that accompany aging. Unfortunately, like those other changes, this adjustment also has a cost.

If these pumps aren't working properly or have shut down, the sarcoplasmic reticulum won't fill as well as it should with calcium, and there won't be enough calcium to fulfill the heart cells' needs, particularly during exercise or stress.

Once scientists learned about the pump protein, the next question was about that protein's gene. Proteins make up a huge category that includes enzymes, growth factors, hormones—almost all the substances that are responsible for the day-to-day functioning of living organisms. Proteins are produced by genes in the nucleus of every cell. Each protein has its own gene. Cells translate gene codes into proteins through a complex, multistep process called gene expression. Any alteration in this process can lead to changes in the end product, the protein.

In the case of the pump protein, the gene that produces it is only about half as active in older hearts as in younger hearts. The end result of all of these changes is a decline with age in the maximum strength of the heart beat during strenuous activity. Reduced calcium pumping also prolongs the time it takes for heart cells—and in turn, the heart as a whole—to return to a relaxed state. As a consequence, the heart can't fill with blood as readily as it once did and prepare for the next heart beat.

Like other changes, the longer calcium transient appears to be one way that the heart adjusts to age, or more specifically to the stiffer arteries that accompany aging. Unfortunately, like those other changes, this adjustment also has a cost.

"It makes sense from an engineering standpoint to have a longer contraction if you're pumping blood into stiffer vessels," Dr. Lakatta says. "The downside is that when you alter the dynamics of calcium, various stresses can more easily throw the calcium out of balance. One consequence of this is that an older person is more apt to feel short of breath during vigorous exercise."

Age Lengthens Action Potential

In addition to calcium transit, two other clusters of events in myocytes seem to be affected by age. One is the action potential. This is a transient alteration in the amounts of positive and negative charges on either side of the myocyte membrane. As mentioned earlier, the action potential triggers the opening of sodium and then calcium channels in the membrane.

The action potential is prolonged in older hearts and may contribute to the longer calcium transient. This occurs because as the heart ages, there are coordinated declines in both the activity and number of proteins involved in the action potential as well as the proteins that respond to its signals. A longer action potential generates a longer calcium transit, which in turn, produces a longer contraction. Each of these processes is controlled by specific proteins.

The prolonged action potential helps older hearts work well in most situations. It does this in two ways. First, pores on the myocyte's membrane stay open longer to allow more calcium to enter the cell between beats. Second, the proteins that carry calcium out of the cell and sodium back in work more slowly. The net result is that more calcium is available within the cell. These effects allow the weaker sarcoplasmic reticulum—which has fewer pumps—to load up on calcium in preparation for the next beat. But these adjustments, like so many other cardiovascular adaptations, may have a downside. For instance, in an aging heart the long action potential adaptation works well at slower heart rates. But during a rapid heart rate, the longer action potential contributes to calcium dysregulation of myocytes. As a result, the older heart doesn't respond as dynamically to the needs of the body as a young heart. So, a prolonged action potential is yet another possible reason that an older person usually can't do as much exercise as someone younger.

Prolonged contractions also allow the older heart to eject blood into the arteries later in the heartbeat. This adaptation is good because it improves the blood flow through an older person's stiffer arteries.

Contractile Proteins

The other mechanisms that change with age involve contractile proteins—actin, myosin, troponin, and others—that interact to shorten, or contract, the myocyte. These contractile proteins pass through a series of steps, triggered by calcium, which bring actin and myosin together into crossbridges. The crossbridges use energy released during the transaction to shorten the cell. With age, one part of the crossbridge alters—the part called the myosin heavy chain.

The myosin heavy chain can be produced in two slightly different forms, one dubbed alpha, the other beta. In experimental animals, the alpha myosin heavy chain decreases with age, while the beta increases. The same seems to be true in the human atrium. When the proportion of alpha myosin heavy chain is reduced in isolated cells, the contraction speed is slower.

Changes in the myosin heavy chain have been traced back to the genes involved—alpha is expressed less with age, beta more. The expression of these genes is regulated by proteins called transcription factors that start or regulate the first steps of cellular reproduction. One of the transcription factors for the myosin gene is the same as that for the sarcoplasmic reticulum pump, suggesting that there is a common aging link between the two cellular mechanisms. Studies in rodents suggest the activity of these factors declines with age. Because of these changes the expression of genes in the aging heart tends to go back to patterns of gene expression seen in the fetus.

These age-related changes in myosin and other contractile proteins, in conjunction with alterations in calcium transit and action potential, actually help the older heart work more efficiently. That's because slower and longer contractions don't use as much energy. Prolonged contractions also allow the older heart to eject blood into the arteries later in the heartbeat. This adaptation is good because it improves the blood flow through an older person's stiffer arteries.

Free Radical Damage

Myocytes produce free radicals, unstable oxygen molecules that can disrupt a cell's inner workings. As the heart ages, these free radicals can greatly alter how well the cellular calcium pumps on the sarcoplasmic reticulum work.

In myocytes, most free radicals are produced in tiny cellular organelles called mitochondria and by an enzyme in cell membranes called NADPH oxidase. Mitochondria convert oxygen and food into an energy-releasing molecule that powers most cellular processes. But during this process they also produce potentially harmful byproducts such as oxygen free radicals. A free radical can be produced by almost any molecule when it loses an electron from one or more of its atoms. In heart muscle cells, they are commonly created when mitochondria combine oxygen with hydrogen to form water. Free radicals can cause extensive damage to proteins, membranes, and DNA. As we age, mitochondria become less efficient, progressively generating less energy-releasing molecules and more free radicals.

In the aging heart, free radicals damage proteins, membranes, and calcium pumps on the sarcoplasmic reticulum that myocytes need to produce contractions. As a result of this cellular damage, myocytes can't process calcium as well. As calcium builds up in the cell, it can begin to contract

erratically, causing an arrhythmia. If this arrhythmia spreads to other cells, it can eventually disrupt beating throughout the heart and lead to serious complications.

Nitric Oxide

Calcium isn't the only factor that helps the heart respond to the body's increased need for blood and oxygen during sustained exertion or times of stress. Nitric oxide, a potent chemical messenger that helps regulate blood flow in the arteries, also signals the heart to pump harder at critical times.

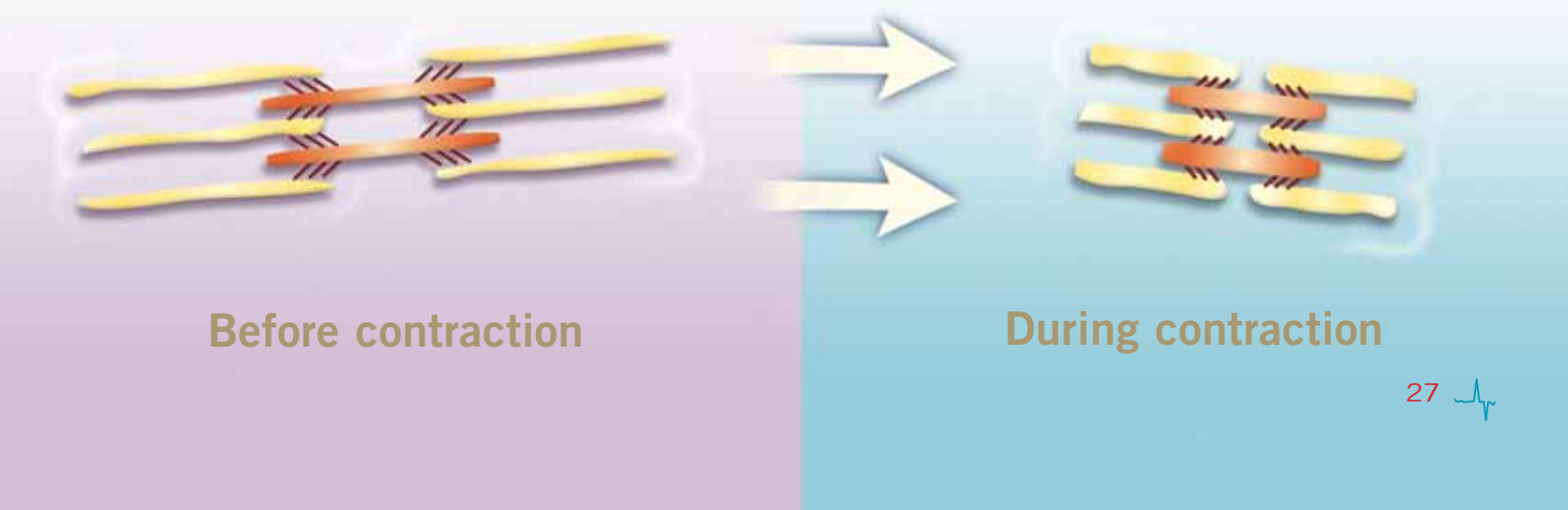
As we just learned, heart cells can increase their contraction force by releasing more calcium from the sacroplasmic reticulum. Once released from this cellular storage bin, calcium binds to troponin and other contractile proteins, which trigger the heart beat. The more calcium that binds to these contractile proteins, the greater the force of the contraction. But there's at least one other pathway, the Frank-Starling mechanism, that can increase the force of these contractions. This mechanism kicks in when increased blood flow into the heart stretches myocytes, signaling them to contract harder and produce more force. Normally, these two pathways work independently to tap the heart's reserve capacity. But if cell stretch is sustained for prolonged periods, the amount of calcium released into heart cells during contractions gradually increases. This suggests that some coordinating mechanism is operating to ensure that, even under duress, the heart continues to pump enough blood to the body. But what this link might be mystified scientists for many years.

Steven Sollott, MD and his colleagues at the NIA theorized that sustained cell stretch prompts an enzyme, nitric oxide synthase, to produce nitric oxide. Nitric oxide, in turn, binds to the calcium release channels in the sarcoplasmic reticulum and promotes the release of calcium into the cell.

To test this theory, the investigators conducted a series of experiments with adult rats and mice—mammals with cardiovascular systems similar to humans. Some rodents were genetically altered so they could not produce the enzyme that makes nitric oxide. Others were given drugs that blocked the production of the chemical messenger. In both cases, sustained cell stretch no longer triggered increased calcium release in heart cells. Previous studies have shown that nitric oxide levels may be diminished in heart failure and other cardiovascular diseases.

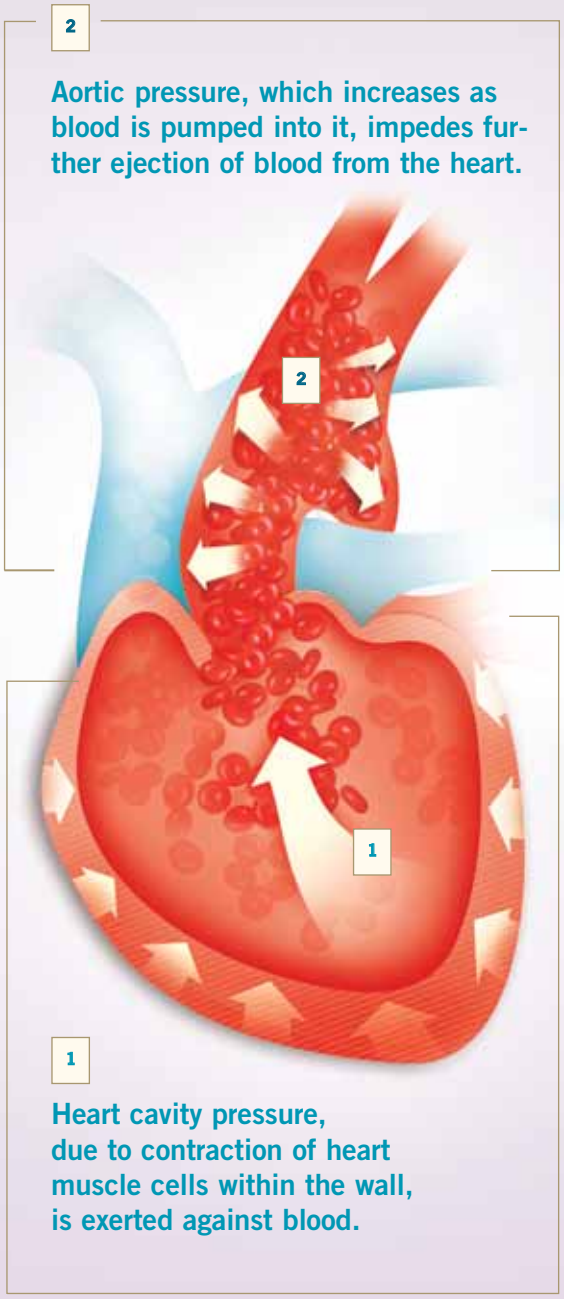
"Knowing that this nitric oxide mechanism exists and how it functions in the normal heart may help us understand what happens to it with age and disease," Dr. Sollott says. "This discovery offers scientists an opportunity to consider whether therapies that sustain or enhance the functioning of this mechanism might help aging hearts stay healthy and continue working properly."

Contractile Proteins



Opposing Pressures:

Heart Cavity Pressure vs. Aortic Pressure



New ideas are also emerging about two other phenomena that have puzzled gerontologists and cardiovascular scientists for decades. As heart cells get older, there are fewer of them to do the necessary work, and those that remain get bigger.

Bigger Heart Cells…

To efficiently pump blood, the stiffness of the heart changes as it beats. When it is filling, the heart needs to be as relaxed as possible to allow blood to freely flow into it. When it contracts, it stiffens so that the pressure it exerts is greater than that found in the arteries. When this happens, blood is forced into the arteries with a minimal amount of effort. If there is a load mismatch—meaning the force differential between the heart and arteries isn't very good—the heart can't empty as well as it once did. As a result, the heart has to work harder to get blood into the arteries. If this occurs on a regular basis, some heart cells die, others enlarge, and the heart walls thicken.

This problem gradually increases as we get older. In some cases, the cells that remain enlarge up to 40 percent. The enlargement of these remaining myocytes seems to be the principal mechanism for the thickening of the heart walls—the hypertrophy—that occurs with normal aging.

Much evidence suggests that myocyte enlargement and the consequent thickening of the heart walls are ways that the heart adjusts to increased loads, especially from the growing stiffness of the arteries. Extra loads also may develop as the result of disease.

One reason cardiovascular researchers are so intrigued by myocyte enlargement is because of its possible links to disease. While enlargement seems to occur in response to aging and stiffening of the arteries, it is exaggerated by disease, such as coronary artery disease and high blood pressure. (However, enlargement occurs with high blood pressure at any age).

While myocyte enlargement seems to be one way that the heart adapts to increased loads, there is also evidence that at the oldest ages, it no longer adapts as much. Older animals, for instance, have less enlargement in response to heart overloads than younger animals. This failure or slowing of the adaptive response may explain why 80-year-olds are much more likely to experience heart failure following a heart attack than 60-year-olds.

These findings are yet another clue suggesting that specific age-associated changes in healthy hearts and blood vessels compromise their ability to respond to everyday stress and strain. In turn, these changes gradually lower the heart's resistance to certain cardiovascular conditions including left ventricular hypertrophy, atrial fibrillation, and congestive heart failure.

…But Fewer of Them

As we age, even the healthiest hearts lose cells. In a robust 70-year-old man without heart disease or high blood pressure, these age-related losses are estimated to account for up to a 30 percent reduction in the total number of myocytes in the heart. Although it's unclear whether this loss of heart cells is good or bad for the body as a whole, evidence suggests that loss of a significant number of heart cells may contribute to the decline in cardiovascular health in older people.

Cardiovascular scientists are exploring why some myocytes die while others continue to thrive. Injury, due to a lack of oxygen or ischemia, seems to be one of the prime killers. But studies suggest that programmed cell death—apoptosis—could be a significant factor as well.

Apoptosis is a process in which a cell orders itself to stop functioning, shrink, and ultimately dissolve. It has been observed in other cells in the body, where it may be a mechanism for adjusting to development or removing unwanted or potentially dangerous cells, such as cancer cells, from the body. At least one study suggests that apoptosis in the heart becomes more common with age. And other research has found that excessive apoptosis may contribute to decline in the aging cardiovascular system.

A number of molecular processes, such as increased free radical production, can activate a cell's apoptotic or self-destruct mechanism. In rodents, for instance, NIA grantee Christiaan Leewenburgh, PhD, of the University of Florida and his colleagues found that cytochrome c, a mitochrondial protein, becomes a signal for cell death if it "leaks" from the mitochondria. The hearts of older rats released greater amounts of that cell-death signal than did the hearts of younger rats. This difference may be partly responsible for the increase in heart cell death.

Christiaan Leewenburgh, PhD

Cardiovascular scientists studying apoptosis are particularly interested in the role of a process called cardiac stretch. Myocytes are connected, so when one dies—for whatever reason—others must stretch to maintain the connections. As myocytes are stretched, they release chemical substances called growth factors, such as norepinephrine and angiotensin. These growth factors may not only help explain why these cells enlarge, but also why some of them die. In laboratory dishes, for instance, the same growth factors that regulate heart cell growth also trigger apoptosis in some myocytes. However, these and other growth factors may have an equally important role in a process that was once thought to be impossible: the replication and regeneration of heart cells.

The Untapped Promise of the Aging Heart

For decades it was believed that the heart had a set number of myocytes, and once one of these cells died, they couldn't be replaced. Because these cells were thought to be unable to divide, according to this view, their numbers progressively decreased with age and ultimately impaired heart function.

While this view was widely accepted, it was never proven. And now, compelling but controversial evidence raises new questions about its validity.

One of the first challenges to this dogma came in 2001 when scientists from New York Medical College in Valhalla, New York found large scale replication of heart muscle cells in two regions of the heart, and identified several other key indicators of cell regeneration. These scientists, led by NIA-grantee Piero Anversa, MD studied myocytes from the hearts of 13 patients, 4 to 12 days after their heart attacks, and from the hearts of 10 patients who did not have cardiovascular disease. Samples were obtained from the border zone near the site of the heart attack and from a more distant site from the damaged tissue.

Piero Anversa, MD

By viewing these areas of the heart with a high resolution confocal microscope, the investigators were able to measure the expression of a protein found in the nucleus of dividing heart muscle cells. This protein is expressed during all phases of a cell's life cycle and is a strong indicator of ongoing cell division.

The scientists also obtained images of cell division and found other evidence of myocyte replication, including the formation of the mitotic spindle, and contractile ring, critical structural indicators of cell division. In comparison with normal hearts, the number of myocytes multiplying in diseased hearts was 70 times higher in the border zone and 24 times higher in the remote tissue.

But where were these new hearts cells coming from? Subsequent studies—in both animals and humans—suggested that, although most adult heart cells probably aren't able to replicate, a small core of adult stem cells might exist in the heart or in the bone marrow that are capable of replenishing and replacing damaged or dying myocytes. However, other scientists have had difficulty duplicating these results. So for now, the notion that adult stem cells can regenerate heart muscle remains a tantalizing, but unproven, possibility.

Some cardiologists theorize that adult stem cells in young hearts might be able to produce enough new myocytes to replace those that are naturally dying. In effect, these stem cells might help keep the total number of myocytes stable in the young heart. But mounting evidence suggests that even if these stem cells exist, their numbers decline with age. As a result, some scientists suspect there are fewer new heart cells to replace older ones which are dying in greater numbers due to age, injury, and other problems. So the deterioration of the older heart could be related, in part, to the inability of aging cardiac stem cells to replace dead and dying myocytes with new ones.

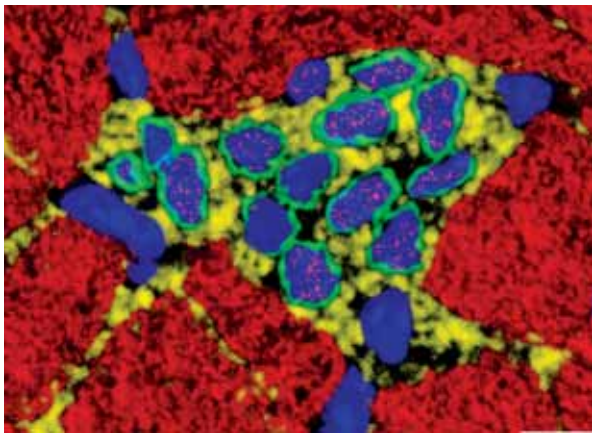
Gerontologists exploring this exciting new area of research have many questions, but few answers at this point. For instance, does the number of cardiac stem cells really decline with age? What role do growth factors play in regulating the activity of these cells? How are the changes in cardiac stem cells linked to other age-related alterations in the heart and arteries? Why are scientists having so much difficulty replicating the earlier findings? Are the myocytes in the heart of an 80-year-old basically the same ones present in his or her heart at birth or have the cells been gradually replaced over the

years like the skin? And perhaps most importantly, if these stem cells exist, can anything be done to stimulate them to produce new myocytes that will counteract the effects of age in the older heart?

The key to answering this final question lies in learning more about stem cells and how they work. Investigators already know that stem cells have important characteristics that distinguish them from other types of cells. Unlike most cells in the body, such as skin or brain cells, which are dedicated to performing a specific function, stem cells are not specialists. But under certain physiologic or experimental conditions, they can be induced to become cells with special functions such as the beating cells of the heart muscle or the insulin-producing cells of the pancreas. Another unique characteristic of stem cells is their ability to renew themselves for long periods through cell division.

Scientists primarily work with two kinds of stem cells from animals and humans: embryonic stem cells and adult stem cells. Most of the basic science research discoveries on embryonic and adult stem cells come from research involving animals, particularly mice. Embryonic stem cells are derived from embryos. Specifically, embryonic stem cells are derived from embryos that develop from eggs that have been fertilized *in vitro*.

Adult stem cells typically generate the cell types of the tissue in which they reside. A blood-forming adult stem cell in the bone marrow, for example, normally produces many types of blood cells such as red blood cells, white blood cells, and platelets. Until recently, it had been thought that a blood-forming cell in the bone marrow—which is called a hematopoietic stem cell—could not give rise to the cells of a very different tissue, such as myocytes in the heart. However, a number of experiments over the last several years have raised the possibility that stem cells from one tissue may be able to make cell types of a completely different tissue, a phenomenon known as plasticity.



In this microscopic image, adult myocytes (red) surround a cluster of stem cells (blue) growing to maturity in the heart. Many questions remain about these cells and their potential role in the aging heart.

Because of this flexibility, stem cells hold enormous potential for cell replacement or tissue repair in heart disease and many other age-associated disorders. Gerontologists are seeking to find out if these cells will yield any practical interventions that might promote healthy aging.

"We've made substantial progress, but there is a lot more to be learned," according to Dr. Lakatta. "Finding ways to activate these cells and get them to where they are needed in the heart and ensuring that they develop into heart cells are significant challenges."

While daunting, these and other challenges are motivating gerontologists to investigate many new interventions that in the future could help keep aging hearts and arteries healthy.

As we age, for instance, pressure increases in the arteries, and this can affect the structure and function of the left ventricle. In fact, a growing number of scientists suspect that age-related changes in the blood vessels may actually instigate many of the transformations that occur in the older heart.

Blood Vessels and Aging: THE REST OF THE JOURNEY

A man is as old as his arteries.

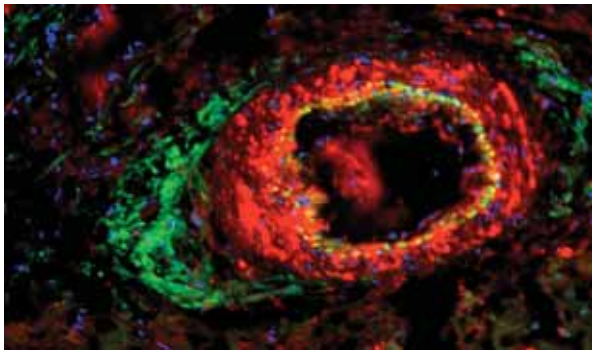
THOMAS SYDENHAM, MD, ENGLISH PHYSICIAN, 1624-1689

Stretched end-to-end, the arteries, veins, and other vessels of the human circulatory system would measure about 60,000 miles. On any given day, the heart pumps about 1,800 gallons of blood through this vast network. In an average lifetime, the heart pumps approximately one million barrels of blood—enough to fill more than 3 supertankers—through the circulatory system.

No doubt about it, the heart and arteries are remarkable. But as we age, the cardiovascular system becomes more susceptible to diseases including high blood pressure and atherosclerosis. Nearly 40 percent of all deaths among those 65 and older can be attributed to heart problems. By age 80, men are nine times more likely to die of chronic heart failure than they were at age 50. Among women, this risk increases 11-fold over the same time period.

Certainly, poor lifestyle—smoking, little or no regular exercise, a diet laden with fat, cholesterol, and sodium—contribute to the development of these cardiovascular disorders. But it is becoming more apparent that like the heart, blood vessels undergo changes with advancing age, and these changes, including arterial stiffening and thickening, are major risk factors for these diseases.

This relationship is complex. In fact, studies—in both animals and humans—have found that many of the factors that underlie the age-related changes in the arteries are also implicated in the development of cardiovascular disease. This suggests that there are some common links between these two distinct, but intertwined processes. Based on these and other findings, some investigators theorize that aging is the driving force in a cycle that begins with age-related changes in the blood vessels. These changes create an environment that promotes arterial stiffening, which



In a healthy artery, the lumen (dark center), where blood flows, is surrounded by arterial wall (red). Age-related changes in the arteries, such as arterial thickening and stiffening, can make them more susceptible to cardiovascular diseases.

contributes to development of hypertension (high blood pressure). At the same time, age-related changes also make it easier for fatty deposits to build up on the inside of arteries. This accumulation, part of a process known as atherosclerosis, can accelerate the aging of the arteries, which, in turn, leads to further fatty build up and narrowing of the vessel. (See *What Happens During Atherosclerosis?* page 35)

In essence, aging arteries form an alliance with risk factors for atherosclerosis, hypertension, and other precursors of heart disease and stroke to profoundly elevate the risk of developing these conditions. However, as scientists learn more about the changes that occur in aging blood vessels, they are making some key discoveries. For instance, in some people these changes occur at an accelerated rate; in others, they occur much more slowly than average. This suggests that how well your arteries perform as you get older depends on a series of complex interactions among age, disease, lifestyle, and genetics, Dr. Lakatta says. In any case, epidemiological studies have consistently shown that people with the greatest amount of arterial stiffening and thickening are at the highest risk for developing stroke, heart attack, and other cardiovascular events.

But investigators also now know that several of these changes, such as arterial stiffening and thickening, don't occur to the same extent in all people. In fact, studies strongly suggest that exercise, good nutrition, and emerging drug therapies can slow the aging of the blood vessels, even among people who are genetically at risk. These interventions could delay or prevent the onset of cardiovascular diseases in many older people.

"We're moving into an era when it will be imperative to find out what your blood vessels are like before clinical disease sets in so that, if necessary, appropriate measures can be taken to keep your cardiovascular system as healthy as possible," Dr. Lakatta says.

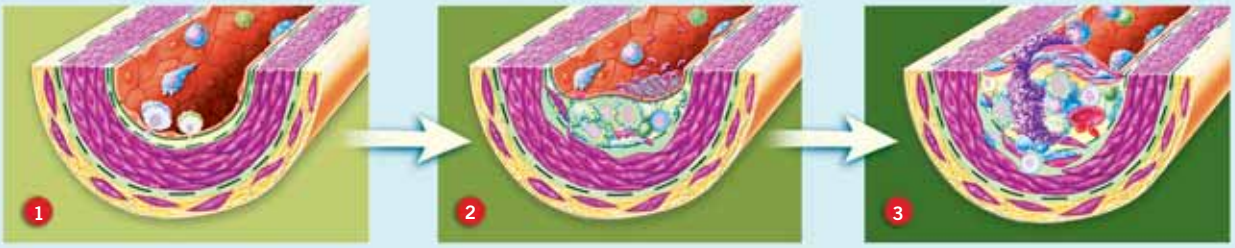
In Search of a Connection

So, what made scientists think there might be a connection between stiffening and thickening of arteries and heart function? It goes back to what they have learned in the past few decades, partly through NIA's Baltimore Longitudinal Study of Aging. By comparing younger and older volunteers, scientists have been able to put together a picture of what happens both in the heart and in the blood vessels as people age.

The heart, they have learned, adjusts in many subtle and interconnecting ways: It develops thicker walls, and it fills with blood and pumps the blood out in a different pattern and even by somewhat different mechanisms than when young. But it is also becoming clear that many of these adjustments are made in response to changes in the structure of the aging blood vessels, particularly the arteries. For instance, NIA studies show that among those with the stiffest arteries, heart walls are thicker.

To picture how these and other changes influence cardiovascular health, imagine an animated computer graphic of the arteries at, say, age 25, when the walls are still fairly smooth, slick, and compliant. As the heart contracts, the aortic valve opens and blood is pumped into the aorta, the largest artery in the body, and flows up toward the neck, where the carotid artery branches off to take blood to the head and brain, and then down toward the rest of the body. When the aorta receives the rushing pulse of blood from the heart, it also receives pressure spreading from the walls of the heart to its own walls. This pressure travels along the aorta's walls in wave after wave until it reaches the walls of the smaller branching arteries that take the blood to the rest of the body. There, the speed of these pressure waves—known as pulse wave velocity—slows, and some are sent back through the aorta walls, becoming what are called wave reflections.

What Happens During Atherosclerosis?



Inflammation is a key factor in the development of atherosclerosis. 1 As LDL cholesterol accumulates in the arterial wall, it undergoes chemical changes and signals to endothelial cells to latch onto white blood cells circulating in the blood. These immune cells penetrate the intima and trigger an inflammatory response, devouring LDLs, to become fat-laden "foam cells" and 2 form a fatty streak, the earliest stage of atherosclerotic plaque. 3 The plaque continues to grow and forms a fibrous cap. Substances released by foam cells can eventually destabilize the cap, allowing it to rupture, causing a blood clot which can block blood flow and trigger a heart attack.

Atherosclerosis (ath-er-o-skle-RO-sis) is the build-up of fatty deposits called plaque on the inside walls of arteries. Plaque is a combination of cholesterol, other fatty materials, calcium, and blood components that stick to the artery wall lining. A hard shell or scar covers the plaque. As plaque builds up in an artery, the artery gradually narrows and can become clogged. As an artery becomes more and more narrowed, less blood can flow through. The artery may also become less elastic.

Most plaque buildup occurs in medium to large arteries and many investigators suspect that this buildup begins with changes in the endothelium, the innermost layer of the artery. These changes cause white blood cells to stick to the endothelial cells, weakening the barrier between the endothelium and the other layers of the artery. This allows fats, cholesterol, calcium, platelets, and cellular debris to accumulate in artery walls. In turn, this accumulation can stimulate other arterial wall changes that lead to the additional thickening of the endothelium and the formation of plaques.

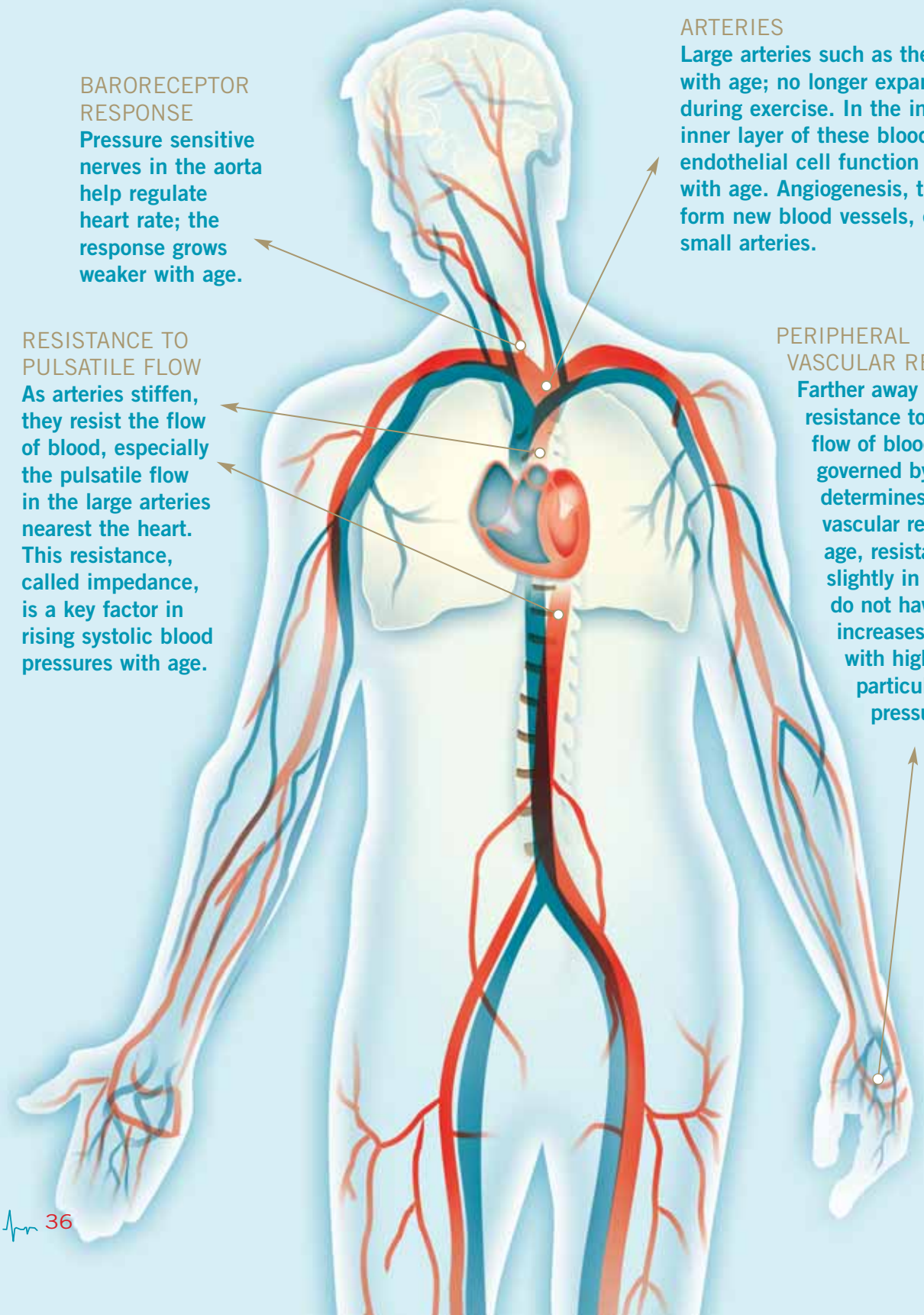
Plaques have various sizes and shapes. Some plaques are unstable and can rupture or burst. When this happens, it causes blood clotting inside the artery. If a blood clot totally blocks the artery, it stops blood flow completely. This is what happens in most heart attacks and strokes. There are usually no symptoms, such as pain, until one or more artery is so clogged with plaque that blood flow is severely reduced.

All of this takes time. In fact, atherosclerosis is a slow, progressive condition that often starts in childhood. But by age 65 it affects one out of every two adults. Scientists at the National Heart, Lung, and Blood Institute are studying why and how the arteries become damaged with age, how plaques develops and changes over time, and why plaques can break open and lead to blood clots. In particular, they have identified the age-related changes in the arteries discussed in this booklet as the major catalyst for the development of atherosclerosis. Research is underway to find drugs that might delay or prevent these age-related vascular changes and, in turn, reduce the risk of atherosclerosis.

There are a number of other risk factors, such as smoking, high blood pressure, and high blood cholesterol that can be modified with a diet, exercise, and other lifestyle changes. The more risk factors you have, the more likely it is that you have atherosclerosis. Talk with your health care provider about your risks for atherosclerosis and cardiovascular disease and what you can do to reduce them. •

Age and Arteries

Blood flows from the heart through the arteries (red blood vessels) and back to the heart through veins (blue blood vessels). Age brings numerous changes to the arteries including:



BARORECEPTOR RESPONSE

Pressure sensitive nerves in the aorta help regulate heart rate; the response grows weaker with age.

ARTERIES

Large arteries such as the aorta stiffen with age; no longer expand as much during exercise. In the intima, the inner layer of these blood vessels, endothelial cell function is impaired with age. Angiogenesis, the ability to form new blood vessels, declines in small arteries.

RESISTANCE TO PULSATILE FLOW

As arteries stiffen, they resist the flow of blood, especially the pulsatile flow in the large arteries nearest the heart. This resistance, called impedance, is a key factor in rising systolic blood pressures with age.

PERIPHERAL VASCULAR RESISTANCE

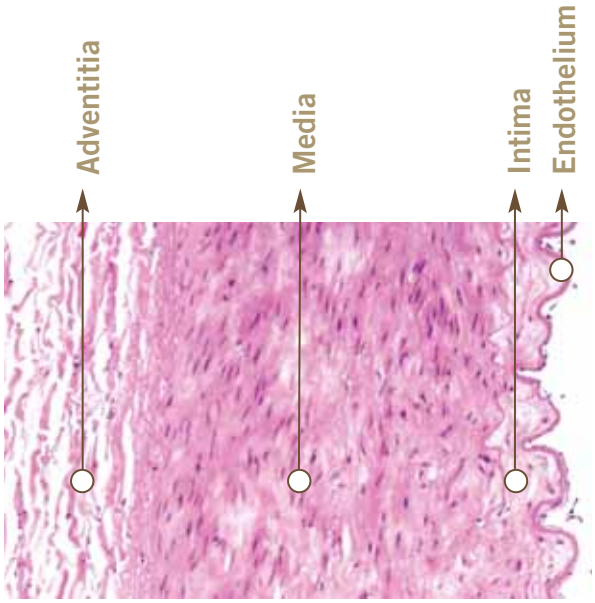
Farther away from the heart, resistance to the smoother flow of blood in the arteries, governed by arterioles, determines peripheral vascular resistance. With age, resistance increases only slightly in most people who do not have hypertension. It increases usually in people with high blood pressure, particularly high diastolic pressure.

Now, add 50 years to this picture. The arteries, including the aorta, grow stiffer and dilate; their walls become thicker, their diameter larger. As a result, the stiffer vessels no longer expand and contract as much as they once did with each heart beat. Eventually, the opposition to the flow of blood by the stiffer aorta walls increases significantly.

Along the walls of the stiffer aorta, the pressure waves move more rapidly, and as a result, the wave reflections occur sooner than they did before. The timing of the wave reflection, in fact, is one of the effects of arterial stiffness that can be measured noninvasively. Epidemiological studies using these measures have determined that high aortic pulse wave velocity (aPWV) is an independent predictor of arterial stiffness and cardiovascular disease and death.

As the walls of the large arteries become stiffer, diastolic blood pressure tends to drop and systolic blood pressure rises. The difference between these two numbers is called pulse pressure. High pulse pressure—greater than 60 millimeters of mercury—is associated with greater thickening and stiffening of arterial walls. In turn, arterial stiffening and thickening contribute to increased pulse pressure. Many studies have found that elevated pulse pressure is also an important risk factor for stroke and heart attack.

Next, picture the effects of movement—when a person sits up, stands up, or begins to walk or run—the heart rate increases and blood pressure changes. A group of pressure sensitive nerves in the base of the carotid artery respond by sending a message to the brain. The brain in turn sends a message back to the heart, which changes its rate and strength of contraction. This arterial/brain/heart message system is called the baroreceptor response. Blood vessels also dilate to allow for the extra blood flow. In addition, blood is turned away temporarily from those organs that don't need it (for instance, the stomach), so that more can be delivered to the working muscles.



A sectional view of the arterial wall. On the right is the intima, topped by a layer of cells called the endothelium. The endothelium acts as a barrier to prevent certain substances from entering the vessel wall. In the center, the media is composed of smooth muscle cells and a network of fibrous proteins. The outermost layer, the adventitia, is composed of connective tissue.

In the older picture, the baroreceptor response is blunted with age, perhaps as a result of stiffer arteries. Also, at maximum exercise, the large arteries do not dilate as much as in the younger picture. In essence, this age-related stiffening impedes pulsing blood flow from the heart and places an increased workload on the heart.

As the blood moves into the smaller arteries, the hydraulics change. The pulse smoothes out, the flow becomes more steady. The opposition to this steady flow is known as peripheral vascular resistance or PVR; so far studies show that among men, resting PVR does not change with normal aging, but that it does rise somewhat in women. PVR is actually elevated in people who have high diastolic blood pressure, but is also elevated, to a lesser extent, in people who have high systolic and nearly normal diastolic blood pressure. This condition, called systolic hypertension, is so common that a person age 55 or older has about a 65 percent chance of developing it. However, PVR is not

usually directly measured outside of a research laboratory setting because of the complexities involved. Instead, physicians monitor diastolic blood pressure. If it remains steady or increases rather than dropping in the presence of aortic stiffening, it's a sign of elevated PVR. (See *The Nitty Gritty of High Blood Pressure,* page 39)

Inside Every Artery…

Scientists are still sorting out why these aging changes in blood pressure and PVR occur and what can be done to prevent them. But one key focal point of research is the inner workings of the arterial wall.

At first glance a large artery resembles a simple rubber tube. But like many first impressions, this is a bit deceiving. The arterial wall is actually comprised of three intricate layers of tissue. The innermost layer, closest to the blood, is called the intima. The part of the intima nearest to the blood is a single layer of specialized cells, called endothelial cells, which sits atop the sub-endothelial space and a wall called the basement membrane. These endothelial cells act as a barrier to prevent certain substances from entering the vessel wall through the intima. Endothelial cells sense mechanical signals, such as blood pressure and flow, and chemical signals, such as oxygen tension, and temperature. In reaction to these signals, they secrete proteins called cytokines and chemokines as well as growth factors and other substances that help regulate the structure and function of the arteries.

The smooth muscle cells in the media, the middle layer of the artery, are surrounded by a network of fibers primarily made of two proteins, collagen and elastin. The elastin forms concentric rings within the vessel wall. The outermost layer, the aventitia, is composed of connective tissue and small blood vessels that feed the walls of large arteries. Together, these three layers of artery wall surround the lumen, the opening that blood flows through on its journey throughout the body. With age, each of these layers change in complex ways.

…Time Takes its Toll

Aging, for instance, triggers thickening of the intima and stiffening of the arterial walls. This occurs, in part, because of a fierce molecular struggle.

Healthy endothelial cells produce nitric oxide, an important signaling molecule that helps keep arteries supple. When nitric oxide enters a cell, it stimulates a biochemical process that relaxes and dilates blood vessels. Nitric oxide also helps keep atherosclerosis in check by preventing platelets and white blood cells from sticking to the blood vessel walls. The molecule also can curb the abnormal growth of vascular muscle, which can thicken blood vessel walls.

But unhealthy endothelial cells are a different story. In these cells, nitric oxide regulation is impaired. To make nitric oxide, endothelial cells need L-arginine, an amino acid that is one of the basic building blocks of proteins, and an enzyme called nitric oxide synthase (NOS). Normally, endothelial cells have plenty of L-arginine and NOS. But NOS is often in short supply in aging blood vessels. In addition, people who have heart disease or who are at high risk of developing it produce a modified amino acid called asymmetric dimethylarginine (ADMA). ADMA blocks the production of nitric oxide from L-arginine. Even if sufficient amounts of nitric oxide are produced, it can be inactivated by oxygen free radicals, unstable molecules that injure vascular tissue. In any case, without adequate levels of biologically available nitric oxide, endothelial cells in the intima can't function properly. In fact, some researchers consider decreased availability of nitric oxide in the endothelium as one of the earliest signs of arterial aging and a pathological sign of atherosclerosis and high blood pressure. However, much of this complex process remains a mystery and scientists continue to explore precisely how nitric oxide production and bioavailability affect blood vessels.

The Nitty Gritty of High Blood Pressure

By age 60, high blood pressure affects one in every two Americans. Hypertension, as doctors call it, was once thought to be a normal part of aging. But researchers now know that high blood pressure is dangerous at any age.

When we talk about blood pressure, what we're actually referring to is the pressure within the aorta and the large arteries that connect to it. Blood pressure is measured in millimeters of mercury (mmHg) and recorded as two numbers. Systolic blood pressure (the top number in a blood pressure reading) is the maximum pressure that occurs in the blood vessels when the heart contracts. As the heart relaxes between beats, the pressure dissipates. This low pressure is measured as diastolic (the bottom number) blood pressure.

Systolic blood pressure is largely determined by the stiffness of the arteries and the amount of blood pumped through them during a heart beat. Many doctors once believed that as we got older our bodies needed increased systolic blood pressure to push blood through stiffened arteries. But researchers now know that this increase is not normal, and that high blood pressure at any age significantly increases the risk of heart attack, strokes, and kidney failure.

Today, most experts recommend that blood pressure not exceed 120/80 mmHg. Smoking, high cholesterol, and diabetes can elevate the risk of developing high blood pressure. Check your blood pressure regularly. If it is elevated, talk with your doctor. Exercise, dietary changes and, in some cases, medication can make a difference. •

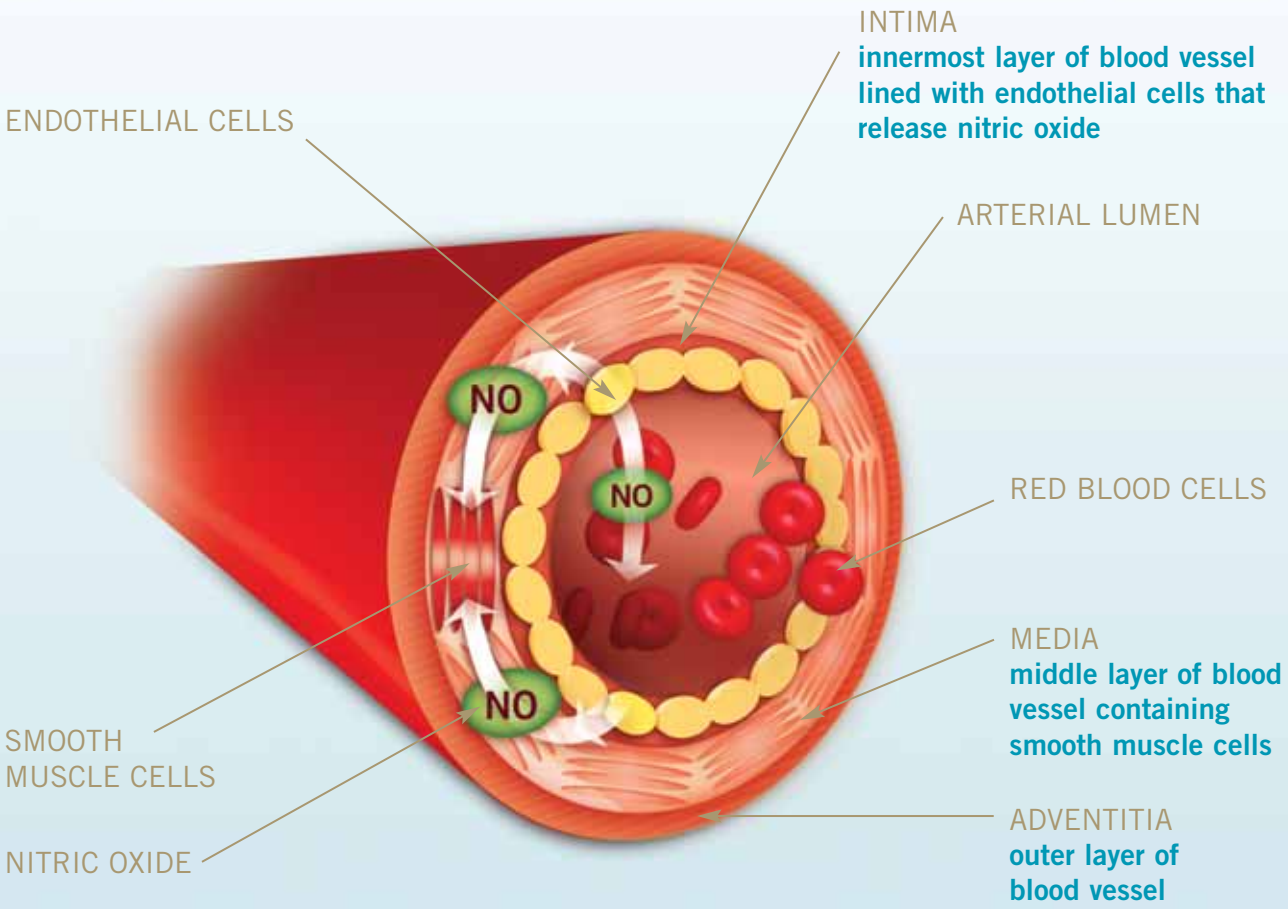
High blood pressure is more common with age. Getting your blood pressure checked regularly is one of the best ways to detect this condition. Regular aerobic exercise can help keep it within the normal range.

But they do know that endothelial cells depend on nitric oxide to help subdue the production of oxygen free radicals. Nitric oxide molecules can eradicate some of these free radicals, but in the process they also destroy themselves. This leaves less nitric oxide available to help endothelial cells keep arteries in tiptop shape.

Angiotensin II, a growth factor involved in this process, is more prevalent in aging arteries. In addition to increasing free radical production, angiotensin II decreases nitric oxide production and stimulates blood vessel inflammation. It also can cause vessels to tighten and raise blood pressure, forcing the heart to work harder.

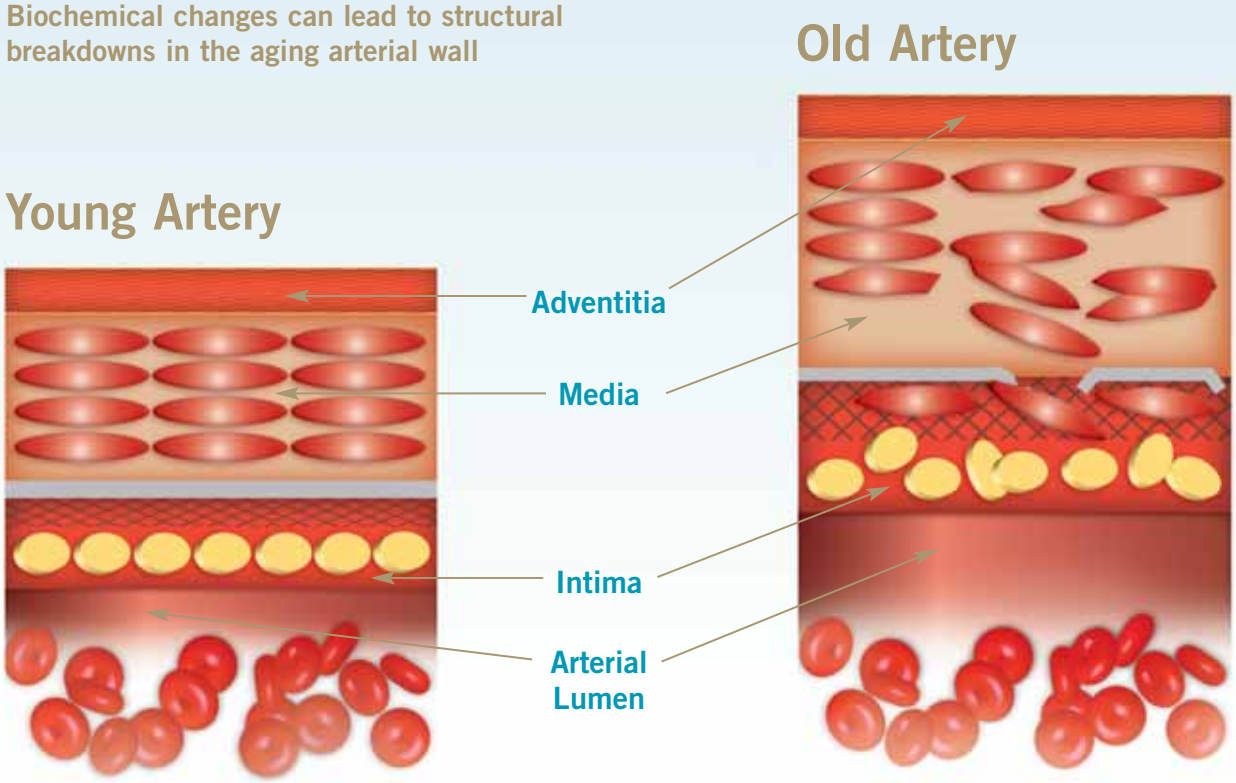
Much of angiotensin II's damage is done in partnership with an enzyme called NADPH oxidase, the primary source of free radicals in the arteries. After angiotensin II activates it, NADPH oxidase causes an increase in production of superoxide, a free radical. Superoxide binds with nitric oxide to create an even more potent free radical called peroxynitrite. Peroxynitrite then binds to proteins and nitrites, harming them. Like other free radical processes, this chain of events steals bioavailable nitric oxide away from endothelial cells, leaving them more vulnerable to damage. But the impact of angiotensin II isn't limited to the intima. It also has an important role in age-associated alterations of the media, the middle layer of the arterial wall.

Production of Nitric Oxide (NO) in Arteries



Arteries: Young and Old

Biochemical changes can lead to structural breakdowns in the aging arterial wall



In addition to depleting nitric oxide, free radicals can damage the membranes and DNA of endothelial cells in the intima and smooth muscle cells in the media. Free radical damage is one of many things that can induce some of these cells to stop functioning, shrink, and ultimately die in a process known as apoptosis. Apoptosis may contribute to the decline in cardiovascular health as we age. Free radicals also can oxidize proteins, altering their structure and function. As a result, these proteins can't work properly, and this can trigger a cascade of cellular alterations that promote stiffening and thickening of arterial walls and contribute to atherosclerotic plaque build up.

Stuck in the Middle with You

With age, some smooth muscle cells in the media die causing the remaining ones to work harder and grow larger. Over time, other alterations cause some smooth muscle cells to stop contracting as usual. Instead, these cells begin producing excessive amounts of proteins and other matrix substances, creating an imbalance of elastin and collagen in the media. As the amount of collagen increases in the blood vessel wall, it tends to bind to glucose molecules, forming crosslinks known as advanced glycation end products (AGES). This process, which has been compared to what happens as turkey is roasted in an oven, is slow and complex. But as more AGES form, the collagen strands in the media turn brown, become crosslinked, and become less supple. Age takes its toll on elastin, too. It becomes overloaded with calcium, stretches out, and eventually ruptures, further eroding an artery's flexibility.

Scientists studying this process are particularly intrigued by matrix metalloprotease-2 (MMP2), an enzyme activated by angiotensin II as well as many

...angiogenesis can stimulate the growth of new collateral small vessels around narrow spots or blockages in the arteries that threaten to reduce blood flow to the heart. Scientists are still unraveling why this happens, but as age-associated changes and damage accumulate in endothelial cells, they secrete less of the critical growth factors needed for angiogenesis.

other signals. Although many of its functions are unclear, studies in rodents, monkeys, and humans suggest MMP2 helps break down key components of the basement membrane, the barrier that separates the intima from the media in artery walls. MMP2, in conjunction with angiotensin II, also activates other growth factors, such as transforming growth factor, which might stimulate collagen and cell growth, the development of fibrous tissue, and contribute to thickening of the intima. In addition, this combination of MMP2 and angiotensin II activates PDGF-B, a growth factor, which acts as an attractant that lures smooth muscle cells to migrate from the media to the intima.

But in smaller blood vessels, the activity of PDGF-B and other growth factors, such as vascular endothelial growth factor (VEGF), tend to decline with age. These growth factors play an important role in a process called angiogenesis that leads to the development of new small blood vessels. In some cases, angiogenesis can stimulate the growth of new collateral small vessels around narrow spots or blockages in the arteries that threaten to reduce blood flow to the heart. As we age, however, this process switches off. Enzymes that break down collagen also seem to be involved in this process and are less active as we get older. Scientists are still unraveling why this happens, but as age-associated changes and damage accumulate in endothelial cells, they secrete less of the critical growth factors needed for angiogenesis. Angiogenesis also depends, in part, on the availability of nitric oxide, which declines with age. In addition, there appears to be an age-associated decrease in the number of endothelial progenitor cells. These adult stem cells are produced in the bone marrow and circulate in the bloodstream.

Under certain circumstances, endothelial progenitor cells can differentiate into endothelial cells, which are needed to form new blood vessels or repair damaged ones. In essence, progenitor cells are the "mothers" of "daughter" endothelial cells. As the number of progenitor cells declines, angiogenesis is less likely to occur. Researchers are investigating ways, such as gene and cell therapy, to reactivate angiogenesis in older people who have cardiovascular disease. But scientists have much to learn about the safety and efficacy of these techniques. (See *Can Gene Therapy Be Used to Treat Heart Problems?* page 43)

From Balloon to Bicycle Tire

Scientists are still piecing together how, or even if, many of these various processes interact. But they do know that, as the result of these and other age-associated changes in large arteries, the endothelial barrier in the intima becomes more porous. Some of the signals these cells transmit to the smooth muscle cells in the media become garbled. In turn, these smooth muscle cells can mistakenly perceive that an injury has occurred. They move into the intima, multiply, and produce collagen and other molecules. In reaction, the endothelial cells produce substances that send signals to circulating blood cells to help out in the repair process. Unfortunately, in their effort to help, blood cells stick to endothelial cells instead of flowing smoothly through the blood vessel. The net impact of these interactions is that the intimal-media layer

Can Gene Therapy be Used to Treat Heart Problems?

In the future an experimental technique, called gene therapy, may allow doctors to treat heart disease and other cardiovascular disorders by inserting a gene into a patient's cells instead of using drugs or surgery. Investigators are testing several approaches to gene therapy including:

- Replacing a mutated gene that causes disease with a healthy copy of the gene
- Inactivating or "knocking out" a mutated gene that is functioning improperly, or
- Introducing a new gene into the body to help fight a disease.

The NIH has been on the cutting edge of this research. More than a decade ago, for instance, cardiovascular investigators began experimenting with ways to increase the supply of certain growth factors through gene therapy. If more growth factors could be produced, scientists theorized they might stimulate angiogenesis—the growth of new small blood vessels called capillaries.

Knowing the genes that code for the growth factors, the investigators found ways to add copies of these genes to heart muscle. To get genes to the myocytes, they engineered molecular delivery trucks called vectors for the genes. These vectors, made from inactivated adenoviruses—the same viral culprits that cause the common cold—were injected into rats. Scientists hoped the vectors would unload their DNA cargo, which then would begin producing the proteins needed to induce capillary growth. And in this experiment, that's exactly what happened. One of the vectors worked.

More recently, scientists successfully used gene therapy in older rats to increase the activity of the gene that produces calcium pump proteins on sarcoplasmic reticulum, the cellular storage bin for calcium. This therapy significantly improved heart muscle contraction in these rodents. In another animal study, researchers at The Johns Hopkins School of Medicine in Baltimore used gene therapy to convert a small region of guinea pig heart muscle tissue into specialized pace making cells. Potentially, this technique could one day lead to the development of genetically engineered, biological pacemakers to replace implantable electronic devices. However, scientists must overcome many technical challenges before gene therapy will be a practical approach to treating disease. •

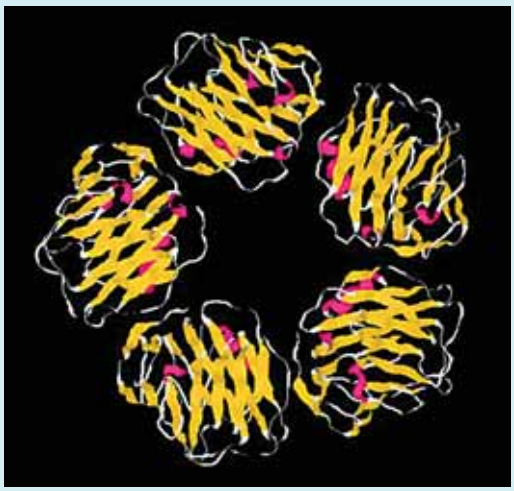
Every day, your body's cells depend on genes, coded segments of DNA (below), to tell them how to work. Gene therapy is an exciting area of scientific research that one day could help treat inherited and acquired diseases, including cardiovascular disorders.

The NIH has been on the cutting edge of this research. More than a decade ago, for instance, cardiovascular investigators began experimenting with ways to increase the supply of certain growth factors through gene therapy.

New Blood Test May Help Doctors Detect Emerging Heart Disease

Blood often tells the story of our lives. Tests that measure blood cholesterol levels and other cardiovascular risk factors have become a routine part of health screenings. And in the future, doctors may check yet another blood test—one that measures inflammation—that may help them better assess the risk of disease in the aging heart and arteries.

The test measures levels of C-reactive protein (CRP), a substance produced in the liver, which is often elevated in people who have rheumatoid arthritis and other diseases that cause chronic inflammation. Several studies have indicated that increased blood levels of CRP in otherwise healthy people are associated with an increased risk of heart attack, stroke, and other cardiovascular problems.



Some studies have linked high-levels of C-reactive protein, above, to cardiovascular disease. In the future, a blood test for this substance might help doctors better evaluate a person's risk of heart attack or stroke.

Scientists are still investigating whether CRP is merely an indicator of inflammation or if it has an active role in this process. In any case, cardiovascular risk factors such as excessive weight, diabetes, and a sedentary lifestyle are associated with high CRP blood levels. Healthy people with CRP levels less than 1 milligram per liter of blood are considered at the lowest risk of a cardiovascular event in the next 10 years. Depending on medical history and other factors, a person at intermediate risk—1 to 3 milligrams of CRP per liter of blood—could have up to a 20 percent risk of having a heart attack in the next decade. Those with CRP levels of 3 milligrams or more per liter have the highest risk.

However, researchers stress that inflammation is just one of many factors that could increase your risk of cardiovascular disease as you get older. To date no evidence has emerged to suggest that treating people for elevated CRP alone improves survival or reduces cardiovascular complications. For now, detection and treatment of more well-established risk factors, such as high blood pressure and high blood cholesterol, remains a greater priority.

But some treatments for these other risk factors could help lower CRP. The same lifestyle changes, for instance, that help lower cholesterol—regular exercise, a healthy diet, weight loss, and quitting smoking—can also help reduce inflammation. Aspirin and other drugs, including cholesterol-lowering medications such as statins, can decrease CRP levels as well. •

...some treatments for these other risk factors could help lower CRP. The same lifestyle changes, for instance, that help lower cholesterol—regular exercise, a healthy diet, weight loss, and quitting smoking—can also help reduce inflammation.

"Endothelial cells are the prima donnas within the blood vessels. They control almost every activity that occurs in the vessels, and they're fundamentally altered with age," Dr. Lakatta says. "People who maintain a healthy endothelium as they get older and those who make an effort to do things that promote the repair of injured endothelium can reduce the risk of heart attacks and strokes caused by atherosclerosis or hypertension."

thickens, contributes to arterial stiffness, and creates a fertile environment for the development of atherosclerosis in aging arteries.

The cumulative effect of all these age-related changes can be boiled down to this: the ability of larger blood vessels to expand and contract diminishes, the lumen enlarges, and the arterial walls thicken. The result is "hardened" or stiffened arteries that set the stage for the onset of high blood pressure, elevated pulse wave velocity, atherosclerosis, and other precursors of cardiovascular disease. The more severe the effects of aging are on the blood vessels, the easier it is for atherosclerosis, hypertension, and other processes to do damage and, in turn, have an effect on the rate of aging in the vessels. Smoking, lack of exercise, a poor diet, and obesity also can exacerbate these effects.

It's this cycle, with age as the principal instigator, which gradually helps change youthful and healthy blood vessels into old and potentially diseased ones. In a sense, this progression transforms a young person's arteries, which are like soft latex balloons, into the equivalent of rigid, bulky bicycle tires in later life.

However, arterial stiffness and intimal-medial thickening occur at varying rates in different people. Studies suggest that the rate of both of these age-related changes predict stroke, heart disease, and other cardiovascular problems. For example, in one large study that followed healthy volunteers who had no previous symptoms of heart disease, those who had the greatest amount of intimal-media thickening were four times more likely to develop cardiovascular conditions over the next 7 years compared to those with the least arterial thickening. Similarly, studies have shown that healthy people with the stiffest blood vessels were three times more apt to develop high blood pressure over a 5-year span than those with more pliable vessels. In yet another large-scale study, involving 3,075 healthy older people, those who had the highest pulse wave velocity (PWV)—a measure of arterial stiffness—were three times more likely to die of cardiovascular disease than those who had the lowest PWVs.

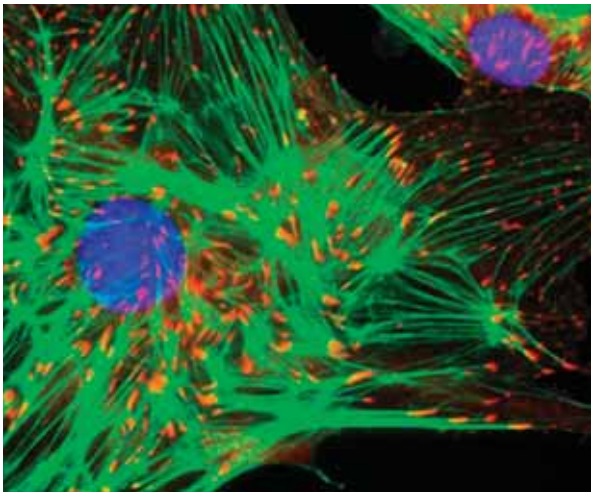
"Clearly, many people of middle and advanced age whom we once thought of as healthy actually aren't," Dr. Lakatta says. "It is becoming more apparent that changes in the aging circulatory system, even among those who don't have outward symptoms, precede and predict a higher risk of developing cardiovascular diseases. The greater these changes are, the greater is the risk for getting these diseases."

Keeping Your Arteries Healthy

The well-being of your arteries depends on a healthy endothelium, the inner lining of your blood vessels.

"Endothelial cells are the prima donnas within the blood vessels. They control almost every activity that occurs in the vessels, and they're fundamentally altered with age," Dr. Lakatta says. "People who maintain a healthy endothelium as they get older and those who make an effort to do things that promote the repair of injured endothelium can reduce the risk of heart attacks and strokes caused by atherosclerosis or hypertension."

...moderate exercise, such as running, walking, or swimming can reduce body fat, increase lean muscle mass, decrease blood pressure, and increase HDL cholesterol levels. All of these exercise-induced changes can have a positive influence on endothelial cells.



Endothelial cells, such as this one, produce substances that regulate the structure and function of the arterial wall. Endothelial cells may play a critical role in the aging of arteries and the onset of high blood pressure and atherosclerosis.

Although scientists still have much to learn about the endothelium and what can be done to keep it healthy, a number of studies suggest that certain modifiable risk factors can have an important impact on the cardiovascular system. For instance, regular moderate exercise, such as running, walking, or swimming can reduce body fat, increase lean muscle mass, decrease blood pressure, increase HDL cholesterol (the "good" cholesterol) levels, and lessen the extent of arterial stiffening. All of these exercise-induced changes can have a positive influence on endothelial cells. (See *Exercise: Your Heart's Best Friend,* page 47)

In addition, scientists have long known that tobacco smoke contains numerous toxic compounds, such as carbon monoxide, that promote endothelial cell damage. Smoking also increases blood pressure and heart rate. Free radicals in smoke slash the amount of nitric oxide available in the blood stream. Nitric oxide, as you may recall, is a signaling molecule that helps keep arteries pliable. Because nicotine causes narrowing of blood vessels, less oxygen is transported to the heart. If you smoke, blood platelets become stickier and are more apt to form clots in your arteries.

As we mentioned earlier, high blood pressure—hypertension—causes blood vessels to thicken, diminishes production of nitric oxide, promotes blood clotting, and contributes to the development of atherosclerotic plaques in the arteries. Blood pressure is considered high when systolic pressure exceeds 140 mmHg and when diastolic blood pressure is higher than 90mmHg.

Excessive weight increases the risk of high blood pressure and can increase the likelihood that you'll have high blood triglycerides and low HDL cholesterol, Dr. Lakatta says. Being overweight can also increase the probability you'll develop insulin resistance, a precursor of diabetes. (See *Metabolic Syndrome Accelerates Aging of Arteries,* page 48)

Diabetes, a disease in which the body does not produce or properly use insulin, becomes more common as we age. In fact, nearly half of all cases are diagnosed after age 55. Atherosclerosis develops earlier and is more aggressive in people who have diabetes. In part, this occurs because diabetes causes the endothelium to produce excessive amounts of superoxide anion, a free radical that destroys nitric oxide. People age 65 and older who have diabetes are nearly four times more likely than those who don't to develop peripheral vascular disease, a condition that clogs the arteries that

Exercise: Your Heart's Best Friend

In one of her better-known gags, comic Ellen DeGeneres quips, "My grandmother started walking five miles a day when she was 60. Now she's 97 years old and we don't know where the heck she is."

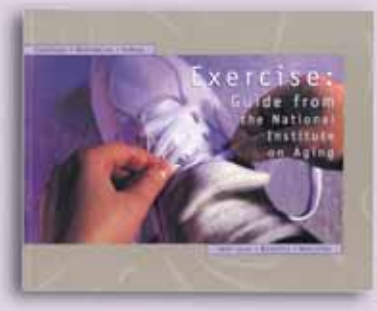
Funny, yes. But regular physical exercise is no joke. In fact, it may be the most important thing a person can do to fend off heart disease, stroke, and other age-associated diseases. Emerging scientific evidence suggests that people who exercise regularly not only live longer, they live better.

Scientists have long known that regular exercise causes certain changes in the hearts of younger people: Resting heart rate is lower, heart mass is higher, and stroke volume is higher than in their sedentary counterparts. These differences make the heart a better pump. Evidence now suggests these changes occur even when exercise training begins later in life, at age 60 or 70, for instance. In other words, you don't lose the ability to become better physically conditioned. In addition, several studies have shown that exercise not only helps reduce debilitating symptoms such as breathlessness and fatigue in people who have heart failure, it also prolongs life.

Exercise training may be effective because it appears to improve the function of virtually every cell in the cardiovascular system. Animal studies, for instance, suggest that regular aerobic workouts help heart muscle cells remove calcium from their inner fluid at a faster rate after a contraction. This improved calcium cycling allows the heart to relax more and fill with more blood between beats.

Exercise also improves blood vessel elasticity and endothelial function, in part, by blocking the production of damaging free radicals and maintaining the production of nitric oxide, an important signaling molecule that helps protect the inner layer of the arteries. Together, these changes can slow the progression of atherosclerosis and other age-related cardiovascular conditions.

Endurance exercises such as brisk walking increase your stamina and improve the health of your heart, lungs, and circulatory system. But other exercises are equally important to maintaining health and self-reliance as you get older. Strength exercises, for instance, build muscles and reduce your risk of osteoporosis. Balance exercises help prevent a major cause of disability in older adults: falls. Flexibility or stretching exercises help keep your body limber. As part of a daily routine, these exercises and other physical activities you enjoy can make a difference in your life as you get older. •



This free booklet is available in both English and Spanish from the NIA. The booklet is also available online at ***www.niapublications.org/exercisebook/index.asp****.*

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Metabolic Syndrome Accelerates Aging of Arteries

Many older Americans have high blood pressure or high blood sugar or just a bit too much fat on the belly. While each of these conditions alone is bad enough, having all of these conditions at once—a cluster called metabolic syndrome—magnifies the risk of developing heart disease and stroke. And NIA scientists may have discovered a reason why: Metabolic syndrome appears to accelerate stiffening and thickening of the arteries.

Angelo Scuteri MD, PhD

Metabolic syndrome—also known as syndrome X or insulin resistance syndrome—may affect as many as 47 million Americans, according to the Centers for Disease Control and Prevention (CDC). After age 50, a person has a better than one in three chance of developing this group of medical conditions characterized by insulin resistance and the presence of obesity, abdominal fat, high blood sugar and triglycerides, low HDL (good) blood cholesterol, and high blood pressure.

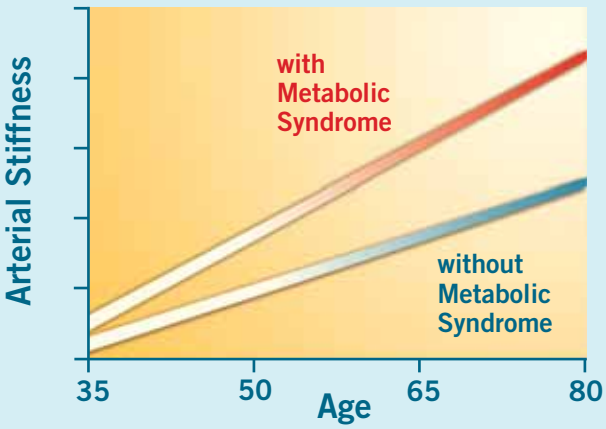
To determine the effects of metabolic syndrome on aging arteries, NIA researchers studied 471 participants—average age 59—in the Baltimore Longitudinal Study of Aging (BLSA). None of these participants had any detectable signs of cardiovascular disease when initially examined. But those who had three or more conditions associated with metabolic syndrome developed stiffer and thicker arteries at earlier ages than those who didn't have the syndrome.

"It's as if the metabolic syndrome makes your blood vessels older," says Angelo Scuteri, MD, PhD, an investigator at the NIA's Laboratory of Cardiovascular Science. "If you have metabolic syndrome, when you are 40 your arteries look like they are 55 or 60."

As this work moves forward, scientists hope they can determine how metabolic syndrome promotes accelerated aging in the arteries and perhaps discover ways to prevent or treat it. •

Arterial stiffness, a risk factor for age-related cardiovascular diseases, increases more rapidly in older people who have metabolic syndrome.

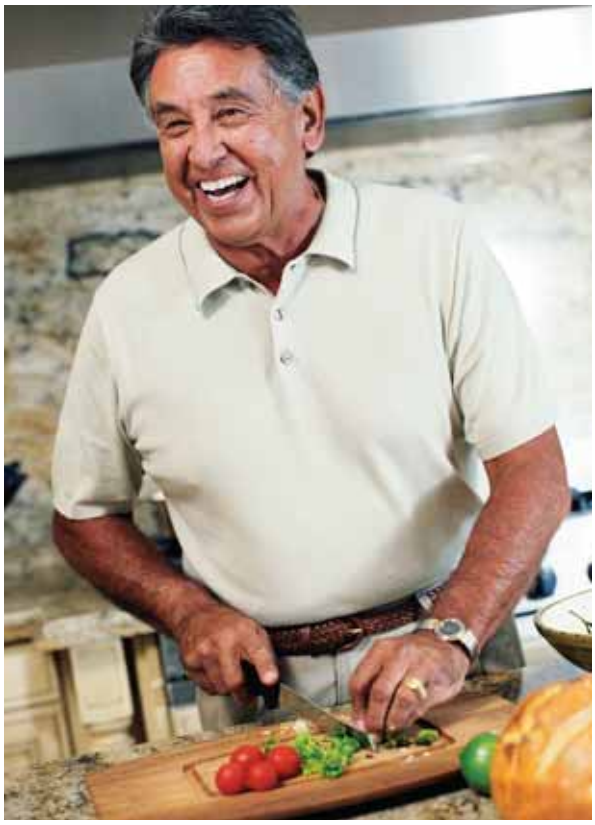
Metabolic Syndrome Increases Arterial Stiffness



Age-effect p<0.0001, MS effect p<0.01, Interaction n.s.

carry blood to the legs or arms. And, cardiovascular diseases and stroke are leading causes of diabetes-related deaths. If you suspect you have or are at risk for diabetes, check with your doctor. Symptoms include increased thirst, increased hunger, fatigue, increased urination—especially at night, unexplained weight loss, blurred vision, and slow healing of wounds and sores.

Researchers have also found that stress reduction techniques, such as taking a walk, practicing yoga, or deep breathing are important to cardiovascular health. Emotional stress triggers the release of adrenaline from the adrenal gland and noradrenaline from the nerve endings in your heart and blood vessels. These hormones make the heart beat faster and adversely affect blood vessels. Under stress, an older person's blood pressure rises more rapidly and stays higher longer than a younger person's because the older person's blood vessels are stiffer and have lost much of their elasticity.



Fruits and vegetables are key components of a heart-healthy diet. These food contain compounds that can help subdue free radicals, prevent oxidation in the arteries, and lower blood cholesterol levels, all of which are important for maintaining a thriving endothelium.

Healthy Foods, Healthy Arteries: Is There a Connection?

What you eat can help keep your heart and arteries healthy—or lead to excessive weight, high blood pressure, and high blood cholesterol—three key factors that increase the risk of developing cardiovascular disease, according to the National Heart, Lung, and Blood Institute. Based on the best available scientific evidence, the American Heart Association (AHA) recommends a diet that includes a variety of fruits, vegetables, and grains, while limiting consumption of saturated fat and sodium.

Fruits and vegetables have lots of antioxidants such as vitamin C and vitamin A that neutralize free radicals and may prevent oxidation in the arteries, dietary experts say. Fruits and vegetables also contain plenty of soluble fiber, a substance that has been shown to reduce blood cholesterol levels, which is healthy for the endothelium.

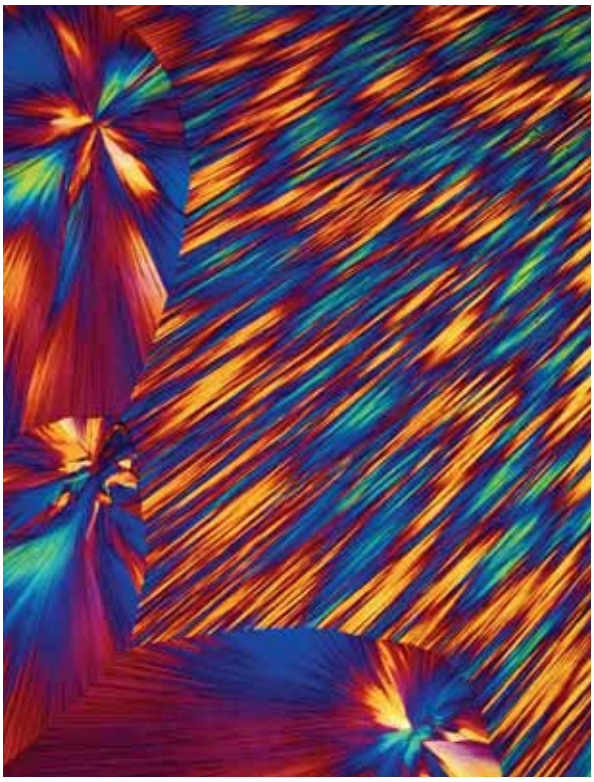
Breads, cereals, and other grain foods, which provide complex carbohydrates, vitamins, minerals, and fiber, are associated with a decreased risk of cardiovascular disease, according to the AHA Dietary Guidelines. However, some studies suggest

Based on the best available scientific evidence, the American Heart Association (AHA) recommends a diet that includes a variety of fruits, vegetables, and grains, while limiting consumption of saturated fat and sodium.

Control over the condition of our arteries may also lie in how much salt we consume. In cultures where little sodium (in the form of salt) is consumed, blood pressures do not rise with age.

eating less sugar, breads, and other simple and complex carbohydrates can lower blood insulin levels and decrease body fat and weight—three factors that are linked to an increased risk of heart disease and stroke. In recent years, a number of dietary recommendations based on these findings have become popular and are currently catching the public's awareness. While contentious, these are important issues and long-term studies are required to determine the risks and benefits of such diets, Dr. Lakatta says.

Blood cholesterol, shown here in a crystallized image, is one of many modifiable risk factors that contribute to the onset of atherosclerosis and cardiovascular disease in later life. Dietary changes and regular exercise can help keep blood cholesterol levels under control.



Saturated fats are usually solid at room temperature. These fats are primarily found in animal foods like meat, poultry, and dairy products like butter. Saturated fats tend to raise levels of "bad" low-density lipoprotein (LDL) and increase the risk of atherosclerosis. In fact, within 2 hours of eating a high saturated fat meal, endothelial cells don't work as well. Such meals can cause a temporary 50 percent dip in endothelial function, even in healthy young people who have no risk factors for atherosclerosis, Dr. Lakatta says.

In addition to saturated fats, some scientists are concerned about trans-fatty acids—unsaturated fats that have been artificially solidified by food manufacturers in a process called hydrogenation to make products like margarine and vegetable shortenings. These scientists suspect that trans-fatty acids, which are often described as hydrogenated or partially hydrogenated fats on many food labels, are more damaging to the heart and arteries than saturated fats.

But researchers have found other types of fats may be beneficial. Monounsaturated fats, found mainly in plant foods such as peanuts and olives, help lower LDL cholesterol. Like polyunsaturated fats, monounsaturated fats are usually liquid at room temperature. Polyunsaturated fats, found in fish, nuts, and dark leafy vegetables, have been getting a lot of attention from scientists in the past few years. They've concluded that one type of polyunsaturated fat—omega-3 fatty acid—found in fish may promote several things that improve endothelial function, including increasing nitric oxide production, slashing the production of free radicals and other substances that cause inflammation, and boosting HDL cholesterol levels. Fish

such as salmon, herring, and mackerel are good sources of omega-3s.

Control over the condition of our arteries may also lie in how much salt we consume. In cultures where little sodium (in the form of salt) is consumed, blood pressures do not rise with age. Cultural differences have also been found in arterial stiffness. One study compared rural and urban populations in China. The urban population consumed much higher levels of sodium than the rural groups. And they had stiffer arteries. Other researchers found that sodium appears to accelerate age-associated stiffening of arteries. In particular, sodium promotes thickening of aging arterial walls, reduces the amount of nitric oxide available to endothelial cells, and promotes the formation of oxygen free radicals. But shifting to a low sodium diet, research suggests, can begin to diminish arterial stiffness in as little as 2 weeks.

Most of the sodium in your diet comes from processed foods. The remaining is added at the table and while cooking. Scientists who study this issue suggest limiting the amount of sodium that you consume from all these sources to no more than 1,500 milligrams (mg) each day (an average American adult consumes about 3,300 milligrams daily). They recommend reading food labels carefully and buying foods that say "reduced sodium," "low in sodium," "sodium free," or "no salt added." Some dietitians suggest seasoning foods with herbs and spices like oregano, onion powder, or garlic instead of sodium.

Scientists suspect the more lifestyle changes, including diet and exercise, you can incorporate into your life, the better off your arteries will be, because these interventions work independently as well as in unison to promote the vitality of endothelial cells and contribute to reducing the risk of cardiovascular disease.

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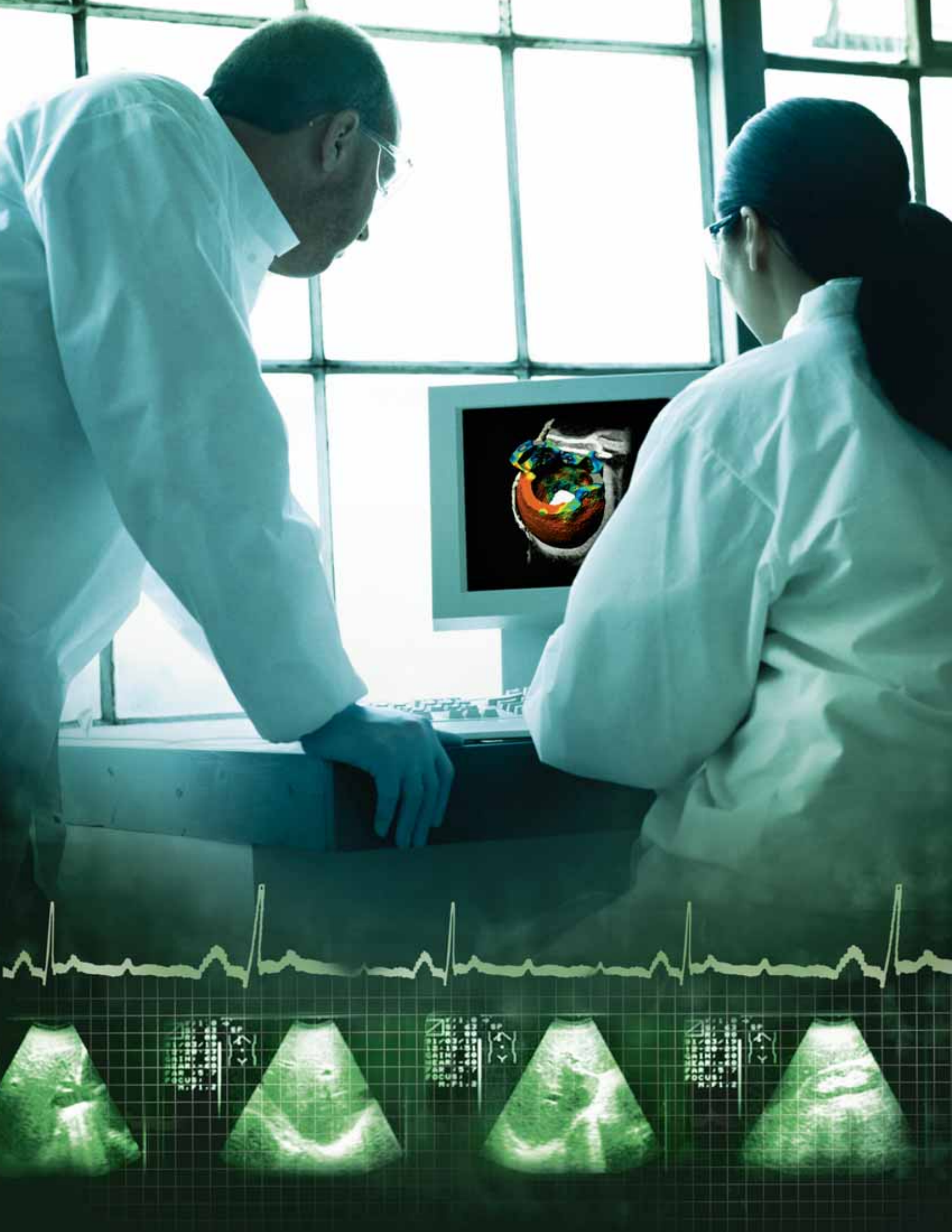


WHAT LIES *Ahead*

He is the best physician who is the most ingenious inspirer of hope.

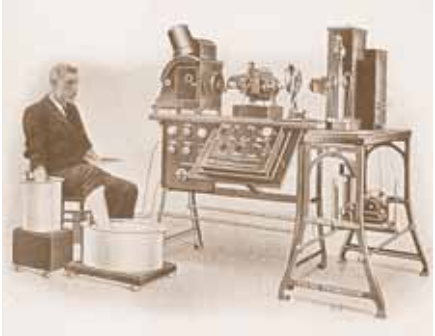
SAMUEL TAYLOR COLERIDGE, ENGLISH POET AND PHILOSOPHER, 1772-1834

In 1903, Dutch physiologist Willem Einthoven, MD, PhD invented the electrocardiograph, a machine that measures the minute electrical currents generated by the heart. Initially, it was a cumbersome and costly device, taking five technicians to operate. During the procedure, patients had to place both hands and both feet in buckets of water. But as a result of this advance cardiologists began, for the first time, to fully understand the electrical processes involved in generating the heart beat. With this knowledge, they were able to more precisely diagnosis certain cardiovascular problems.

A little more than a century later, scientific ingenuity has led to the development of many other advances. Scientists, for instance, have developed magnetic resonance imaging and other noninvasive ways to study the aging heart. Researchers have discovered a host of innovative drug treatments to help the ailing heart and arteries work better. And cardiologists and surgeons have successfully pioneered the use of cardiac catheterization, cardiovascular stents, implantable pacemakers, bypass surgery, and heart transplants.

No doubt about it, doctors know more about the heart and how to keep it healthy than at any other time in history. In just the past 30 years, gerontologists have revolutionized ideas about what happens in the older heart. They've learned, for instance, that age-related changes in the structure and function of the heart occur in virtually every person. Mounting evidence suggests that some of these changes, previously thought to be a part of normal aging, precede and predict the onset of cardiovascular diseases, even among those who do not yet have signs or symptoms of disease. But they've also learned that preventive measures, such as getting regular exercise, eating a healthy diet, and not using tobacco, can have a profound impact on the aging cardiovascular system.

In the future, interventions to slow accelerated aging of the heart and arteries in apparently healthy young and middle-age people could prevent or delay the onset of heart disease, stroke, and other cardiovascular disorders in later life, Dr. Lakatta says. These interventions may take many forms. For instance, the more we understand about the changes that take place in cells and molecules during aging, the closer we get to the possibility of designing drugs targeted to those changes. Gene therapies can also target specific cellular changes and could potentially be a way to intervene in the aging process.



Willem Einthoven, MD, PhD, Dutch physiologist

Achieving these goals will likely require considerable effort and as much, or perhaps even more, ingenuity and innovation in the coming years as has been shown in the past. NIA investigators and others are already taking steps to meet these challenges. They still have many questions to answer and mysteries to solve. But as this work progresses and scientists unravel more of the aging heart's secrets, the hope of forestalling cardiovascular disease and improving the quality of life for older people may come closer to reality.

GLOSSARY

ACTION POTENTIAL – An abrupt, transient change in the electrical charge along a heart muscle cell membrane; the first of several steps leading to the cell's contraction.

ADVENTITIA – The outermost layer of arterial wall; it is composed of connective tissue.

AFTERLOAD – The mechanical load encountered by the heart following the onset of contraction; the forces that resist the flow of blood from the heart. The afterload may increase with age due to increasingly stiff arteries and an increased tone of the smaller arteries.

ANGIOTENSIN – A chemical that constricts blood vessels, which raises blood pressure.

AORTA – The largest artery in the body. It conducts blood away from the heart, then branches into many smaller arteries that take blood to the rest of the body. The diameter of the aorta enlarges with age and its walls become stiffer.

ARTERIES – Blood vessels that carry blood away from the heart to all parts of the body. Some enlarge with age and become thicker and stiffer. Arterial walls consist of three layers: the intima, media, and adventitia.

ARTERIOLES – The very small arteries that take blood from the arteries to the capillaries.

ATHEROSCLEROSIS – A condition of the arteries in which the interior of the artery wall is made thick and irregular by deposits of fatty substances and invasive cells from the blood and arterial wall and matrix substances synthesized by the cells.

ATRIOVENTRICULAR NODE – A group of special conduction fibers at the base of the wall between the right atrium and ventricle. They relay the electrical impulses to the ventricle to initiate contraction. These electrical impulses originate in the heart's pacemaker, the sinoatrial node within the right atrium.

ATRIUM – One of the two upper chambers of the heart. The right atrium receives blood depleted of oxygen from the veins; the left atrium receives blood with fresh oxygen from the lungs. The left atrial cavity enlarges with age.

AUTONOMIC NERVOUS SYSTEM – That part of the nervous system that controls involuntary muscles, such as the heart. It uses chemicals, such as catecholamines, to send messages from the brain to the heart. With age, the body's response to cathecholamines withers.

BARORECEPTOR RESPONSE – The body's response to pressure sensitive nerves in the carotid artery that help regulate heart rate and arterial pressure; the response grows weaker with age.

BLOOD PRESSURE – The force that flowing blood exerts against artery walls. Systolic blood pressure occurs when the heart contracts and pumps blood into the aorta. Diastolic blood pressure occurs when the aortic valve closes and the heart relaxes and refills with blood.

CALCIUM PUMP PROTEINS – Proteins on the sarcoplasmic reticulum that remove calcium from the cell cytosol after a contraction. The number of these pump proteins declines with age.

CALCIUM TRANSIENT – The transient increase in calcium in the cytosol following excitation, which causes a contraction. It grows longer with age.

CAPILLARIES – The smallest blood vessels that take blood from the arterioles to cells in the body.

CARDIAC CYCLE – The cycle of synchronized activities that occurs during one heart beat.

CARDIAC OUTPUT – The amount of blood a heart pumps each minute. It is calculated by multiplying heart rate by stroke volume.

CARDIOVASCULAR – Of or pertaining to the heart and blood vessels.

CHEMOKINES – A type of cytokine that carries messages between cells. In a sense, they tell cells where to go. If chemokines are increased in a particular tissue, such as an artery, the cell with the receptor, or partner, for that particular molecule is attracted to move into that tissue.

CHOLESTEROL – A waxy, fat-like substance present in cell walls or membranes everywhere in the body, including the heart. Excess cholesterol is deposited in arteries, including the coronary arteries, where it contributes to the narrowing and blockages that cause the signs and symptoms of heart disease. Cholesterol is carried in small packages called low density (LDL) and high density (HDL) lipoproteins.

CONTRACTILE (MYOFILAMENT) PROTEINS – Proteins in myocytes that change their configuration in order to bring about a shortening or contraction of the cell. This may change with age.

CONTRACTILE STATE – The ability of the heart muscle cells to contract, also referred to as contractility.

CORONARY HEART DISEASE – Also called coronary artery disease ischemic heart disease. A narrowing of the coronary arteries due mostly to atherosclerosis resulting in a decreased flow of blood to the heart muscle and thus lower levels of oxygen reaching the heart.

CORONARY FLOW – The flow of blood through the coronary arteries that nourish the heart muscle.

CYTOKINE – Proteins that are secreted by cells and regulate the behavior of other cells by binding to receptors on their surfaces. This binding triggers a variety of responses depending on the nature of the cytokine and the target cell.

CYTOSOL – The fluid inside heart and blood vessel cells.

DIASTOLE – The period during a heart beat when the chambers are filling with blood and the heart muscle is relaxed.

DNA – Abbreviation for deoxyribonucleic acid, the molecule that contains the genetic code for all life forms except for a few viruses. It consists of two long, twisted chains of molecules in the nucleus of each cell that carries the genetic information necessary for all cellular functions, including the building of proteins.

ECHOCARDIOGRAM (ECG OR EKG) – A visual record of the heart's electrical activity.

EJECTION FRACTION – The fraction of end diastolic volume pumped out with each beat.

ELECTROCARDIOGRAPHY – A method of graphically recording the structure and movement of the heart by the echo caused by beams of ultrasonic waves.

END DIASTOLIC VOLUME – The volume of blood in the left ventricle at the end of diastole, just before the next beat.

ENDOTHELIUM – The smooth inner lining of many body structures, including the heart and blood vessels. Endothelial cells are a primary component of the intima.

END SYSTOLIC VOLUME – The volume of blood left in the heart at the end of the heartbeat.

ENZYME – A protein that promotes a specific biochemical reaction in the body without itself being permanently changed or destroyed. Enzymes may have an important role in the age-associated changes in structure and function that occur in the heart and arteries.

FRANK-STARLING LAW OF THE HEART – A phenomenon in which the more the heart muscle is stretched the more vigorously it contracts.

FREE RADICALS – Molecules with unpaired electrons that react readily with other molecules. Free radicals can damage myocytes as well as the membranes and DNA of endothelial cells in the intima and smooth muscle cells in the media. This damage can promote stiffening and thickening of arterial walls. Free radicals also can contribute to atherosclerotic plaque build up.

GENE – A segment of DNA that codes for a specific protein or other molecule. Each gene contains a specific sequence of chemicals. The sequence is referred to as a "code" because it specifies the order of amino acids (chemical building blocks of proteins) in the end product.

GENE EXPRESSION – The process by which the information contained in genes is transcribed and translated into proteins. Age-related changes in gene expression may account for some changes in heart and artery function.

HEART ATTACK – The death of a portion of heart muscle, resulting when an obstruction in one of the coronary arteries prevents an adequate oxygen supply to that muscle. Heart attacks may be referred to in terms of obstruction (coronary thrombosis) or in terms of the damage done (myocardial infarction).

HEART FAILURE – A condition in which the heart is unable to pump the amount of blood needed by the body. Heart failure can develop from many heart and circulatory disorders, such as high blood pressure heart attack. It often leads to congestion in the body tissues, with fluid accumulating in the abdomen and legs and/or in the lungs. This condition is often called congestive heart failure.

HEART RATE – The number of beats per minute.

HIGH BLOOD PRESSURE – An unstable or persistent elevation of blood pressure above the normal range. Blood pressure often increases with age. High blood pressure increases the risk of heart disease and stroke; also known as hypertension.

HIGH DENSITY LIPOPROTEINS (HDL) – The "good" cholesterol. HDL carries cholesterol in the blood from other parts of the body back to the liver, which leads to its removal from the body. HDL helps keep cholesterol from building up in the walls of the arteries.

HYPERTROPHY – Enlarge or enlargement. The myocytes that make up the walls of the heart hypertrophy with age.

ISCHEMIA – Decreased blood supply to the heart muscle.

INTIMA – The innermost layer of arterial wall closest to the blood. It is composed of a single layer of specialized cells, called endothelial cells, which sit atop the sub-endothelial space and a wall called the basement membrane.

LOW DENSITY LIPOPROTEIN (LDL) – The "bad" cholesterol. High LDL cholesterol leads to a build up of cholesterol in arteries. The higher the LDL level in your blood, the greater chance you have for getting coronary heart disease.

LUMEN – The tube-like opening in arteries and other vessels that blood flows through on its journey throughout the body.

MAXIMUM HEART RATE – The number of beats per minute during rigorous exercise. It declines by about 25 to 30 percent between the ages 20 and 80, regardless of physical fitness status. Scientists estimate maximum heart rate by subtracting your age from 220.

MAXIMUM OXYGEN CONSUMPTION – The amount of oxygen used by the body at peak exercise capacity. Also known as VO2 max, it is considered the best measure of cardiorespiratory physical fitness. Women tend to have less lean muscle mass than men, and it is lean muscle mass that needs the most oxygen. When studies compare oxygen consumption based on the amount of lean muscle rather than overall body size, the gender differences disappear. Women, in other words, use the same amount of oxygen as men.

MEDIA – The middle layer of the arterial wall. It is composed of smooth muscle cells surrounded by a network of fibers primarily made of two proteins, collagen, and elastin. The elastin forms concentric rings within the vessel wall.

MITRAL VALVE – The valve between the left atrium and ventricle. It closes more slowly with age because the rate of blood flow into the left ventricle that pushes it closed decreases with age.

MYOCARDIUM – The heart muscle.

MYOCYTE – A heart muscle cell. Myocytes decline in number but grow larger with age.

NONINVASIVE TECHNIQUES – Medical procedures that do not require needle puncture, surgery, or entering the artery.

ORGANELLE – A structure inside a cell, such as the sarcoplasmic reticulum.

OXYGEN CONSUMPTION – The amount of oxygen the entire body uses in a certain time period. It is calculated by taking the amount of oxygen in the arteries and subtracting the amount left in the veins after the body's cells have taken out oxygen. The result is then multiplied by cardiac output.

PRELOAD –The amount of blood in the left ventricle before contraction.

PROTEINS – Molecules composed of amino acids arranged in a specific order. Certain proteins, such as the calcium pump protein and the contractile protein myosin, appear to change with age which may account for some alterations in the function of the aging heart.

SARCOPLASMIC RETICULUM – A structure or organelle inside a myocyte. Its function is to store and release calcium for use during a contraction and to remove calcium after calcium transient causes a contraction. It removes calcium more slowly with age.

SINOATRIAL NODE – The heart's pacemaker. A group of specialized cells in the right atrium wall that give rise to the electrical impulses that initiate contractions.

STROKE VOLUME – The amount of blood pumped with each heart beat.

SYSTOLE – The period during a heart beat when the heart muscle contracts and blood is pumped out.

VEINS – The blood vessels that return blood to the heart after the body's cells have extracted oxygen.

VENTRICLE – A chamber of the heart that pumps blood out. The right ventricle pumps blood to the lungs where it picks up oxygen; the left ventricle pumps blood into the aorta, which distributes it to the rest of the body.

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Of the heart. This moves of itself and does not stop unless forever.

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