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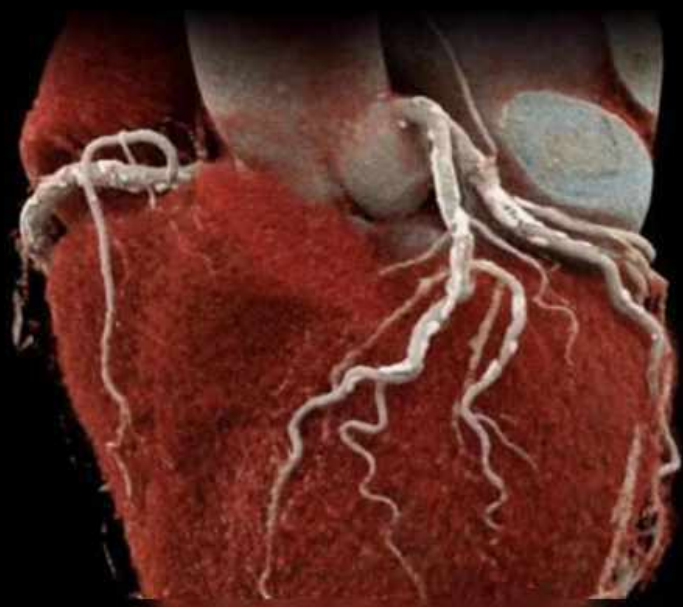

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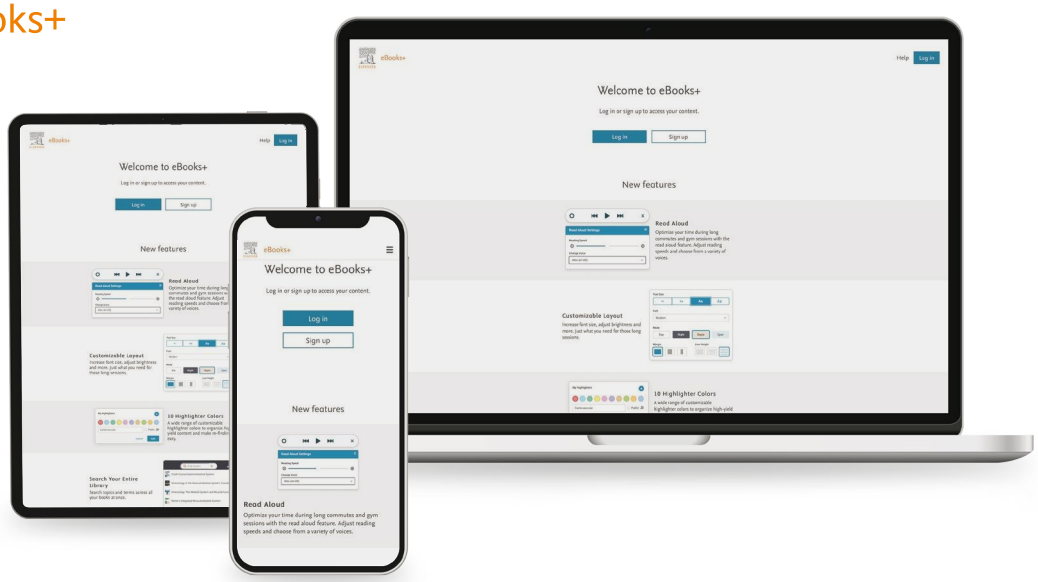

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BRAUNWALD'S HEART DISEASE

A Textbook of Cardiovascular Medicine

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Preface to the Thirteenth Edition

The editors are pleased to present the 13th edition of *Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine*. With the steady accelerating pace of cardiovascular science and the accompanying deluge of new knowledge, *Braunwald's Heart Disease* continues to serve as a trusted resource in which new research is scrutinized, collated, and integrated into the foundational evidence base that informs the practice of cardiology. This edition aims to provide practitioners, physicians-in-training, and students at all levels with the tools needed to keep abreast of the rapidly changing face of our discipline. With the twice monthly updates by Dr. Braunwald to the online edition, the 13th edition will again enrich a living textbook, supported by the *Heart Disease* family of 18 subspecialty companions.

This new edition has undergone thorough revision with 20 new chapters and 41 new authors, each highly accomplished and recognized in their respective areas of expertise. All chapters carried forward from the 12th edition have been thoroughly updated and extensively revised, with the vast majority of references from 2017 onward. The 13th edition includes more than 3000 figures, most of which are in full color. We have continued to provide updated sections on current guidelines recommendations in the online edition that complement each of the appropriate individual chapters in the main textbook. The online version of each chapter of the textbook has additional figures and tables, along with 200 videos.

The editors recognize the truly transformative potential of artificial intelligence (AI) technology and its ascendency in current and future cardiovascular care. Few topics in medicine have captured the attention of clinicians and the lay public to a similar extent. In addition to an updated chapter dedicated to AI, every chapter in this edition in which AI has an established or potential role has a section focusing on AI applications.

A new chapter on obesity and the role on weight-reducing medications in cardiology helps to keep our readers abreast of this rapidly evolving topic, which is also discussed in the chapters on diabetes and heart failure. Several chapters address the growing attention to cardio-renal-metabolic health. Additional chapters focus on other important cross-discipline topics such as cardio-oncology, gerontology, women's cardiovascular health, pregnancy, and stroke.

We are indebted to all of our authors for their considerable time, effort, and commitment to maintaining the high standards of *Braunwald's Heart Disease*. We would like to also acknowledge the long-standing central role of Debra Beck, who has worked closely with Dr. Braunwald through many of the recent past editions to update the text and references of the online edition to include new evidence emanating from important clinical trials and registries. She has been a key member of the *Heart Disease* team to ensure that our content is timely and comprehensive. Finally, we express enormous gratitude to Dolores Meloni, Anne Snyder, and their team at Elsevier, without whose support and commitment this edition would not be possible.

We are delighted that Dr. Braunwald has again authored the first chapter of this edition of the textbook that he published initially as the single editor 45 years ago. His chapter addresses his visions for the future of cardiovascular care. Dr. Braunwald has been a mentor to us, and we have done our very best to live up to the standards that he created throughout his distinguished career as a physician, scientist, author, and editor.

Robert O. Bonow
Douglas L. Mann
Gordon F. Tomaselli
Deepak L. Bhatt
Scott D. Solomon
Peter Libby

Preface to the First Edition

Today cardiovascular disease is the greatest scourge afflicting the population of industrialized nations. As with previous scourges—bubonic plague, yellow fever, and smallpox—cardiovascular disease not only strikes down a significant fraction of the population without warning but causes prolonged suffering and disability in an even larger number. In the United States alone, cardiovascular disease was responsible for almost one million deaths in 1979—*well over one-half of all reported deaths*. Almost 5 million persons afflicted with cardiovascular disease are hospitalized annually. The cost of these conditions in terms of human suffering is almost incalculable.

Fortunately, research focusing on the causes, diagnosis, treatment, and prevention of heart disease is moving ahead rapidly. In the last 25 years we have witnessed an explosive expansion of our understanding of the structure and function of the cardiovascular system—both normal and abnormal—and of our ability to evaluate these parameters in the living patient. Simultaneously, remarkable progress has been made in preventing and treating cardiovascular disease by medical and surgical means.

An attempt to summarize our present understanding of heart disease in a comprehensive textbook for the serious student of this subject is a formidable undertaking. Following the untimely death of Dr. Charles K. Friedberg, whose masterful text served as a bible to me and to a whole generation of cardiologists during the 1950's and 1960's, the W.B. Saunders Company, Friedberg's publisher, invited me to accept this responsibility. Younger colleagues, particularly cardiology fellows and medical residents at the Brigham whom I consulted, convinced me of the need for such a book.

A single text—even a long one—cannot adequately cover every aspect of a subject as extensive as cardiovascular disease. Thus, my first task was to define those areas of the field to be included. Since the early part of this century, clinical cardiology has had a particularly strong foundation in the basic sciences of physiology and pharmacology. More recently, the disciplines of molecular biology, genetics, biochemistry, experimental pathology, and bioengineering have also begun to provide critically important information about cardiac function and malfunction. Although it was decided that *Heart Disease* was to be primarily a clinical treatise and not a textbook of fundamental cardiovascular science, an effort was made to explain, in some detail, the scientific basis of cardiovascular diseases.

In order to provide a comprehensive, authoritative text in a field that has become as broad and deep as cardiovascular medicine, I chose to enlist contributions from a number of able colleagues. However, my personal involvement in the writing of about half of this first edition has made possible a deliberate effort to reduce the fragmentation, gaps, inconsistencies, organizational difficulties, and impersonal tone that plague some multiauthored texts. I sought a compromise between a book that is too long as a result of excessive repetition and one in which all duplication is eliminated, resulting in fragmented coverage of certain subjects. Some material is repeated within the text, but this has been done deliberately for the convenience of the reader. Particular emphasis has been placed on insuring comprehensive and up-to-date bibliographies. Considerable revisions have been made in both galley and page proofs to include the most recent advances in the field; several hundred references to publications appearing late in 1979 and early in 1980 have been inserted.

To the extent that this book proves useful to those who wish to broaden their knowledge of cardiovascular medicine and thereby aids in the care of patients afflicted with heart disease, credit must be given to the many talented and dedicated persons involved in its preparation. I offer deep appreciation to my fellow contributors for their expertise, knowledge, and devoted scholarship which has so enriched this book. I am deeply in their debt for their cooperation and willingness to deal with a demanding editor. It has been a personal pleasure for me to deal with the W.B. Saunders Company, especially Mr. John Hanley, Vice President and Editor of Health Sciences, whose wise counsel at several critical junctures have been particularly helpful.

Without question, this book could not have become a reality were it not for the skill and dedication of two very special persons. My responsibilities to the Harvard Medical School and the Peter Bent Brigham Hospital during my sabbatical year were shouldered most effectively by my friend and colleague Dr. Marshall Wolf, who provided the Department of Medicine with exemplary leadership during my absence, and my administrative assistant, Mrs. Mary Jackson. They expended incalculable time and effort to aid me in the completion of this project while simultaneously maintaining the orderly flow of activity essential to a busy Department of Medicine.

EUGENE BRAUNWALD
1980

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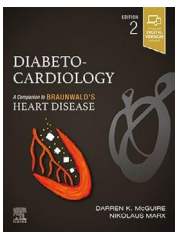
Braunwald's Heart Disease Family of Books



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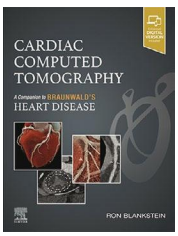

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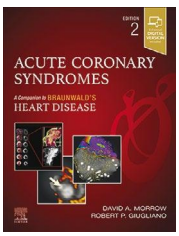

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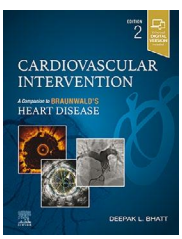

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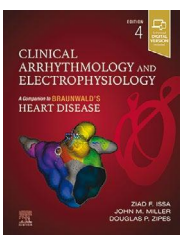

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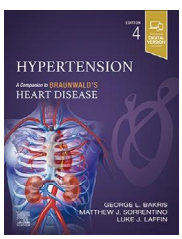

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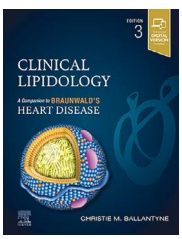

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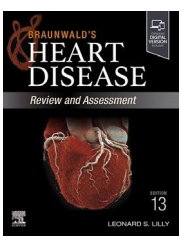

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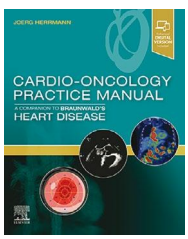

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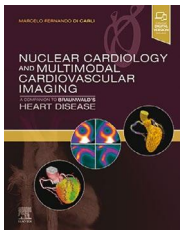

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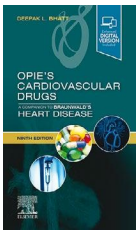

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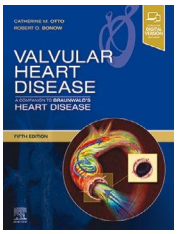

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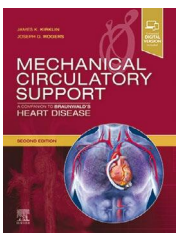

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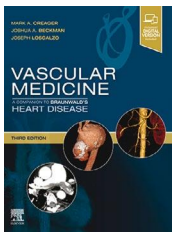

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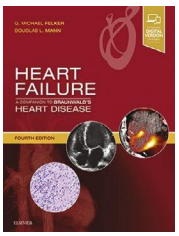

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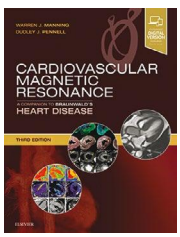

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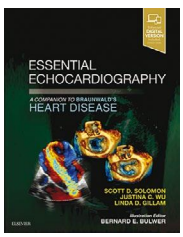

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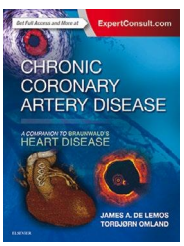

DE LEMOS AND OMLAND
Chronic Coronary Artery Disease

1 Cardiovascular Disease: Past, Present, and Future

EUGENE BRAUNWALD

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KEY POINTS

- Cardiology was fathered by William Harvey in 1628. Its growth reflects the biomedical and technological advances of the last four centuries and was driven by the insights of generations of dedicated physician-scientists.
- During the 18th and 19th centuries, pathologists discovered a number of cardiac disorders, first at the autopsy table and then using the microscope. The development of the stethoscope in 1816 helped extend these observations to patients.
- Cardiology emerged as an important clinical specialty between 1895 and 1905 with the development of roentgenography, sphygmomanometry, and electrocardiography. These advances permitted noninvasive examination of the structure and function of the normal and diseased heart.
- During the first half of the 20th century, the clinical importance of arteriosclerotic cardiovascular disease became apparent and the natural history of many other cardiovascular disorders—both congenital and acquired—were elucidated.
- During the second half of the 20th century, clinical electrophysiology, echocardiography, and several other noninvasive imaging techniques that greatly enhanced diagnosis of many cardiac disorders became available. Potent therapies, including a variety of effective drugs, cardiovascular surgery, and catheter-based interventions were developed.
- In the first quarter of the 21st century, prevention of cardiovascular diseases assumed increasing attention. Bioengineers are providing improved life-prolonging circulatory assist devices. The clinical application of genetics, genomics, and artificial intelligence are contributing to the development of personalized, precision medicine.

HISTORY

The Birth

Although the heart was recognized as a vital organ in early human history, its function was not understood but was widely debated over millennia. In 1628, William Harvey, a London physician (Fig. 1.1) who had trained in the great medical school in Padua, Italy, published a monograph, *De Motu Cordis, An Anatomical Treatise on the Motion of the Heart and Blood*,[1] which concluded simply, "The blood in the animal body moves around in a circle continuously, and the function of the heart is to accomplish this by pumping." Harvey based this conclusion on detailed anatomic studies that included the valves in the veins that appeared to permit blood to flow only toward the heart. He conducted experiments in humans and rabbits and estimated cardiac output. Importantly, Harvey's research was the first major hypothesis-driven research in biology. Although his findings were not uniformly accepted during his lifetime, they are now considered to be one of the scientific triumphs of the high Renaissance, along with the works of Isaac Newton and Galileo Galilei.

Harvey's conclusion was buttressed by two findings. The first was the description of the capillary circulation in 1661 by Marcello Malpighi,[2] who identified this last anatomic link in the circulatory chain. The other, by Richard Lower in 1668, was the role of pulmonary circulation in changing the color of the blood as it is exposed to the air in the lungs.[3]

Early Stirrings

In 1733, Steven Hales measured arterial and venous pressures in horses and other mammals.[4] "Direct" auscultation (placing the ear on the precordium) to hear the heartbeat was used later in the 18th century. Cardiac examination accelerated after 1823, when René Laennec, a French physician, described the stethoscope.[5] In his 1775 monograph on foxglove (digitalis), William Withering described its effectiveness in the treatment of patients with "dropsy," that is, edema, presumably the result of heart failure (HF).[6] William Heberden described angina in 1772,[7] and 40 years later the *first* paper in the *first* issue of the *New England Journal of Medicine* by John Warren, a Boston physician, discussed this symptom.[8] However, as pointed out by William Osler in

FIG. 1.1 William Harvey (1578–1657).

1910, angina was not recognized frequently.[9] In 1879, F.A. Mahomed described hypertension *not* associated with renal disease, the forerunner of what is now referred to as primary or essential hypertension.[10] Several important arrhythmias were described in the mid-to-late 19th century. These included severe bradycardia by Stokes in 1854 and ventricular fibrillation (VF) by MacWilliam in 1887.

By the end of the 19th century, physiologists and clinicians were aware of electrical depolarization and repolarization of the heart and could recognize some cardiac arrhythmias by cardiac auscultation and palpation of the pulse. They also knew that hypertension could occur in both the presence and absence of advanced renal disease and was often associated with left ventricular (LV) hypertrophy. They recognized congenital and valvular heart disease, angina pectoris, and HF. However, cardiovascular (CV) disease was not considered to be common; it was treated with bed rest, digitalis, nitrates, and sometimes morphine.

Emergence of a Specialty

The decade from 1895 to 1905, bridging the 19th and 20th centuries, was probably the most important in the history of cardiology because of the development of three critically important technologies. In 1895, Wilhelm Roentgen,*,[11] a German physicist, discovered the use of x-ray, the first technique for imaging the body, allowing estimation of the heart's size and shape. The noninvasive measurement of blood pressure (BP) was developed by Riva Rocci, an Italian physician, in 1896[12] and Korotkoff in Russia in 1905.[13] The first recording of the electrocardiogram (ECG) using a string galvanometer by Willem Einthoven,* a Dutch clinical physiologist, was reported in 1903.[14] When added to the clinical examination, these new technologies permitted clinical assessment of key elements of the CV system. It soon became apparent that heart disease was far more common than had been suspected. Physicians who became experts in using and interpreting these new technical wonders were dubbed "heart specialists" or "cardiologists."

Advances came rapidly in this new specialty, and it soon became necessary to develop medical journals to record them. The earliest were the *Zentralblatt für Herz Krankenheiten* in Germany and the *Archives des Maladies du Coeur* in France, both in 1908. Subsequently, an enormous expansion of cardiac journals occurred. As of 2024, hundreds of CV journals are published on a regular basis.

National cardiac societies were created to bring cardiologists and their trainees from each country together to share experiences and describe advances in CV science and clinical cardiology. The first of these, the British Cardiac Club, was organized in 1922, and in 1937 it morphed into the British Cardiac Society. In addition to organizing meetings, these societies also publish national cardiology journals. Beginning in the last third of the 20th century, the societies developed and promulgated clinical practice guidelines that have improved the accuracy of CV diagnosis and the quality of care. National cardiac societies have joined with their continental neighbors to form regional societies, such as the European Society of Cardiology. The development of the World Heart Federation reflects the globalization of clinical cardiology and CV research.

CARDIAC IMAGING (SEE PART 3)

The Past

After the development of roentgenography, venous angiography was begun in the 1920s. Selective angiography allowed enhanced visualization of specific sites in the heart and great vessels. In 1952, Edler and Herz, a Swedish cardiologist/physicist team, developed echocardiography.[15] This technique assumed growing importance for assessing cardiac structure and function noninvasively, becoming the workhorse of cardiac imaging. The devices became smaller, more portable, and even handheld. By the end of the 20th century, stress echocardiography, color Doppler, transesophageal echocardiography, and three-dimensional (3D) echocardiography had become valuable and widely used clinical tools.

The development of computed tomography (CT) by Hounsfield* and Cormack* in 1973[16] and of cardiovascular magnetic resonance (CMR) imaging by Lauterbur* and Mansfield* in the same year[17] has revolutionized cardiac diagnosis. Both technologies provide precise 3D displays of the cardiac chambers and great vessels. CMR became especially useful in assessing regional myocardial perfusion, tissue characteristics, and systolic and diastolic function. Although coronary arterial calcium had been noted occasionally by fluoroscopy, the field leaped forward in 1990, when Agatston, a Florida cardiologist, introduced calcium scoring by CT.[18] Larger and more extensive calcium deposits in the coronary arteries were associated with a higher incidence of subsequent coronary events, thereby enhancing risk assessment. Absence of coronary calcium, however, does not exclude coronary arterial disease, especially in patients younger than 50 years.

The Present

Nuclear cardiology, developed in the 1930s, is now used largely to detect the presence and assess the severity of myocardial ischemia.[19] CMR imaging is used routinely in the diagnosis and assessment of cardiomyopathies and in the assessment of cardiac fibrosis and masses. Dobutamine stress CMR is a sensitive, accurate method of detecting and quantifying myocardial ischemia.[20] Because CMR does not require ionizing radiation, it can be used repeatedly to track the progression of disease and the effects of therapeutic interventions.

Coronary computed tomographic angiography (CCTA) with intravenous injection of contrast material provides accurate, high-quality, noninvasive visualization of the epicardial coronary arteries. This technique is widely employed in patients with chest pain of possible cardiac ischemic origin, in whom it has reduced the need for invasive coronary arteriography.[21] Quantitative positron emission tomography (PET) has become useful in the assessment of myocardial ischemia and viability and in the evaluation of inflammatory cardiomyopathies and infective endocarditis.[22,23]

*Names followed by an asterisk were awarded a Nobel Prize.

The Future

As outlined in Chapter 10, the clinical implications of artificial intelligence (AI), now widely used in all modes of CV imaging, are profound. AI can analyze the structure and function of all four cardiac chambers and distinguish among causes of ventricular hypertrophy. AI also delineates and quantifies scarred areas detected by CMR. AI can combine findings of different imaging modalities in the same individual, relate these to the clinical features, and establish a likely diagnosis. It can also compare images obtained at intervals and quantify changes over time.

These advances will greatly extend the information provided by noninvasive imaging to further reduce the need for invasive diagnostic cardiac catheterization and selective angiography.

INVASIVE PROCEDURES (SEE CHAPTERS 19, 20, AND 38)

Cardiac Catheterization

In 1929, the first human cardiac catheterization was performed (on himself!) by Werner Forssmann,* a German surgical resident who was forbidden to repeat the procedure but wisely published his experience[24] (Fig. 1.2). In the late 1940s, the technique was applied to a variety of congenital and acquired cardiac disorders by Andre Cournand*[25] and Dickinson Richards,*[26] in New York. In addition to measuring pressures in the chambers of the right heart and pulmonary arteries, they determined cardiac output at rest and during exercise. In 1948, Mason Sones, a cardiologist in Cleveland, described and perfected coronary arteriography, which provided anatomic assessment of the coronary arterial bed.[27] By the third quarter of the 20th century, cardiac catheterization had become extremely important in the diagnosis of many forms of heart disease.

Cardiovascular Surgery

After some early failures, CV surgery began in earnest in 1938, when Robert Gross of Boston successfully closed a patent ductus arteriosus.[28] Operative correction of coarctation of the aorta and of a variety of other congenital cardiac malformations soon followed. Mitral valvulotomy for stenosis was begun in 1946 almost simultaneously by Bailey and Harken. A major step forward was taken by John Gibbon of Philadelphia, who developed a "heart-lung" machine in 1953, which was used for cardiopulmonary bypass[29] and led to the era of open heart surgery. This allowed repair of a large number of congenital and acquired disorders. In 1961, Albert Starr reported mitral valve replacement with a prosthetic ball valve.[30]

Beginning in the 1940s, a variety of attempts were made to treat patients with coronary artery disease (CAD) and severe angina by surgery; most were unsuccessful. In 1968, René Favaloro, a cardiac surgeon in Cleveland, Ohio, described coronary artery bypass grafting (CABG),[31] which proved to be very effective in the management of severe angina pectoris and was shown in randomized clinical trials to prolong survival in patients with severe, multivessel CAD. At present, the most frequently performed cardiac operation is CABG, with upward of 210,000 per year in the United States.[32] Currently, cardiac surgery continues to play a vital role in many complex congenital heart disorders, multivalvular disease, assisted circulation, and cardiac allotransplantation.

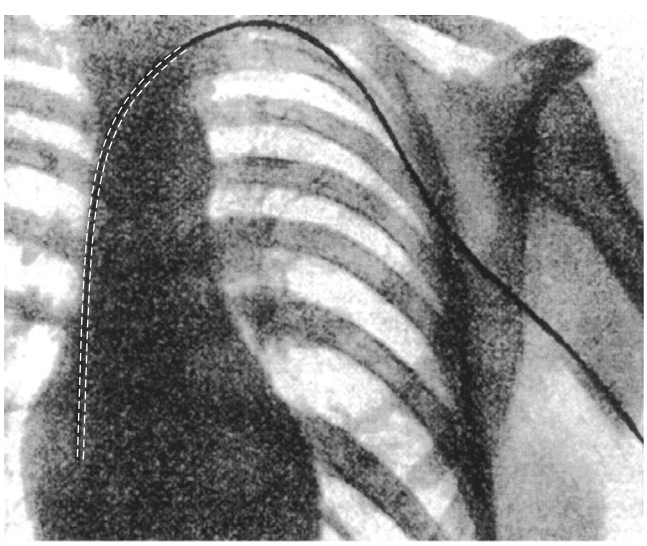

FIG. 1.2 Cardiac catheter introduced by Werner Forssmann into his own right atrium. (From Forssmann W. Die Sondierung des rechten Herzens. *Klin Wochenschr.* 1929;8:2085–2087. Permission from Springer-Verlag, Munich, FRG.)

Percutaneous Coronary Intervention

The field of invasive interventions virtually exploded in 1977, when Andreas Grüntzig, a Swiss cardiologist, described a new technique—percutaneous transluminal coronary angioplasty (PTCA), thereby ushering in a new subspecialty, interventional cardiology.[33] PTCA began with the treatment of patients with poorly controlled angina and an obstructive plaque in a proximal coronary artery. It was applied to progressively more complex lesions, and then on an emergent basis to patients with acute myocardial infarction (AMI) (see later).[34] In the late 1980s, coronary arterial stents were introduced to prevent restenosis.[35] Percutaneous coronary intervention (PCI) expanded rapidly and began to compete with CABG. In properly selected patients it was of equivalent safety and efficacy and greatly preferred by patients who recovered in a day or two, compared with the weeks or months required after CABG.

Comments

During the last third of the 20th century, cardiology went through a major evolution. Between 1950 and 1970, the diagnosis of many congenital and acquired cardiac disorders was established predominantly by cardiac catheterization, often aided by selective angiography. If a mechanical therapeutic intervention was required, it was usually surgical. By the end of the century, as a consequence of the important advances in cardiac imaging described previously, the need for diagnostic cardiac catheterization had declined. Simultaneously, catheter-based therapy advanced rapidly and expanded widely to patients with congenital and valvular heart disease. PCI rapidly became the most frequent therapy for improving coronary perfusion in acute coronary syndromes (ACSs) (see later). Surgical therapy was reserved primarily for patients in whom catheter-based therapy was not possible or in whom it had failed.

HYPERTENSION (SEE CHAPTER 23)

The Past

The recognition of hypertension as a critically important clinical entity was made possible by the noninvasive measurement of BP[12,13] leading to the recognition of its high prevalence. The close relation between renal disease and hypertension goes back to Richard Bright, an English physician, who suggested in 1827 that patients with chronic kidney disease often had LV hypertrophy.[36] In 1897, Robert Tigerstedt, a Swedish physiologist, injected an extract of rabbit kidney into a normal rabbit and observed a prolonged elevation of arterial pressure; he appropriately named the pressure-raising substance "renin."[37] In 1934, Harry Goldblatt, a Cleveland pathologist, demonstrated a rise in arterial pressure in dogs in which renal ischemia had been induced.[38] In 1940, Braun-Menendez in Buenos Aires,[39] Argentina, and Irvine Page in Cleveland, Ohio, reported independently that renin is an enzyme that acts on a glycoprotein, *angiotensinogen* (AGT), to produce a polypeptide with pressor properties, which they named *angiotensin*, presumably produced by the ischemic kidney described by Goldblatt. In the first quarter of the 20th century, it became clear that in addition to

kidney disease, coarctation of the aorta, pheochromocytoma, and other endocrinopathies were causes of secondary hypertension. However, a large majority of patients with hypertension had no discernable cause and were referred to as having primary (essential) hypertension.

In 1930, the clinical importance of hypertension was recognized and explicitly summarized by Soma Weiss, a Boston physician (who was my predecessor at Harvard and at Brigham and Women's Hospital).[40] In 1948, Walter Kempner, an internist at Duke University, emphasized the use of an extremely low-salt diet (<200 mg Na^+ daily) based on rice, fruit, and juice for the treatment of primary hypertension. Although this strict regimen reduced elevated BP, it was difficult to sustain. The most widely used antihypertensive drugs in the mid-20th century were reserpine, which depresses cerebral sympathetic centers, and hexamethonium derivatives, which block transmission through autonomic ganglia; these drugs were associated with severe side effects. In patients with malignant hypertension who were not responsive to or could not tolerate potent hypotensive drugs, a splanchnic sympathectomy, championed by Reginald Smithwick, a Boston surgeon, could be considered.[41] Although it usually reduced BP, the risks and adverse effects of this difficult operation were substantial.

In the 1960s, two well-designed, well-executed placebo-controlled trials in US Veterans Hospitals, led by Edward D. Freis, a cardiologist in Washington, DC, provided the first *definitive* evidence of the benefit of antihypertensive therapy. The first, conducted on patients with severe hypertension (diastolic pressures 115 to 129 mm Hg) compared treatment using the combination of hydrochlorothiazide, reserpine, and hydralazine, with placebo. The second had a similar design and studied patients with diastolic pressures between 90 and 114 mm Hg. In both trials, the risks of severe vascular events, especially HF and stroke, were markedly reduced in the treated group.[42]

The Present

By the end of the 20th century, it became clear that hypertension is the most important risk factor for the development of atherosclerotic cardiovascular disease (ASCVD). Many advances have been made in the treatment of essential hypertension. These include lifestyle changes focusing on weight reduction, dietary salt restriction, and interdicting smoking. Of the large number of approved antihypertensive drugs, the primary agents include (1) chlorothiazide or thiazide-like diuretics; (2) blockers of the renin-angiotensin system (RAS); and (3) calcium channel blockers. Patients whose BP is not controlled with the maximum tolerated doses of a combination of these drugs are considered to have resistant hypertension and may require intensification of their lifestyle changes and/or the addition of a drug from another class, such as a mineralocorticoid receptor blocker, beta blocker, and/or vasodilator.

The drugs for the treatment of hypertension are now usually well tolerated, readily available, and inexpensive. However, elevated BP is controlled in only a minority of hypertensive patients, largely because of poor adherence. One explanation is that hypertension per se causes few if any symptoms, leading to a combination of both physician and patient inertia; it has been termed "the silent killer."

The Future

AGT, a hepatocyte-derived protein, stimulates the RAS, thereby exerting a pressor effect. Zilebesiran is an RNA that inhibits the production of AGT and thereby lowers BP. It requires subcutaneous injection only twice a year and may thereby improve adherence.[43] Recent studies have shown a previously unrecognized elevation of circulating aldosterone in many patients with essential hypertension. Such patients might be managed with a nonsteroidal mineralocorticoid receptor antagonist or an aldosterone synthase inhibitor, baxdrostat, which is under development for treatment-resistant hypertension.[44] Renal denervation has been shown to reduce BP modestly; its role in the management of hypertension has not been clearly defined.[45]

Multiple efforts have been made to understand the genetic basis of essential hypertension. In a genome-wide association study (GWAS) in 331,000 persons, Cho and colleagues concluded that a BP polygenic risk score (see later) may place persons at high risk of developing hypertension.[46]

Looking ahead, research on the combination of genomic and phenotypic features of hypertension is likely to provide clinically useful, actionable findings.[47] An important goal is to identify responders and nonresponders to specific antihypertensive agents *before* the onset of therapy.

VALVULAR HEART DISEASE (SEE PART 8)

The Past

Cardiac involvement in rheumatic fever was described by Wells, a British physician, in 1812.[48] Acute rheumatic fever and its sequel, chronic rheumatic valvular heart disease, were common in Europe and North America until the mid-20th century and then declined with the introduction of penicillin and some relief of extreme poverty. However, almost simultaneously, a reciprocal increase in degenerative calcific disease of the aortic and mitral valves occurred in the rapidly growing elderly population. Acute rheumatic fever and its sequelae are still observed frequently in developing nations in tropical and subtropical latitudes.

The Present

MITRAL STENOSIS

In the mid-20th century, surgical treatment of symptomatic severe MS (valve area <1.5 cm^2) carried out by closed mitral valvulotomy was the most frequently performed cardiac operation. In 1983, percutaneous balloon mitral valvulotomy (PBMV) was described by Inoue, a Japanese cardiologist.[49] Employing transseptal left heart catheterization[50] and echocardiographic guidance, he introduced a balloon catheter into the mitral orifice; balloon inflation opened the fused commissures. The indications for and results of PBMV are generally similar to those for closed surgical valvulotomy. PBMV has gained worldwide popularity because it is relatively safe and shortens the duration of hospitalization and recovery. Favorable results have been sustained for upward of 15 years.[51] When the valve is calcified, severely fibrotic, with subvalvular fusion, and/or accompanied by more than slight mitral regurgitation, valvulotomy on cardiopulmonary bypass is carried out. In some instances, mitral valve replacement is necessary.

MITRAL REGURGITATION

Primary mitral regurgitation (MR) is caused by abnormalities of the mitral valve leaflets and/or supporting structures; it may be congenital or acquired, as in mitral valve prolapse or rheumatic heart disease. Secondary MR usually results from ventricular dilation caused by ischemic or nonischemic cardiomyopathy, which prevents coaptation of the normal leaflets. In 2001, Ottavio Alfieri, an Italian cardiac surgeon, treated MR by approximating the free edges of the mitral leaflets with a running suture, sometimes referred to as the "Alfieri stitch."[52] In 2003, St. Goar working with a porcine model developed an endovascular edge-to-edge repair of the mitral valve with a valve clip. Transcatheter mitral valve repair was then extended to patients by Feldman.[53] Two large, randomized trials compared transcatheter edge-to-edge repair with guideline-directed medical therapy (GDMT) in secondary MR with HF. One of these showed superiority of the transcatheter approach,[54] whereas the other showed equivalence.[55] The 2021 American College of Cardiology/American Heart Associate (ACC/AHA) Guidelines recommended edge-to-edge repair in patients with moderate or severe secondary MR with persistent symptoms despite intensive GDMT.[56] If necessary, a prosthetic valve can be inserted. Catheter-based replacement or repair of the mitral valve is currently under active investigation, and early results are encouraging.[57] Transcatheter mitral valves are increasing rapidly and have overtaken surgical mitral valve replacement.[32]

Percutaneous tricuspid transcatheter edge-to-edge repair for serve tricuspid regurgitation has also been reported.[58,59]

AORTIC STENOSIS

In the last third of the 20th century, symptomatic adult patients with severe aortic stenosis (AS) (mean gradient >40 mm Hg) were generally treated by surgical aortic valve replacement (SAVR). In 1992, Andersen and colleagues described the successful placement of a catheter-based inflatable bioprosthetic aortic valve in a closed-chest porcine model.[60] This was followed a decade later by the first human percutaneous implantation of an aortic valve by Cribier and associates.[61] In 2006, Webb and colleagues implanted a bioprosthetic valve using a catheter that was passed retrograde from the femoral artery.[62] The first large transcatheter aortic valve replacement (TAVR) trial was conducted by Leon and coworkers on patients whose operative risk was too high to undergo SAVR; survival was prolonged when compared with that obtained with GDMT.[63] Both SAVR and TAVR are effective treatments for adults with severe symptomatic AS.[64] Importantly, the length of hospital stay and recovery are much shorter for TAVR and greatly preferred by patients. With advances in the procedure, the mortality has declined and now is approximately 2.5% in experienced centers.[65]

TAVR was approved for high-risk patients with severe AS by the US Food and Drug Administration (FDA) in 2011; the indication was extended to intermediate-risk and low-risk patients in 2019. TAVR is generally preferred to SAVR for patients with severe, symptomatic AS. However, the longer-term durability of the bioprosthetic valves currently used are not yet clear; this remains a concern when selecting TAVR for younger patients, particularly those with bicuspid aortic valves. Nonetheless, TAVR has transformed the management of patients with severe AS and has greatly overtaken SAVR.[32]

ARRHYTHMIAS (SEE PART 6)

The Past

A "tumultuous" heartbeat was recognized in the 15th century. In 1769, Morgagni, an Italian physician, described patients with very slow heart rates and transient asystole. Although graphic tracings of irregular cardiac movements were made late in the 19th century, the development of the string galvanometer electrocardiograph in 1903 led Einthoven,*[14] Thomas Lewis, and other early cardiologists to describe the majority of clinical arrhythmias.

In 1749, Senas recommended use of the bark of the cinchona tree (which contains quinine) for the treatment of palpitations. In 1918, the superiority of quinidine over quinine was recognized and subsequently a variety of other antiarrhythmic agents were developed. The mechanisms of action of these drugs were classified by Vaughan-Williams.[66] Suspicions arose in the 1970s that many of these agents had both antiarrhythmic and proarrhythmic properties. These suspicions were proven in 1991 when the Cardiac Arrhythmia Suppression Trial (CAST) showed that several antiarrhythmic drugs that markedly reduced premature ventricular contractions in patients who have had an AMI were associated with an *increased* mortality.[67] Since then, the use of antiarrhythmic agents other than beta blockers, amiodarone, and some calcium channel blockers has been curtailed, especially in patients with structural or ischemic heart disease.[68]

In 1952, Paul Zoll, a Boston cardiologist, developed closed-chest cardiac stimulation for the treatment of complete heart block and asystole.[69] In 1958, William Chardack, an American surgeon, implanted a pacemaker powered by a rechargeable battery.[70] In the same year, William Kouwenhoven, an engineer in Baltimore, described closed-chest cardiac massage.[71] In 1962, Bernard Lown, a Boston cardiologist, described direct-current cardioversion of a variety of tachyarrhythmias, including atrial fibrillation (AF) and VF.[72] In 1980, Michel Mirowski, a Baltimore cardiologist, described the implanted cardioverter-defibrillator (ICD). This device successfully detects and treats life-threatening arrhythmias, including ventricular tachycardia (VT) and VF, leading to sudden cardiac death (SCD).[73]

The Present

Multicatheter-based invasive electrophysiologic testing, developed in the early 1970s, includes programmed electrical stimulation and recording of electrocardiographic responses of a number of intracardiac leads before and after administration of pharmacologic agents. This technique is extremely useful in identifying the mechanisms of arrhythmias, distinguishing among automaticity, reentry, and triggered activity, as well as for risk stratification and selection of appropriate therapy.

Acute supraventricular and nodal tachycardias are usually treated by vagal maneuvers, intravenous calcium channel blockers, or electrical cardioversion. To suppress chronic tachyarrhythmias, radiofrequency catheter ablation or amiodarone are frequently employed. VT is generally managed by cardioversion followed by ablation.[74] AF can often be abolished early in the course by electrically disconnecting the source of arrhythmia triggers by pulmonary vein isolation, sometimes by cryoballoon ablation.[75]

SCD is responsible for approximately 15% of all deaths in industrialized countries. It occurs most frequently in patients with ASCVD, especially after AMI or in patients with HF, and is often preceded by VT leading to VF. In a minority of patients, pulseless electrical activity and asystole are responsible for SCD, which also may occur in children and young adults as a consequence of mutations in genes encoding ion channels (channelopathies)[76] or sarcomeric proteins, as in hypertrophic cardiomyopathy. Patients at high risk for SCD are managed by implantation of a ventricular defibrillator (see earlier).

The Future

The increasing use of wearable devices to track fitness is expanding to the identification of a variety of arrhythmias. Wrist-worn watches and finger-worn devices provide signals of a variety of physiologic parameters, including heart rate and rhythm, ECG, and oxygen saturation[77,78] (Fig. 1.3), which can be stored or transmitted by smartphone to a receiving station with patients at rest, during activity, or during sleep, and their responses to therapy. A multilead vest can also contain a wearable cardiac defibrillator.[79]

There has been increasing interest in pulsed field ablation, which uses very brief (microsecond) voltage impulses instead of thermal tools to enhance efficacy and safety of ablation[80,81]; it has been approved for clinical use by the FDA for the management of both paroxysmal and persistent AF. Sodium-glucose cotransporter 2 inhibitors (SGLT2is), which are effective in the treatment of HF (see later), have been reported to reduce a variety of arrhythmias, including AF and VT, and prevent SCD.[82] Further studies of the properties of this drug class are under investigation.

As discussed in Chapter 10, AI is able to identify and classify both symptomatic and asymptomatic arrhythmias. It can also detect *previous* AF from an ECG recorded from the person in sinus rhythm and can identify appropriate sites for ablation in patients undergoing electrophysiologic study.

DYSLIPIDEMIAS (SEE CHAPTERS 23 AND 25)

The Past

During the 20th century, ASCVD emerged as the most common cause of adult death in industrialized nations and elevation of serum cholesterol was recognized as a key risk factor for its development and progression. In 1913, Nikolai Anitschkov, a pathologist in St. Petersburg, fed large quantities of cholesterol to rabbits, raising their serum concentrations to about 1000 mg/dL and producing cholesterol-containing deposits in the aorta.[83] In 1938, Carl Müller, a Norwegian physician, described families with a high incidence of both hypercholesterolemia and ASCVD, thus describing what we now know as heterozygous familial hypercholesterolemia.[84]

In 1954, John Gofman, a biochemist in Berkeley, California, fractionated cholesterol and identified its low-density lipoprotein (LDL-C) involved in atherogenesis.[85] In 1964, Bloch*[86] and Lynen*[87] independently described the multiple steps in the biosynthesis of cholesterol. This work led to the discovery of 3-hydroxy-3methylglutaryl co-enzyme A (HMG-CoA) reductase, the enzyme that catalyzes the synthesis of a critically important intermediary. In 1976, Akira Endo, a pharmacologist

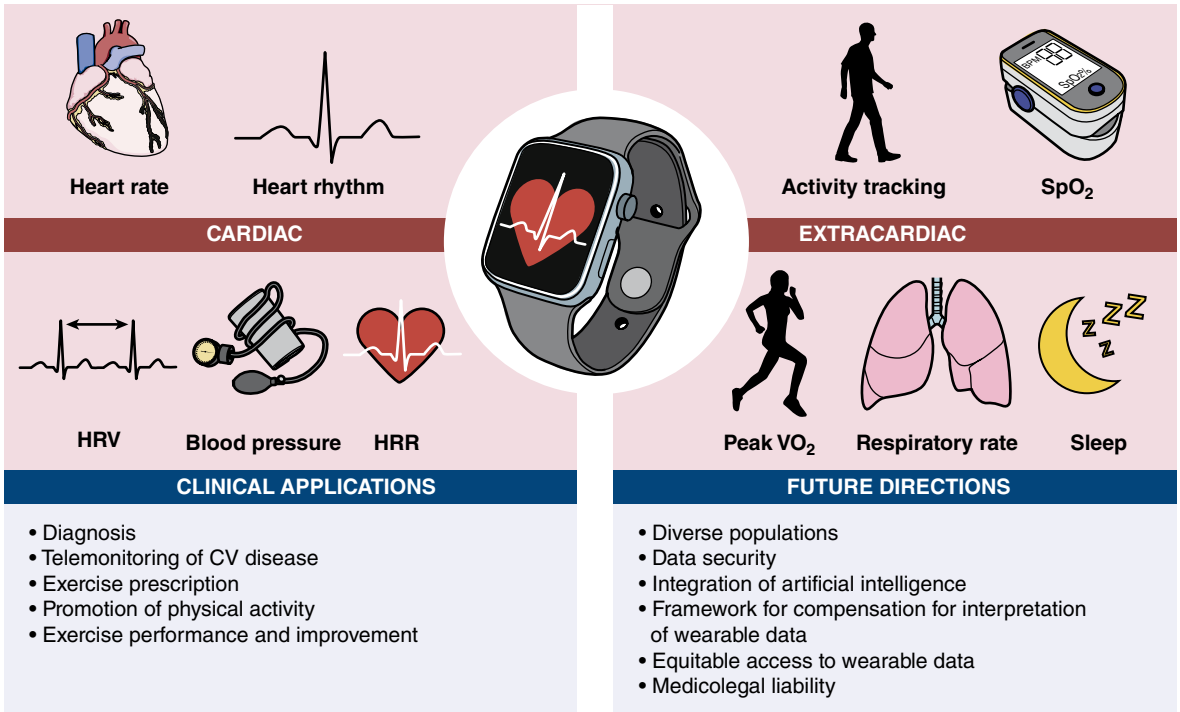

FIG. 1.3 Common health metrics provided by consumer wearable devices. (From Petek BJ, Al-Alusi MA, Moulson N, et al. Consumer wearable health and fitness technology in cardiovascular medicine. *J Am Coll Cardiol.* 2023;82:245–264.)

in Tokyo, identified an inhibitor of this enzyme that reduces the biosynthesis of cholesterol and lowers the concentration of circulating LDL-C.[88] In the 1970s, Michael Brown* and Joseph Goldstein* in Dallas, Texas, isolated, characterized, and cloned the LDL-C receptors on cell membranes.[89] These receptors are key to the cellular uptake of LDL-C and are normally upregulated when the biosynthesis of cholesterol is inhibited, thereby reducing atherogenesis.[90] Several large clinical trials showed that the administration of these inhibitors (statins) reduced the incidence of ACS and chronic ASCVD.[91] These agents have prolonged and improved the lives of millions of persons worldwide and along with the development of the coronary care unit (see later) represent one of the triumphs of CV medicine in the 20th century.

In 2003, Marianne Abifadel, a postdoctoral fellow working in Paris, discovered two gain-of-function mutations in a gene that encodes proprotein convertase subtilisin/kexin type 9 (PCSK9) in patients exhibiting autosomal dominant hypercholesterolemia.[92] PCSK9 shortens the half-life of intracellular LDL-C receptors, thus reducing their recycling to the cell surface, thereby raising circulating LDL-C and the incidence of ASCVD. With reduced concentration of PCSK9 within hepatocytes or in the circulation, the degradation of the LDL-C receptor is reduced, raising its concentration at the cell surface, lowering circulating LDL-C and the incidence of ASCVD.[93]

The Present

In two large phase III clinical outcome trials totaling more than 45,000 patients with ASCVD, administration of monoclonal antibodies to circulating PCSK9 lowered LDL-C by about 55% and reduced the composite endpoint of CV death, AMI, or stroke.[94,95] Robert Giugliano, a Boston cardiologist, reported that extremely low levels of circulating LDL-C (<20 mg/dL) appear to be safe and well tolerated.[96] It now appears to be appropriate to reduce LDL-C to below 55 mg/dL in patients at high risk of developing ASCVD, and even lower, perhaps below 30 mg/dL in patients with established ASCVD.

siRNA-INCLISIRAN

The need for monthly or biweekly injections of monoclonal antibodies to PCSK9 has hindered adherence to this approach for long-term therapy. In 1998, Fire* and Mello* and colleagues described a small, double-stranded RNA (siRNA) that can interfere with gene expression.[97] This fundamental discovery has led to a new class of drugs that include inclisiran, a small, synthetic siRNA that inhibits hepatocellular synthesis of PCSK9, thereby reducing circulating PCSK9, upregulating LDL-C receptors on the cell surface, and lowering circulating LDL-C. In contrast to the PCSK9 monoclonal antibodies, inclisiran requires subcutaneous administration only twice yearly to reduce LDL-C by about 50%. This reduction has been observed in studies in healthy volunteers and in patients with elevated LDL-C levels at high vascular risk, including patients with heterozygous familial hypercholesterolemia and in patients receiving statin therapy.[98] Based on the drug's biochemical efficacy, safety, and tolerance, it has been approved for lowering LDL-C. Two large phase III double-blind, placebo-controlled trials of patients with a history of ASCVD and one trial of high-risk primary prevention patients are currently testing whether the administration of inclisiran reduces major cardiac events. The ability to reduce LDL-C by about 50% in patients already receiving maximal LDL-C–lowering therapy and requiring only two injections annually augurs well for LDL-C control.

Triglycerides (TGs) have long been known to be coronary risk factors, although not as potent as LDL-C. Genetic activation of the lipoprotein lipase gene *(LPL)* reduces serum TGs and is associated with a low incidence of CAD. However, in a large clinical trial, in which moderately elevated TG concentrations were reduced with pemfibrate, CV events did not decline,[99] raising the question of whether reduction of moderate elevations of TG is clinically beneficial. On the other hand, the REDUCE-IT trial showed that in patients with moderate hypertriglyceridemia, the administration of icosapent ethyl was associated with a 25% reduction of adverse ischemic events, including CV death[100]; it is not clear whether this benefit was related to the reduction of TGs.

The Future

It appears likely that continued reduction of ASCVD will occur with further attacks on the hyperlipidemias. Angiopoietin-like 3 (ANGPTL3), a protein that is synthesized by hepatocytes, inhibits expression of lipoprotein lipase, thereby increasing circulating TGs. Loss of function mutations of ANGPTL3 are associated with reductions of LDL-C and

TG,[101] lowering the risk of the development of ASCVD.[9] Several approaches to reducing ANGPTL3 are currently under investigation[102]: (1) the more widespread use of evinacumab, a monoclonal antibody against ANGPTL3 that has been approved to reduce LDL-C in patients with homozygous familial hypercholesterolemia[103]; (2) hepatocyte-directed antisense oligonucleotides that inhibit apoCIII production[102]; (3) an siRNA inhibitor (ARO-ANG3)[104]; and (4) vaccines producing antibodies against ANGPTL3, editing the gene encoding ANGPTL3; if the latter proves to be successful, it could provide a "one-shot" long-term therapy. Similarly, CRISPR base editing of PCSK9 has been shown to lower LDL-C in nonhuman primates and is undergoing clinical studies in patients at the time of this writing.[105]

LIPOPROTEIN (A)

Elevations of circulating lipoprotein (a) are associated with four interrelated phenotypic changes, each of which increases CV risk: (1) accelerated atherogenesis, (2) intensification of vascular inflammation, (3) worsening of calcific AS, and (4) enhancement of a prothrombotic state.[106] Lp(a) can be reduced with antisense oligonucleotides that target the *LPA* gene, thereby inhibiting hepatic production of Lp(a),[107] as well as with an siRNA.[108] Studies on the clinical effects of reducing Lp(a) are ongoing.

OBESITY (SEE CHAPTER 28)

It is well established that obesity, generally defined as a body mass index (BMI) ≥30 kg/m^2, is a serious, chronic health problem affecting more than 650 million adults worldwide, including 40% of American adults, and contributes importantly to the global burden of disease.[109] Obesity is frequently accompanied by dyslipidemia, hypertension, AF, and type 2 diabetes mellitus (T2DM).[110] In 1983, in a long-term follow-up of participants in the Framingham Heart Study (FHS) (see later), obesity was shown to be an *independent* risk factor for ASCVD, coronary death, and HF.[111] Subsequently, it was reported that marked weight loss induced by bariatric surgery in obese persons resulted in reductions in the incidence of AMI and HF as well as prolonged survival.[112]

In 1987 a glucagon-like peptide–1 (GLP-1) produced by incretin cells was discovered.[113,114] GLP-1 receptor agonists (GLP-1RAs) and their analogues stimulate insulin secretion and suppress glucagon secretion. Importantly, they also inhibit gastrointestinal motility, slow food absorption, and reduce appetite. In addition to being potent antidiabetic agents, this drug class is effective in weight control in obese and overweight persons.[115,116] GLP-1RAs have been combined with other insulinotropic polypeptides, some of which exhibit more superior antiglycemic and weight loss actions. One such agent, tirzepatide, has gained approval for both the management of T2DM and weight control.[117]

Semaglutide is a GLP-1RA that has been studied in several double-blind, randomized, placebo-controlled trials in patients with CV disease to whom it was administered subcutaneously weekly. In patients with T2DM and at high CV risk, semaglutide reduced the composite of CV death, nonfatal myocardial infarction (MI), and nonfatal stroke.[115] GLP-1RAs are generally well tolerated, although mild to moderate gastrointestinal disturbances have been reported and can be avoided or minimized by low initial dosing and gradual dose increments. Two trials have examined semaglutide's effects in HF with preserved ejection fraction (HFpEF). In the STEP trial, conducted on obese patients *without* T2DM, semaglutide reduced body weight and symptoms of HF, lowered C-reactive protein (CRP), and improved exercise function.[118] The SELECT trial was carried out in 17,604 patients with preexisting CV disease with a BMI of ≥27 kg/m^2. Semaglutide led to a 20% reduction in the composite of CV death, nonfatal MI and nonfatal stroke, and the combination of CV death and hospitalization for HF, the progression of kidney disease, CRP, lipid measurements, BP, and all-cause mortality, the latter by 19%.[119] Based on these two trials, excessive weight may now be regarded as a risk factor for the progression of further CV disease that can be reduced by a potent GLP-1RA.

ACUTE CORONARY SYNDROMES (SEE CHAPTERS 34, 35, AND 36)

The Past

In the 19th century, physiologists observed that ligation of a major coronary artery in dogs led rapidly to fatal VF. It was assumed that in patients with ASCVD, coronary artery thrombosis suddenly led to occlusion, which was responsible for SCD; indeed, this condition, now named *acute myocardial infarction* (AMI), was called *coronary thrombosis* for many years. In 1910, Obastov and Straschenko, two Ukrainian physicians, reported that some patients who experienced attacks of severe anginal chest pain survived initially and later at postmortem examination exhibited myocardial necrosis in the distribution of the occluded coronary artery.[120] This finding was confirmed by Herrick, a Chicago physician, who also reported accompanying ECG changes.[121] Thus, at the beginning of the 20th century, CAD manifested in two forms: chronic stable angina, which had been described by Heberden in 1732,[7] and AMI, which was frequently but certainly not always fatal.

By mid-century AMI was recognized to be a major contributor to ASCVD. Many of the SCDs were caused by VF. The introduction of the coronary care unit in 1961 by Desmond Julian, a British cardiologist,[122] was critical to the prevention of these arrhythmic deaths, leading to a reduction of hospital mortality in AMI from about 30% to 15%. Appropriately, these units spread rapidly around the world.

The major remaining risk of AMI, especially with ECGs showing ST segment elevations (STEMIs), was due to large infarctions that caused LV failure. To improve clinical outcomes, efforts were made to reduce infarct size, which required immediate correction of the large imbalance between the O_2 supply and demand of the severely ischemic but still viable myocardium.[123] The first successful restoration of perfusion of a coronary artery obstructed by a thrombus in a patient with AMI was reported in 1976 by Yevgeny Chazov, a Soviet cardiologist, who infused a thrombolytic agent related to streptokinase directly into the affected coronary artery[124] (Fig. 1.4). In 1986, a large multicenter trial of AMI carried out in Italy, the GISSI trial, demonstrated a reduction in mortality with *intravenous* streptokinase.[125] GISSI was closely followed by the ISIS 2 trial led by Peter Sleight, a British cardiologist who demonstrated that the combination of streptokinase and aspirin was even more effective than streptokinase alone.[126] Myocardial reperfusion improved further with the development of a more potent fibrinolytic agent, tissue plasminogen activator,[127,128] followed by the use of balloon angioplasty (PTCA) and then the insertion of drug-eluting coronary artery stents.

To be effective, coronary reperfusion must be carried out as soon as possible after the onset of symptoms, leading to the motto "time is muscle." At present, patients with suspected STEMI are rushed to a hospital, usually by emergency services. If the diagnosis is confirmed, PCI is performed immediately; if it is not available, a rapid interhospital transfer is attempted, and/or a fibrinolytic agent is administered. However, in many instances, reperfusion is delayed for a variety of reasons.

Other immediate treatments of AMI include the administration of aspirin and an anticoagulant, beta-adrenergic blocking agents, and inhaled oxygen. After stabilization, colchicine, an antiinflammatory agent, has recently been added[129] as well as agents that inhibit the RAS.[130] With successful early reperfusion and these other therapies, the early mortality in STEMI has declined to an average of approximately 5%, depending on age, infarct size, and comorbidities. Remaining problems include the development of acute HF and cardiogenic shock; the latter still has a mortality rate of about 50%, and in patients undergoing fibrinolysis the development of intracranial hemorrhage is a serious but uncommon complication.

In 1937, Feil, an American physician, described patients with episodes of prolonged severe anginal pain at rest, often preceding an AMI.[131] This was followed by the recognition of a condition, named unstable angina (UA), that was considered to be intermediate between chronic stable angina and AMI.[132] With progressive increases in the sensitivity of biomarkers of myocardial necrosis, culminating in high-sensitivity troponin (hsT), it became evident that a majority of patients with UA actually had AMI without the characteristic ST

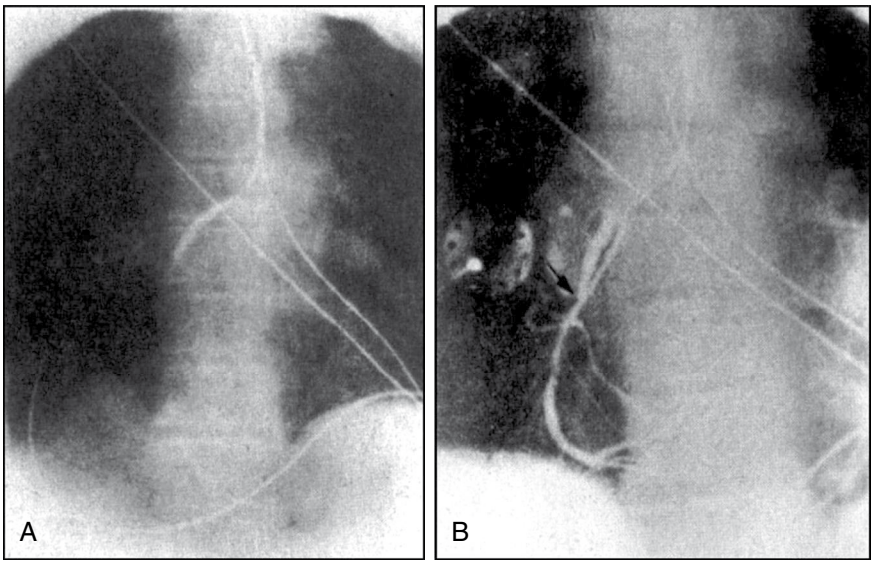

FIG. 1.4 Acute myocardial infarction. A, Pretreatment total occlusion of right coronary artery (RCA). B, Post-treatment with intracoronary fibrinolytic (largely streptokinase). There is persistent nonocclusive narrowing of the RCA, with perfusion of the inferior wall of the left ventricle. (From Chazov EI, Matveeva LS, Mazaev AV, et al. Intracoronary administration of fibrinolysin in acute myocardial infarction. *Ter Arkh.* 1976;48:8–19.)

segment elevation. Thus, patients with AMI can present with or without STEMI.[133] The latter often exhibit coronary arterial narrowing without total occlusion and is termed non-STEMI (NSTEMI) and can usually be corrected by PCI.

Coronary Risk Factors

In 1948, US President Truman established the National Heart Institute (now the National Heart, Lung, and Blood Institute; NHLBI). An early effort by the institute was an epidemiologic study of CAD, carried out in Framingham, a town near Boston. The FHS was the first large, prospective, multigenerational observational study in the United States; it was established primarily to identify the determinants and natural history of CAD.[134] In addition to the initial clinical assessments, imaging studies, biomarkers, genomics, and other "omics" were included as they became available. In 1961, William Kannel, an epidemiologist in the FHS, reported that the risk factors for CAD were hypertension, elevated serum cholesterol, diabetes, electrocardiographic LV hypertrophy, and male sex.[135] This led to the development of the FHS risk score, a simplified version of which has been used widely in clinical practice. More recently it has been updated to the Pooled Cohort Equations.[136]

HEART FAILURE (SEE PART 7)

The Past

Forty years after Harvey's publication of *De Motu Cordis*,[1] Richard Lower, an Oxford physician, described HF as "when the heart lacks the strength to preserve a constant circulation of the blood. This can occur when the heart is too laden with fat or suffers from inflammation, so that it is unable to pulsate and contract."[3] In 1831, James Hope described the "backward theory of HF," with elevation of pressures upstream of the affected ventricle or valve.[137] In opposition, about a century later, James Mackenzie,[138] also a British physician, asserted that diminished cardiac output was the principal problem in HF: the "forward failure theory of HF." Irrespective of which theory was accepted, it was agreed that retention of sodium and water caused dyspnea and edema in HF.

Before the 20th century, there was no effective treatment for HF other than bed rest and digitalis; the clinical efficacy of this drug is now in question. Mercurial diuretics became available in the 1920s and were widely used but required deep intramuscular injection and were only moderately effective. By the 1950s, a benzothiadiazine (chlorothiazide), an orally active diuretic, was developed and greatly improved the care of patients with HF. The more potent loop diuretics were introduced in the 1960s.

Two classes of neurohormonal blockers, beta-adrenergic blockers, discovered by James Black,*[139] a British pharmacologist, as well as inhibitors of the RAS (angiotensin-converting enzyme inhibitors [ACEIs][140] and angiotensin receptor blockers) reduced the symptoms and prolonged the life of patients with HF. Cardiac transplantation, introduced in 1967 by Barnard, a surgeon in South Africa,[141] extended life in patients with advanced HF whose disease was not controlled by GDMT and for whom a donor heart could be identified.

During the 19th and most of the 20th centuries, CV physiologists and cardiologists assumed that HF was caused only by the inability of the left ventricle to eject blood during systole, and because the ventricle became dilated, its ejection fraction declined, thus causing HF with reduced ejection fraction (HFrEF). In the 1980s, patients with HF in whom systolic function was largely preserved, but in whom ventricular filling (diastolic function) was impaired, were described.[142] This led to HFpEF, which by the end of the 20th century was responsible for about half of all patients with HF.

The Present

Four disease-modifying drugs have been shown to reduce CV mortality and to reduce symptoms in patients with HFrEF. The first two are the beta-adrenergic blockers and the inhibitors of the RAS. An alternative to the latter is sacubitril/valsartan, a first-in-class angiotensin neprilysin inhibitor (ARNi) that was shown by McMurray to be superior to enalapril, a widely used ACEI.[143] The third are mineralocorticoid receptor antagonists (MRAs), shown by Pitt and Zannad to be life-prolonging in patients with HFrEF.[144] The fourth are the SGLT2is, which cause glucosuria and were shown to improve cardiac function and reduce HF symptoms and hospitalization in patients with HF.[145–147] Each of these four drug classes has been reported to prolong survival in patients with HFrEF. The aggregate life-prolonging effect of this drug combination GDMT is substantial.[148] The SGLT2is and MRAs are effective in patients with HFpEF and HFrEF[149–151] and have also been shown to be renoprotective in patients with chronic kidney disease.[146]

Three types of devices introduced in the last quarter of the 20th century have had beneficial effects in the treatment of HF: (1) cardiac resynchronization therapy,[152] in which multisite pacing of the ventricles enhances ventricular performance; (2) implanted cardioverter-defibrillators, which reduce the incidence of SCD, not uncommon in patients with HF; and (3) left ventricular assist devices (LVADs) (see later).

The Future

A number of additional pharmacologic agents in varying stages of development will be useful in preventing or delaying the development of HF. In patients with persistent and/or resistant hypertension, these include an inhibitor of ATG,[43] an aldosterone synthase inhibitor,[44] transthyretin tetramers in the treatment of amyloidosis, inhibitors of inflammation (see later), and a battery of powerful weight loss drugs for obese and markedly overweight patients with HFpEF.[115–119] There will be increasing use of wearable and implanted devices that will transmit heart rate, rhythm, respiratory, and left atrial pressure continuously[77] (see Fig. 1.3). Allotransplantation will increase with the growing use of donor hearts after circulatory death and of the use of technology that will prolong their viability[153] (Fig. 1.5). In the more distant future, xenotransplantation of porcine hearts obtained from pigs bred with "humanized" genes will become frequent.[154]

As discussed in Chapter 10, AI can detect asymptomatic reduction of LV function from a 12-lead (and in some instances single-lead) ECG. This can serve as a useful screening test that, if it is positive, could lead to further studies and earlier treatment that delays or even prevents the development of overt HF.

ASSISTED CIRCULATION (SEE CHAPTER 66)

The Past

In 1968, the use of an intraaortic balloon pump (IABP), was reported by Kantrowitz, a cardiac surgeon, and colleagues in New York.[155] This device has been employed in patients with cardiogenic shock secondary to AMI or after cardiotomy. Although the IABP exerted a modestly favorable effect on hemodynamics, it has not proved sufficient to improve clinical outcomes, and more powerful devices were required for the treatment of advanced HF. During the 1980s and 1990s, a variety of pneumatic LVADs underwent extensive animal testing and clinical trials. Although they were used in the treatment of patients in cardiogenic shock and as a bridge to cardiac transplantation, it was not clear whether they were superior to existing GDMT.

The REMATCH trial in 2001, led by Eric Rose, a New York cardiac surgeon, was the first controlled randomized trial that compared long-term LVAD support with optimal GDMT in patients with advanced (class IV) HF who were ineligible for cardiac transplantation. This trial showed that 1 year after randomization, survival in the LVAD group was twice that in the GDMT arm.[156] This landmark trial served as a potent stimulus to the field and led the FDA to approve the LVAD employed in the trial as a bridge to allotransplantation or for destination therapy, that is, for the patient's lifetime. The device, although reflecting the state of the art at the turn of the century, was bulky and noisy, with the large pulsatile pumping chamber placed in the abdomen. Although its use prolonged survival, it was associated with many complications, including local and systemic infections, stroke, excessive bleeding, thrombosis, and device failure.

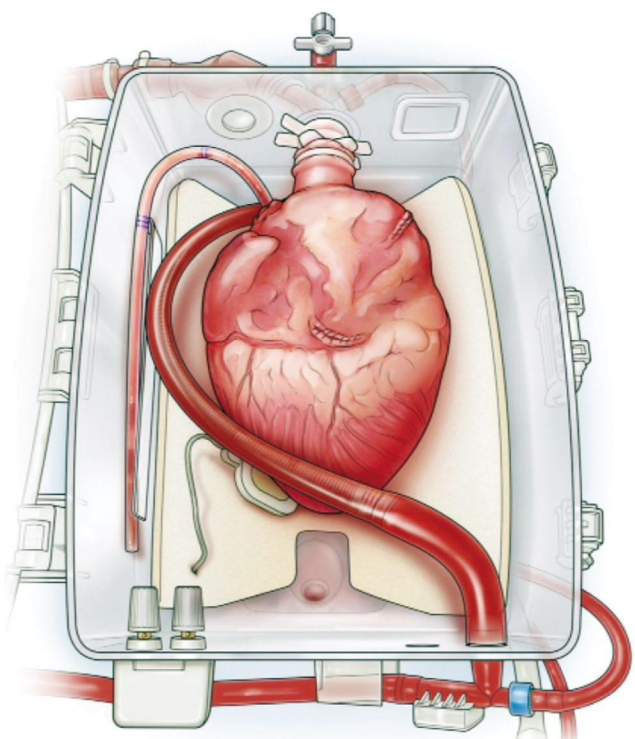

FIG. 1.5 Ex vivo perfusion of donor hearts for human heart transplantation. (From Ardehali A, Esmailian F, Deng M, et al. Ex-vivo perfusion of donor hearts for human heart transplantation (PROCEED II): a prospective, open-label, multicentre, randomised non-inferiority trial. *Lancet*. 2015;385:2577–2584. Courtesy Transmedics, Andover, MA.)

The Present

Many refinements were made in LVADs in the last quarter century. An important step was the development of an intrathoracic continuous axial flow pump,[157] which was associated with better outcomes than the pneumatic device used in REMATCH. A further development was the HeartMate 3, a magnetically levitated centrifugal flow pump, which was smaller, and in a trial led by Mandeep Mehra, a Boston cardiologist, was also shown to be safer, with marked reductions in pump thrombosis, lower stroke rates, and bleeding.[158]

Early in the 21st century, several reports appeared on a small fraction of patients receiving LVAD support who exhibited sufficient recovery of cardiac function to allow explantation of the device. Teams in London,[159] Louisville, Kentucky,[160] and Berlin described the patients in whom recovery was possible; they were younger than the patients usually receiving an LVAD, had a shorter duration of HF, and were more likely to have had a dilated rather than an ischemic cardiomyopathy.

LVADs are currently employed in patients with advanced HF, often defined as having been hospitalized for HF and having not responded to GDMT that usually included an inotropic agent. The quality of life and functionality are improved, and the median survival is now 5 years. However, rehospitalization for infection, bleeding, other CV events, or comorbidities still occurs.

The Future

Although the currently available LVADs reflect striking advances when compared to their predecessors, further improvement is likely. With the demand for these devices increasing steadily and the rapid strides in bioengineering and material science, it is likely that the next generation of LVADs will be less expensive, easier to implant, and even less likely to thrombose, with transcutaneous transmission of power eliminating the need for drive lines and thus less likely to become infected.

It has been suggested that mechanical-assisted circulation might also be provided by an implanted extra-aortic counterpulsation system for patients with moderately severe, chronic HF. Such a device, designed for chronic ambulatory use, would not be in contact with blood and therefore would not require anticoagulation; it might be activated only intermittently when required. A second possible form of partial ventricular support might be implanted via a minithoracotomy and positioned in a subclavicular subcutaneous pocket, like a pacemaker. In a feasibility trial, it exhibited significant hemodynamic benefits and appeared to slow the progressive deterioration of advanced HF.[161] Although neither of these approaches are ready for clinical application, they do point to possible future directions. It is likely that further technologic advances will provide sufficient mechanical support of the circulation at an earlier stage of HF and thereby reduce the need for inotropic support, the need for an LVAD of the current variety, and the need for cardiac transplantation.

GENETICS AND GENOMICS (SEE CHAPTER 7)

The Present

The first decade of the 21st century was ushered in by one of the most important scientific accomplishments in the history of biology—the initial draft of the Human Genome Project (HGP), which provided an analysis of approximately 90% of the human genome. The HGP was developed by a team at the National Institutes of Health led by Francis Collins and simultaneously by Celera Genomics, a private company led by Craig Venter. Each group provided maps that defined the positions of individual genes and their DNA sequences. The "finished" sequence, more than 99% complete, was published by the HGP in 2004.[162] This was soon followed by the genomes of many animal species, bacteria, and viruses and the partial genome from extinct Neanderthals,[163] the latter rewarded by a Nobel Prize to Svante Pääbo, a Swedish geneticist.

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