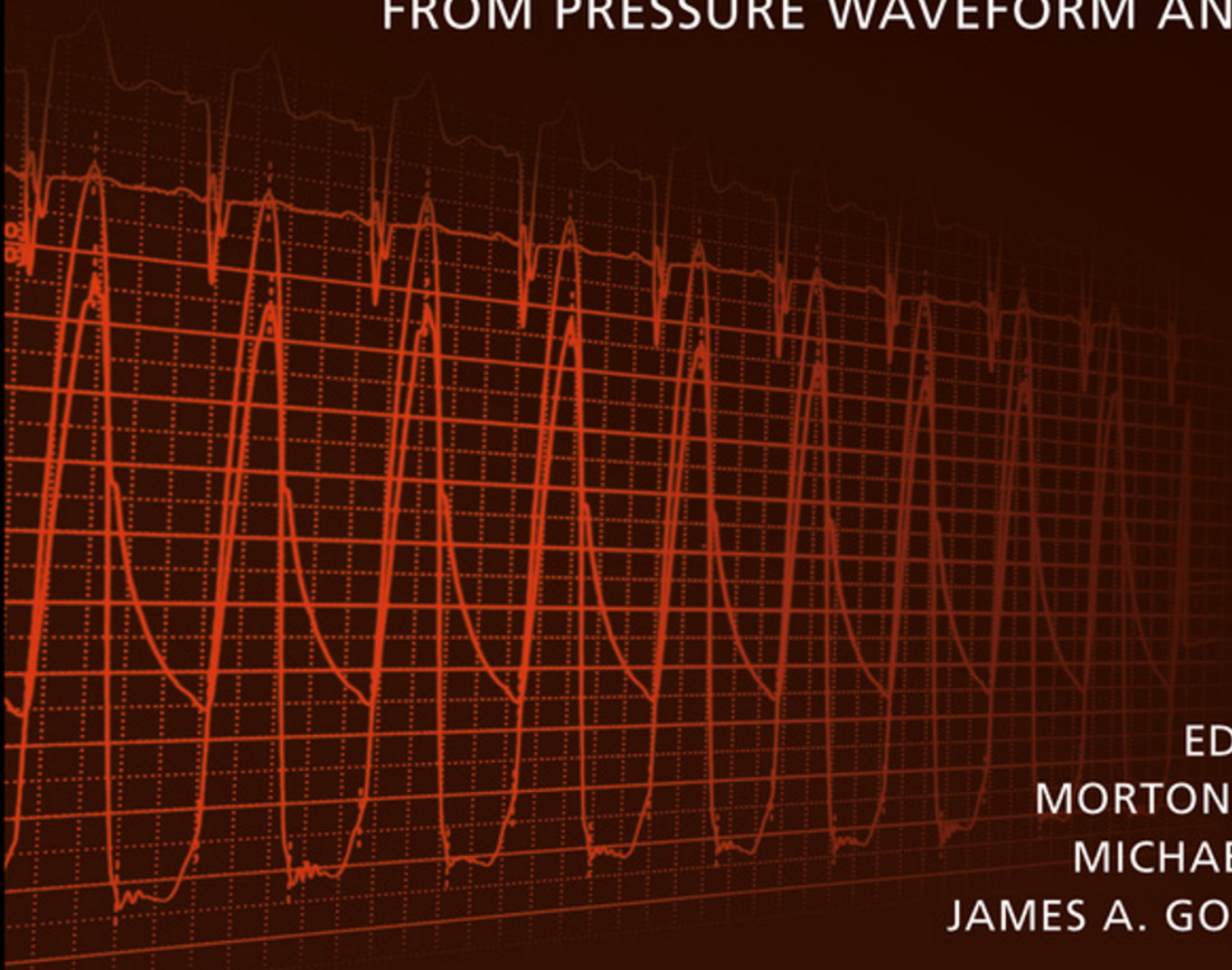
FOURTH EDITION

HEMODYNAMIC ROUNDS

INTERPRETATION OF CARDIAC PATHOPHYSIOLOGY FROM PRESSURE WAVEFORM ANALYSIS



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Hemodynamic Rounds

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Interpretation of Cardiac Pathophysiology from Pressure Waveform Analysis

Fourth Edition

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MJK—I thank Margaret and Anna Rose, the continuing systole of my life, and my deepest appreciation to my fellows-in-training, for without them there would be no point in these exercises.

MJL—To Amy, Parker, and Taylor, the essential pieces to my life.

JAG—To my wife Cindy, who keeps life fun while I am working.

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Preface to the Fourth Edition

Although superseded by modern echocardiography, invasive hemodynamic data continue to be an integral part of cardiology training and comprise validation for much of the pathophysiology obtained from clinical examination, echocardiography, and new imaging modalities. With the advances in imaging technology, the continued reliance on the graphics of hemodynamics has been in decline. However, hemodynamics remain useful for diagnosis and treatment of the multitude of cardiovascular conditions. In the care of the cardiac patient, a critical integration of clinical symptoms, anatomical disorders, and the physiologic underpinnings of these disorders often leads to the best diagnosis and treatment. The understanding of hemodynamic waveforms and the insights provided into the patient's pathophysiology remain the cornerstone for this text.

The first edition of *Hemodynamic Rounds* emphasized the interpretation of hemodynamic waveforms for clinical decision-making as presented from a series of cases published in *Catheterization and Cardiovascular Diagnosis*, now known as *Catheterization and Cardiovascular Interventions*. The case-based format limited itself to description of individual hemodynamic tracings, but was not presented in a formalized textbook fashion. The subsequent two editions of *Hemodynamic Rounds* extended this work, enlarged it, and reorganized it into new sections, providing a more logical approach to the study of pressure waveforms and the associated pathology.

This fourth edition further expands a more thematic approach to the understanding of pathophysiologic waveforms. Since the last edition new procedures such as TAVR (transaortic valve replacement) have provided unique insights into intraprocedural hemodynamics as guides or warning signs of impending complications. The text has been divided into six major parts, logically arranging the previously material and adding new and dynamic tracings, incorporating some of the latest publications on novel hemodynamic topics as they continue to evolve and move into our modern practice.

Part One describes normal and pathophysiologic hemodynamic waveforms and is organized according to the study of pressure wave measurement systems, artifacts, and normal waveforms. The hemodynamics of the tricuspid valve, the mitral valve, and left-sided V waves are reviewed. Left ventricular end diastolic pressure, simultaneous right and left heart pressures, and effects of nitroglycerin and pulsus alternans are also discussed.

Parts Two, Three, and Four cover valvular, constrictive, and restrictive physiology and structural heart disease hemodynamics, respectively. In Part Three, constrictive, restrictive, and tamponade physiologic waveforms are described in detail. Among the topics in valvular heart disease in Part Two, hypertrophic obstructive cardiomyopathy is included in an expanded presentation on the history of the TASH methodology and its outcomes. More uncommon hemodynamics are provided again in Part Five, which covers several topics including coronary and renal hemodynamic assessment along with congenital heart disease, and a unique chapter on left ventricular support devices and "extra" hearts, both transplanted and mechanical. The material on coronary hemodynamics has been expanded given a decade of new studies demonstrating better outcomes using interventions guided by FFR (fractional flow reserve) and the emergence of basal indices to assess coronary stenoses. Of course, after two decades of study and publications, coronary hemodynamics can be used for better decision-making during coronary angiography in daily practice.

The concluding Part Six on clinical-pathophysiologic correlations is dedicated to a discussion of crucial clinical and bedside correlations of hemodynamics, describing the anatomic and pathophysiologic presentations of dyspnea, edema and anasarca, syncope, hypotension, and low cardiac output in four distinct blocks, presenting correlative findings between anatomy, hemodynamics, and clinical manifestations.

It is the hope of the authors that this work will be of lasting value to students, trainees, practicing physicians,

and all related health-care personnel dealing with the important subject of cardiac hemodynamics. We thank Dr. Frank Hildner, first editor and founder of *Catheterization and Cardiovascular Interventions*, formerly *Catheterization and Cardiovascular Diagnosis*, for his encouragement and involvement with this work, without which this book would never have been published.

Morton J. Kern, MD
Michael J. Lim, MD
James A. Goldstein, MD

Introduction

Morton J. Kern and James A. Goldstein[1]

Historical Review

On February 28, 1733, the president of the Council of the Royal Society, Sir Hans Sloane, requested that Stephen Hales, one of the counselors, present his information on the mechanics of blood circulation from a previous presentation of a series of hemodynamic experiments reported in his book *Haemastaticks* [1]. Hales took his place in medical history next to William Harvey in studies of the human and animal circulation. *De Motu Cordis* [2] and *Haemastaticks* stimulated scientists' interest in the newly developed principles and mathematical computations of fluid mechanics as applied to circulatory physiologic events. The simple measurement of blood pressure now became a subject of great scientific concern.

From such basic interests, experimental physiologists at Oxford University in the 1800s, investigating the physiology of the circulation, began estimating the output of ventricular contraction and velocity of blood flow in the aorta, based on relatively primitive measurements of cardiovascular structures. These data remain valid today and correspond to those currently accepted and obtained by modern quantitative techniques. Cardiologists interested in hemodynamics should continue to emulate Stephen Hales, who relied on direct measurements and observations repeatedly checked and applied on simple but confirmed computations. Hales's numerous original achievements in hemodynamics are remarkable even by today's standards and include the first direct and accurate measurement of blood pressure in different animals (see Figure I.1) under different physiologic conditions such as hemorrhage and respiration; cardiac output estimated by left ventricular systolic stroke volume measured from the diastolic volume after death of the animal; calculations of pressure measured on the internal surface of the left ventricular at the beginning of systole; and determination of blood flow velocity in the aorta approximating 0.5 m/sec. Hales introduced the concept of the wind castle or capacitance effect in the transformation of pulsatile flow in large vessels to continuous flow in smaller vessels. He also made the first direct measurement of venous blood pressure and correct interpretation of venous return on cardiac output in relation to contraction and respiration. Since recording equipment documenting Hales's observations was unavailable, understanding the unique collection of data depends on interpreting descriptive material.

Our current appreciation of hemodynamics, hopefully enhanced in this book, comes to us from a small group of modern physiologists active in the 1920s, among whom Dr. Carl Wiggers, from Western Reserve University in Ohio, emerges as a major figure. Advances in hemodynamic research arose from the development of recording instruments with fidelity, able to capture and reproduce the waveforms of rapidly changing pressures during the various phases of cardiac contractions. Importantly, Dr. Wiggers and colleagues also employed the newly developed electrocardiogram to obtain simultaneous pressure waveforms and electrical activity and, thus, establish the fundamental electrical–mechanical intervals. These relationships are the benchmark against which the observations of the pressure tracings of classical diseased conditions can be compared [4]. Almost a hundred years separate Wiggers and other originators of clinical cardiovascular physiology from today's cardiologists.

From the time Claude Bernard (1840) coined the phrase "cardiac catheterization" [5], laboratories of that type and name had been examining human physiology, ultimately incorporating radiologically determined anatomic information during the development of cardiac angiography in the 1960s. In 1929, Werner Forssman performed the first documented human

1 With special acknowledgments to Frank Hildner, MD for his contribution.

Figure I.1 Drawing depicting Dr. Stephen Hales (seated) directing and observing the measurement of arterial pressure in a sedated horse circa 1730. *Source:* Lyon 1987 [3]. Reproduced with permission of John Wiley & Sons.

cardiac catheterization—on himself [6]—changing the nature of the work from exclusively animal to human subjects. In the late 1930s, Cournand and Ranges [7] used the new right-heart catheterization technique to investigate pulmonary physiology. World War II expanded the scope and direction of their work to include hemorrhagic shock and drug effects on the circulation. However, in those days the most serious problems patients presented related to congenital and rheumatic heart disease. Accordingly, laboratories around the world began publishing data on the hemodynamics and physiology of atrial septal defects [8], ventricular septal defects [9], stenotic and insufficient mitral and aortic valves, and ventricular function. The beginning of invasive cardiology had now evolved into a distinct field of study that would produce valuable diagnostic and therapeutic results.

Without doubt, the most crucial development needed for the advancement of the field was the cathode ray tube, a direct result of the war. Before the image intensifier [10, 11], cardiac fluoroscopy utilized high-dose radiation and required physicians to accommodate their eyes to a green fluorescent screen by wearing red goggles for 15–20 minutes before starting. Indeed, the faintly glowing image in a completely dark room frequently failed to reveal even the position of the catheter [12]. Without the additional light provided by the image intensifier, "angiocardiography" was nothing more than a simple flat-plate radiograph, or perhaps a sequence of cut films obtained on the newly developed serial film changer [13]. Cineangiography was developed in the late 1950s through the persistent efforts of lanker (1954) [14] and Sones (1958) [15]. Advanced radiographic imaging spurred the development of catheter invasive techniques, permitting the investigation of heretofore unapproachable anatomical sites, clinical conditions, and disease entities. The findings in turn resulted in more effective and novel cardiac surgical techniques.

After the basic mechanics of congenital anomalies and rheumatic abnormalities were confirmed, expanded study was undertaken of conditions related to occlusive coronary artery disease such as myocardial infarction, left ventricular aneurysms, mitral chordal, and septal rupture. The concepts of systolic and diastolic myocardial mechanical function, hypertrophic obstructive and nonobstructive cardiomyopathy, electrophysiologic relations, and other previously unappreciated conditions came under scrutiny. The result was a new body of knowledge leading to the development and use of remarkable noninvasive techniques, including phonocardiographs, ballistocardiographs, exercise stress testing, radionuclide imaging, and echocardiography. While echocardiography and other important imaging techniques have superseded invasive approaches to some diagnoses, the acquisition and interpretation of hemodynamics remain critical to a proper understanding and appreciation of all cardiovascular conditions and situations.

Approach to Hemodynamic Waveform Interpretation

In the first edition of *Hemodynamic Rounds*, each chapter had been published in the journal *Catheterization and Cardiovascular Diagnosis*, now known as *Catherization and Cardiovascular Interventions*, in a case-based format. The material was intended to provide both novice and advanced cardiologists with classical and, at times, unique pressure tracings to emphasize the value of careful waveform observation as it relates to different cardiac pathophysiologies. This fourth edition of the book carries this format forward and expands and updates the discussions to those areas where new information has been acquired, such as transaortic valve replacement (TAVR) procedures.

High-quality hemodynamic data are required for accurate hemodynamic determinations. As in the days of Stephen Hales, some hemodynamic data are

extraordinarily simple, such as using a sphygmomanometer for indirect assessment of systemic arterial pressure. Some hemodynamic data are complex, requiring placement of multiple and specialized catheters within various locations and heart chambers to determine valvular gradients, myocardial contraction, relaxation, compliance, impedance, and work [16–18]. Percutaneous coronary and structural heart interventions prompted the development of the study of human coronary hemodynamics, now available easily to all on a daily basis. For coronary stenosis assessment, intracoronary pressure and flow measures are indispensable for accurate diagnosis beyond angiography alone. Intravascular ultrasound and optical coherence tomographic imaging catheters provide unique complementary anatomic information only dreamed about by the founders of our field.

As with all laboratory data, the significance of various hemodynamic findings should be placed in context of the ancillary historical, clinical, echocardiographic, roentgenographic, and electrocardiographic data. Acting on isolated laboratory values is dangerous and continues to be the nemesis of all technical innovations in medicine.

Methodologies Involved in Hemodynamic Data Collection

Each laboratory, and preferably all physicians, should establish protocols for right- and left-heart catheterization. A uniform and consistent approach to data collection insures complete, accurate, and reliable data for the majority of clinical problems. The standardized routine also obviates easily overlooked data collection steps being missed. Further, time is saved during procedure setup and data recording. The technical staff do not have to rethink what will happen for the unique and personal hemodynamic protocol of each different operator. Right-heart catheterization, sometimes performed sequentially with left-heart catheterization, may often be combined with it simultaneously to provide the most complete data. In most academic laboratories, a combined methodology is preferred.

The methodology for performing right-heart catheterization has been reviewed previously [19], but the indications have changed [19,20]. In general, routine right-heart catheterization is not indicated, but certainly should be liberally employed when patient care demands it. Shanes *et al.* [21] and Barron *et al.* [22], though arriving at opposite opinions, agree that right-heart catheterization is critical to evaluate patients with previous congenital heart disease, valvular heart disease, left- or right-heart failure, cardiomyopathy, or any unexplained significant clinical historical or physical findings.

Left-heart hemodynamic measurements most often use a single pressure transducer which screens for LV–aortic gradients. For accuracy, simultaneous left ventricular (LV) and central aortic pressure can easily be obtained using a dual-lumen pigtail catheter with two transducers. Measurements of cardiac work, calculation of flow resistance, valve areas, and shunt calculations require accurate hemodynamic data, arterial and venous blood oxygen saturations, and cardiac output determinations.

If hemodynamic information is considered important, the operators should take the time to obtain reliable and unequivocal pressure waveforms, separating artifact from true pathology. To achieve this goal, operators must be familiar with the equipment producing the waveforms and the sources of error found in recording techniques, tubing, transducers, and catheters. A complete description of the mechanics, techniques, pitfalls, and errors of hemodynamic data recording is provided in the *Cardiac Catheterization Handbook*, sixth edition, 2015 [23].

Initiating the Study of Pressure Waveforms

Pressure waveforms may be confusing for both the cardiovascular fellow-in-training and the clinician trying to understand the results of the procedure. After an intense training period in which the components of all pressure waves found in cardiovascular structures are reviewed and discussed, the young physician must be encouraged to continue practicing pattern recognition, deductive analysis, and a systematic approach to understanding the full meaning of the complete pressure data obtained. This systematic waveform interpretation includes consideration of the following key points:

1) Identify the cardiac rhythm. Most cardiac events can be identified by their timing from within the R–R cycle. Hemodynamic data obtained during arrhythmias may be confusing, since the various irregular contraction sequences distort pressure waves.
2) Determine the pressure scale on which the waveform is recorded and verify the pressure per division to be certain there is no recording artifact. Also, note the recording speed to assess the appropriate cardiac rhythm and timing of events occurring within one cardiac cycle. The comparison of waveforms for the chamber of interest should be made against known waveforms of normal physiology. The type of artifacts due to catheter fling or over- or underdamping will be discussed in the initial chapters.
3) Interprete the waveforms in conjunction with the clinical presentation and suspected diseased conditions

of the patient. A large V wave does not always represent valvular regurgitation. The equilibration of right and left ventricular diastolic pressures may be hypovolemia rather than pericardial constriction. Consider alternative clinical and physiologic explanations.

The examination, consideration of possible mechanisms, and clinical interpretation of the various waveform phenomena form the rationale for this book. We hope that this approach will enhance accuracy and lead to the best decisions for your patients' clinical care.

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Part One

Normal Waveforms

1

Principles of Normal Physiology and Pathophysiology

James A. Goldstein and Morton J. Kern

Pathophysiologic derangements of cardiac anatomic components and mechanics manifest as "cardinal" cardiovascular symptoms, most of which are reflected in distinct hemodynamic disturbances. These symptomatic–hemodynamic constellations include (i) dyspnea, reflecting pulmonary venous congestion; (ii) fatigue, attributable to inadequate cardiac output; (iii) syncope, resulting from transient profound hypotension; and (iv) peripheral edema, related to systemic venous congestion. Chest pain typically suggesting ischemia does not usually result directly from primary hemodynamic derangements, does not lend itself to this anatomic–pathophysiologic hemodynamic approach, and will not be addressed in these discussions.

It is important to emphasize that these symptom groups in isolation are nonspecific. Identical complaints reflecting disparate pathophysiologic processes can occur due to a variety of mechanisms. For example, dyspnea is an expected symptomatic manifestation of pulmonary venous hypertension attributable to a spectrum of left-heart derangements, the underlying mechanisms of which vary greatly (e.g., mitral stenosis, mitral regurgitation, left ventricular cardiomyopathy, etc.). The treatments and prognoses also vary greatly. Dyspnea is also commonly of pulmonary origin, with circumstances in which the heart may be completely normal or impacted only as an innocent bystander (e.g., cor pulmonale).

Similarly, peripheral edema and ascites reflect systemic venous congestion resulting from a spectrum of right-heart failure mechanisms (e.g., tricuspid valve disease, right ventricular cardiomyopathy, pericardial disorders, etc.). However, edema may also develop under conditions with normal systemic venous pressures, as may occur in patients with cirrhotic liver disease, nephrotic syndrome, inferior vena cava (IVC) compression, and so on. Thus, for cardiovascular assessment, symptoms and signs must be characterized according to the underlying anatomic–pathophysiologic mechanisms.

To establish an anatomic–pathophysiologic differential diagnosis, first consider the anatomic cardiac components (myocardium, valves, arteries, pericardium, and conduction tissue) that may be involved and then focus on the fundamental mechanisms that impact each anatomic component, finally asking how such anatomic–pathophysiologic derangements and hemodynamic perturbations are reflected in the symptoms, physical signs, and invasive waveforms.

Cardiac Mechanical Function and Hemodynamics

Hemodynamic assessment is an integral part of the anatomic–physiologic approach to circulatory pathophysiology, employing bedside examination with confirmatory or complementary invasive and noninvasive (echo-Doppler data) hemodynamic information.

The purpose of the cardiovascular system is to generate cardiac output to perfuse the body. However, although perfusion is the heart's "bottom line," perfusion depends on pressure to drive the blood through the tissues. Organ perfusion is determined by arterial driving pressure modulated by vascular bed resistances. The regulation of the circulation (pressure and flow) can be understood by the application of Ohm's law–related resistance to pressure and flow. In classical physics applied to an electrical circuit, Ohm's law is expressed as:

$$\Delta V = I \times R$$

where ΔV is the driving voltage potential difference across the circuit, I is the current flow, and R is the circuit resistance. Thus, circuit output or current flow is a function of the "driving" voltage divided by circuit resistance, or $I = \Delta V/R$. Translating Ohm's law to the cardiac circulation, blood pressure (dV) = cardiac output

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(I) × systemic vascular resistance (R) and can be applied to the systemic circulation or to individual organ beds.

The key components of blood pressure can be further considered. Thus, cardiac output (CO) = heart rate (HR) × stroke volume (SV). Furthermore, SV is a function of three cardiac mechanisms: preload, afterload, and contractility. Systemic vascular resistance is determined by total blood volume and vascular tone (a function of intrinsic vessel contraction or relaxation interacting with systemic and local neuro-hormonal influences, metabolic factors, other vasomotor mediators, etc.).

Fundamentals of Hemodynamic Waveforms: The Wiggers Diagram

All pressure waves of the cardiac cycle can be understood by reviewing and knowing how electrical and mechanical activity of the heart's contraction and relaxation are related. Every electrical activity is followed normally by a mechanical function (either contraction or relaxation), resulting in a pressure wave. The timing of mechanical events can be obtained by looking at the electrocardiogram (ECG) and corresponding pressure tracing (Figure 1.1) [1].

The ECG P wave is responsible for atrial contraction, the QRS for ventricular activation, and the T wave for ventricular relaxation. The periods between electrical activation reflect impulse transmission times to different areas of the heart. These time delays permit the mechanical functions to be in synchrony and generate efficient cardiac output and pressure. When the normal sequence of contraction and relaxation of the heart muscle is disturbed by arrhythmia, cardiac function is inefficient or ineffective, as demonstrated on the various pressure waveforms associated with the arrhythmia.

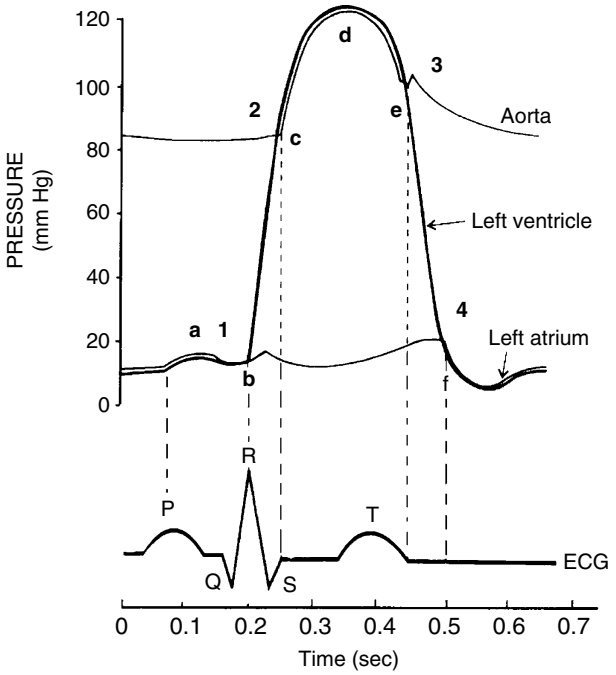

Figure 1.1 The Wiggers diagram. *Source:* Opie 2015 [1]. Reproduced with permission of Elsevier.

The cardiac cycle begins with the P wave. This is the electrical signal for atrial contraction. The atrial pressure wave (A wave; Figure 1.1, #1) follows the P wave by 30–50 msec. Following the A wave peak, the atrium relaxes and pressure falls, generating the X descent (point b). The next event is the depolarization of the ventricles with the QRS (point b). The left ventricular (LV) pressure after the A wave is called the end-diastolic pressure (LVEDP). It can be denoted by a vertical line dropped from the R wave to the intersection of the LV pressure (point b). About 15–30 msec after the QRS, the ventricles contract and the LV (and right ventricular, RV) pressure increases rapidly. This period of rise in LV pressure without change in LV volume is called the isovolumetric contraction period (interval b–c). When LV pressure rises above the pressure in the aorta, the aortic valve opens and blood is ejected into the circulation (point c). This point is the beginning of systole. Some hemodynamicists include isovolumetric contraction as part of systole.

About 200–250 msec after the QRS, at the T wave, repolarization starts and the heart begins relaxing. By the end of the T wave (point e), the LV contraction has ended and LV relaxation produces a fall in the LV (and aortic pressure). When the LV pressure falls below the aortic pressure, the aortic valve closes (point e). Systole concludes and diastole begins. After aortic valve closure, the ventricular pressure continues to fall. When the LV pressure falls below the left atrial (LA) pressure, the mitral valve opens and the LA empties into the LV (point f). The period from aortic valve closure to mitral valve opening is call the isovolumetric relaxation period (interval e–f). Diastole is the period from mitral valve opening to mitral valve closing.

Observing the atrial pressure wave across the cardiac cycle, it should be noted that after the A wave, pressure slowly rises across systole, continuing to increase until the end of systole when the pressure and volume of the LA are nearly maximal, producing a ventricular filling wave (V wave). The V wave (point f, #4) peak is followed by a rapid fall when the mitral valve opens. This V wave pressure descent is labeled the Y descent and usually parallels LV pressure. After the V wave, the LV is filled by the small pressure gradient assisting blood flow from the atria into the ventricles over the diastolic period (called diastasis), until the cycle begins again with atrial pressure building, until again atrial activation and contraction

generate the A wave, ejecting atrial blood into the LV. The peaks and descents of the atrial pressure waves are changed by pathologic conditions and are used to support the diagnosis of these pathologies, as will be seen in the examples dealing with heart failure, constrictive physiology, and RV infarction.

Valve Hemodynamics

To appreciate hemodynamic valve dysfunction, consider when cardiac pressure normally opens and closes the valves. The aortic and pulmonary valves open in systole, when ventricular pressure exceeds aortic pressure (and RV exceeds pulmonary artery or PA pressure). Stenosis of these valves produces systolic pressure gradients and characteristic high-velocity heart murmurs. The mitral and tricuspid valves are closed in systole when LV pressure is greater than atrial pressure. A mitral or tricuspid regurgitant valve that fails to close is characterized by a low-velocity systolic murmur with a rumbling quality. Conversely, incompetent aortic valves fail to seal and let blood continue to rush backward into the LV in diastole. The blood rushes into the LV with a diastolic murmur. At the beginning of diastole, LA pressure is at its highest. If the mitral valve is stenotic, the high LA pressure emptying into the LV produces a diastolic rumble. When reviewing the cardiac hemodynamics, we can always refer to the Wiggers diagram for what the expected normal hemodynamic responses should be.

Systolic and Diastolic Performance

The hemodynamic evaluation of the circulation may be considered as two sides of a single coin of cardiac function: (i) systolic function, the ability of the heart to pump, generate pressure, and perfuse the body; and (ii) diastolic performance, the ability of the chambers to fill at physiologic pressures with the preload necessary to generate SV.

Systolic Function

Systolic function reflects the ability of the ventricle to contract and generate output or stroke work, a function determined by its loading conditions, including both preload (determined by venous return and end-diastolic volume), afterload (related to aortic impedance and wall stress), and the contractile state (the force generated at any given end-diastolic volume).

The Frank–Starling mechanism established the relationship between end-diastolic volume (preload) and ventricular performance (stroke volume, cardiac output, and/or stroke work), wherein isovolumetric force at any given contractile state is a function of the degree of end-diastolic fiber stretch (also known as a force–length relationship; Figure 1.2). Thus, the normal LV functions are on the ascending limb of this force–length relationship. Afterload, the impedance during ejection, is defined as the force per unit area acting upon myocardial fibers, a force resulting in wall stress, which is expressed by the Law of Laplace (Wall stress = Radius/2 x Thickness). Afterload is influenced by changes in ventricular volume and wall thickness, as well as aortic pressure or aortic impedance.

Frank–Starling and Ventricular Waveforms

Ventricular waveforms reflect both systolic and diastolic function and include the effects of chamber preload, contractility, and afterload. The upstroke of RV or LV pressure (+ dP/dt) is influenced by preload and contractility, but is a poor measure of either. A brisk upstroke suggests reasonable function versus a sluggish or delayed pressure rise of depressed performance. The peak amplitude reflects both contractility and afterload.

In diastole, ventricular relaxation (- dP/dt) is an active energy-requiring process and reflects intrinsic aspects of myocardial contractility as the ventricle actively "relaxes." The pressure wave of the downstroke relaxation phase is an active process requiring adenosine triphosphate (ATP) and closely mirrors systolic function. The pressure downstroke can also be used to assess cardiac dysfunction. A slurred or retarded negative dP/dt (also known as tau, a LV relaxation measurement) may indicate cardiomyopathy and adversely influenced diastolic properties.

Arterial Waveforms

Arterial waveforms reflect the ejection of blood from the LV (and therefore its preload, contractility, and afterload), together with the intrinsic resistance and compliance of the pulmonary or systemic circuit. Filling pressures in the ventricles reflect diastolic properties, influenced by intrinsic chamber factors (e.g., pressure overload hypertrophy, volume overload, ischemia, infiltration, inflammation), as well as extrinsic effects from the pericardium or contralateral ventricle through diastolic ventricular interactions. The arterial waveform reflects dynamic interactions between SV and the capacitance (distensibility) of the peripheral arterial tree (which determines the rate at which the ejected volume of blood flows from the proximal arterial compartment into the peripheral tissues). The first peak of the arterial pressure waveform is the percussion wave, which reflects

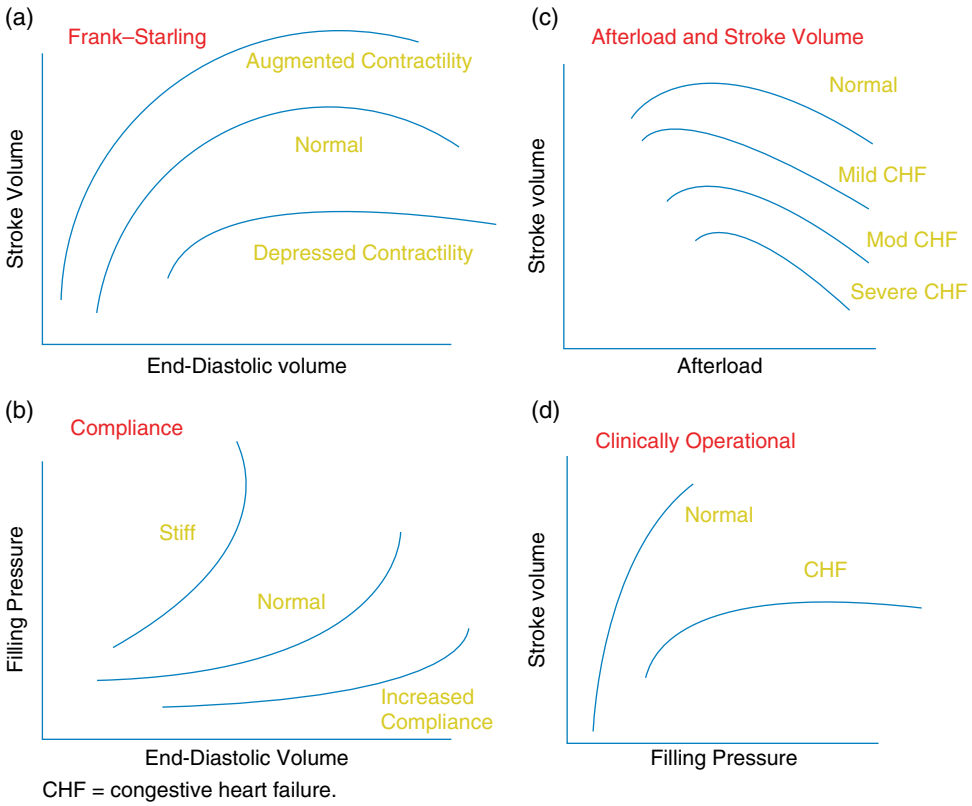

Figure 1.2 Family of cardiac function curves illustrating and combining principles of systolic function, diastolic compliance, effects of excess afterload, and a symphysis pertinent to clinical day-to-day life. (a) Classic Frank–Starling relationship of true end-diastolic volume output. (b) Compliance curves illustrating rapid rise in pressure attributable to impaired ventricular compliance. (c) Adverse effects of increasing afterload on ventricular stroke volume, particularly deleterious under conditions of depressed LV systolic function. (d) "Clinically operational" graph illustrating hemodynamic impact of mechanical abnormalities on patients who normally generate optimal stroke volume with low filling pressures, compared to dysfunctional ventricles (from both systolic and diastolic abnormalities) in which despite high filling pressures stroke volume is low.

the impulse of the LV stroke modulated by the reflected pressure from the vascular tree (and therefore its compliance); therefore, the arterial upstroke to its peak reflects LV preload, contractility, and afterload (both that imposed by the aortic valve and the stroke volume ratio or SVR). A secondary tidal wave follows, reflecting primarily the returning pulse wave from the upper body (peripheral tone), which then smoothly falls to the dichrotic notch (incisura) which corresponds to aortic valve closure. The subsequent decline in aortic pressure represents pure diastolic runoff. In early diastole, a small positive wave may be seen, the dichrotic wave, most likely an effect of reflected pulse from the lower body.

Pulse Amplification

As the pulse wave travels distally through the arterial circulation, the waveform may increase, a phenomenon termed peripheral amplification [2]. Amplification is characterized by a taller systolic peak, delayed dichrotic notch, lower end-diastolic pressure, and later pulse arrival. The systolic peak is steeper going to the periphery, attributable to summated reflected waves which develop as the narrowing and branching of blood vessels reflect some of the pulse back toward the aortic valve (Figure 1.3). As the resistance of the branching arterial tree increases, the more of the pressure wave is reflected. The more resistant the tree (i.e., the more atheromatous, hypertrophic, and calcified the arteries), the greater the magnitude of reflection. This is particularly relevant in those with stiff, noncompliant vessels (e.g., the elderly or hypertensive patients), in whom the pulse wave velocity is rapid and reflected waves from both upper and lower body return quickly during late systole, causing a more prominent tidal wave, which may even exceed the percussion wave. This condition may explain the absence of pulsus parvus et tardus in very elderly aortic stenosis patients in whom the carotid pulse is preserved and reflects an exaggerated peripheral amplification from noncompliant vessels). However, there is little change in mean arterial pressure (MAP) because there is little change in the resistance to flow from aorta to radial

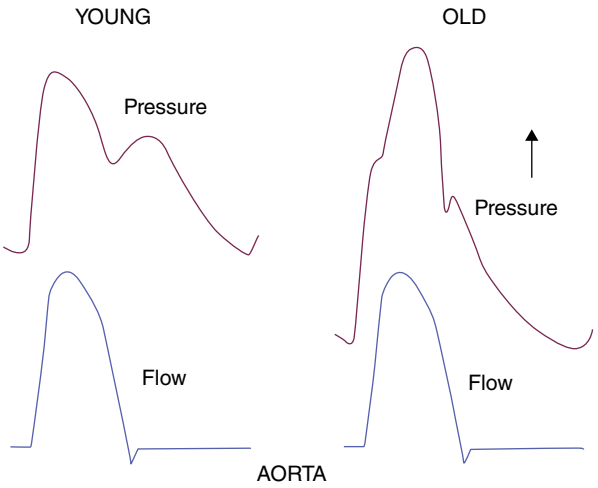

Figure 1.3 Arterial pressure wave reflection comparing manifestations in young versus elderly patients. The pressure wave reflection arises from the junction of conduit and low-resistance arteries with high-resistance arteries. Given that there are firmer junctions in the lower versus upper body, most reflection returning from the periphery comes from the lower body up into the proximal thoracic aorta. This reflected wave injects stroke volume, giving rise to the peak systolic pressure in the contour of the tidal wave. In older patients with nondistensible vasculature, the augmented reflected wave results in higher peak systolic pressure for any given stroke volume. *Source:* O'Rourke 2006 [2]. Reproduced with permission of Elsevier.

artery; rather, MAP changes more dramatically at the arteriolar level.

Aortic diastolic pressure reflects the aggregate resistance of the systemic arterial tree back upon the aortic valve. Noncompliant vessels similarly cause this pressure to be raised. In contrast, the soft vasoplegic (dilated or relaxed) vessels of a septic patient will offer little resistance, and the diastolic pressure will be lower. A regurgitant aortic valve will also cause this pressure to be lower than normal, because the pressure wave travels all the way through to the ventricle manifested as the regurgitant jet.

Pulse pressure is the difference between peak systolic and end-diastolic aortic pressures. A widened pulse pressure suggests aortic regurgitation, because in diastole the arterial pressure drops to fill the left ventricle though the regurgitating aortic valve, and at the same time forward runoff is great, since peripheral resistance is also reduced. In contrast, a narrow pulse pressure may occur in conditions such as cardiac tamponade, or any other low-output state (e.g., severe cardiogenic shock, massive pulmonary embolism or tension pneumothorax).

Pressure–Volume Loops

In aggregate, the relationships between preload, afterload, and contractility are illustrated in ventricular pressure–volume (PV) loops which plot the changes of these variables over a cardiac cycle [3]. Each PV loop (Figure 1.4) represents one cardiac cycle. Beginning at end diastole (point a), LV volume has received the atrial contribution and is maximal. Isovolumic contraction (a to b) increases LV pressure with no change in volume. At the end of isovolumic contraction, LV pressure exceeds aortic pressure, the aortic valve opens, and blood is ejected from the LV into the aorta (point b). Over the systolic ejection phase, LV volume decreases and, as ventricular repolarization occurs, LV ejection ceases and relaxation begins. When LV pressure falls below aortic pressure, the aortic valve closes, a point also known as the end-systolic pressure–volume (ESPV) point (c). Isovolumic relaxation occurs until LV pressure decreases below the atrial pressure, opening the mitral valve (point d).

The stroke volume is represented by the width of the PV loop, the difference between end-systolic and end-diastolic volumes. The area within the loop represents stroke work. Load-independent LV contractility, also known as Emax, is defined as the maximal slope of the ESPV points under various loading conditions, and the line of these points is the ESPV relationship (ESPVR). Effective arterial elastance (Ea), a measure of LV afterload, is defined as the ratio of end-systolic pressure to stroke volume. Under steady-state conditions, optimal LV contractile efficiency occurs when the ratio of Ea:Emax approaches 1.

The PV loop describes contractile function, relaxation properties, SV, cardiac work, and myocardial oxygen consumption. Hemodynamic alterations and interventions change the PV relationship in predictable ways and comparisons of various hemodynamic interventions can be made more precisely by examining the PV loop (Figures 1.5 and 1.6).

Acute changes in cardiac function such as might occur with acute myocardial infarction (AMI) are also easily demonstrated. In AMI, LV contractility (Emax) is reduced; LV pressure, SV, and LV stroke work may be unchanged or reduced, and LVEDP is increased. In cardiogenic shock, Emax is severely reduced, LV afterload (Ea) may be increased, LVEDV and LVEDP are increased, and SV is reduced, findings easily seen to display reduced LV contractile function, acute diastolic dysfunction, elevated LVEDV and LVEDP, and increased LV work (oxygen demand). In more severe cases of myocardial infarction that evolve into cardiogenic shock, LV contractile function is more severely reduced, with associated significant increases in end-diastolic pressure and volume. The LV impairment results in a markedly reduced SV, with an increased myocardial oxygen demand.

The most common applications of PV loops characterize only left ventricular hemodynamics. For research into right ventricular function or extracardiac problems,

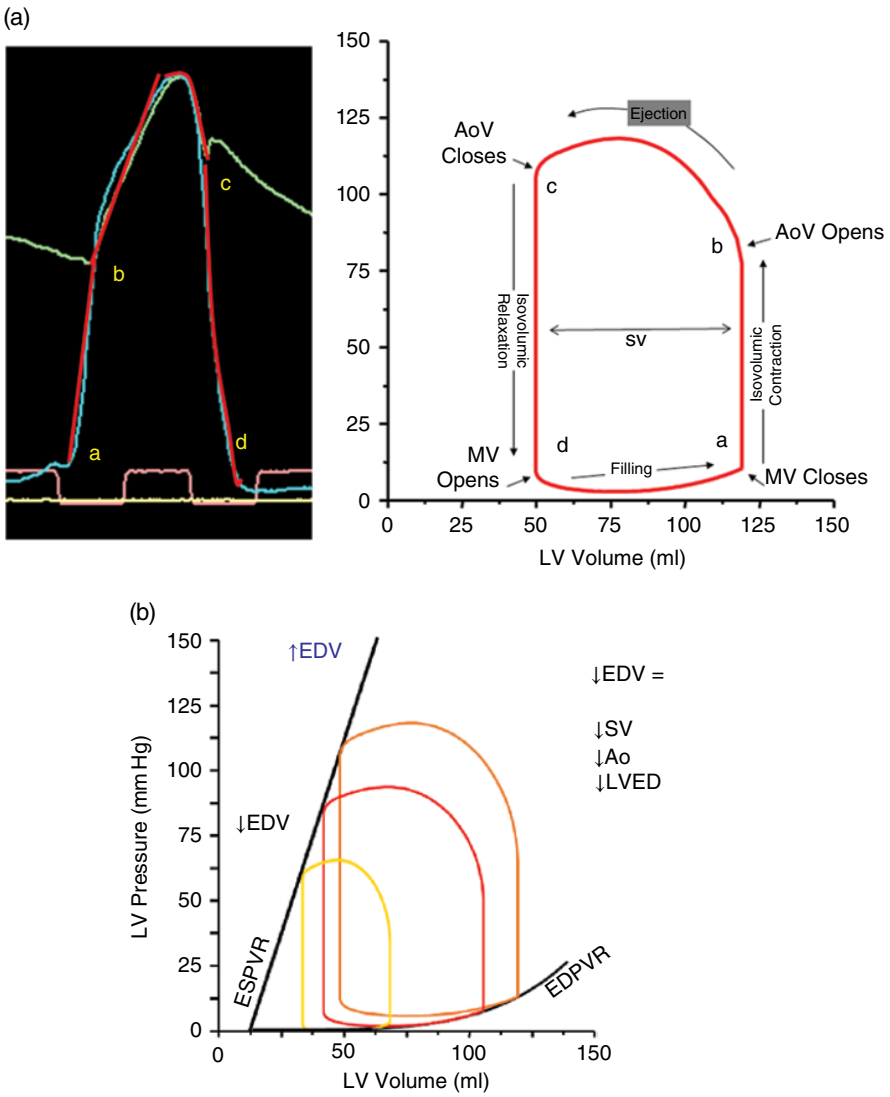

Figure 1.4 (a) The pressure–volume (PV) loop characterizes the changes in pressure flow over the course of one cardiac cycle. Left panel, the left ventricular (LV) and aortic pressure as measured during cardiac catheterization. Right panel, the PV loop derived from the hemodynamics of LV pressure and volume. Point a, LV end-diastolic pressure is followed by isovolumetric contraction ending at point b, the aortic valve (AoV) opening. Ejection continues until the repolarization of the LV produces a fall in LV ejection. LV pressure falls pasts point c, aortic valve closure, and continues to fall along the line of isovolumetric relaxation to point d, mitral valve (MV) opening. Changes in the shape of the PV loop demonstrate changes in contractility and cardiac output (stroke volume, SV). Load-independent LV contractility, also known as Emax, is defined as the maximal slope of the end-systolic pressure–volume (ESPV) point under various loading conditions, known as the ESPV relationship (ESPVR). Effective arterial elastance (Ea) is a measure of LV afterload and is defined as the ratio of end-systolic pressure and stroke volume. (b) The effect of changes in LV preload. Increasing the left ventricular end-diastolic pressure (LVEDP) along the line of the end-diastolic pressure–volume relationship (EDPVR). As volume is increased, LVEDP, SV, and aortic pressure increase. (*See insert for color representation of the figure.*)

the standard PV loops become complex and affected by additional factors, altering the PV loop configuration and interpretation.

Left Ventricular Rotational Mechanics: Systolic Twist and Diastolic Suction

Due to the spiral architecture of its myofibers, the LV twists or rotates from apex to base in a systolic "wringing" motion, generating the SV pathway through the LV outflow tract, an action that contributes significantly to LV systolic performance [4]. The LV twist also stores potential energy during the systolic phase. During subsequent isovolumic relaxation (an active ATP requiring process to re-sequester Ca++ into the sarcoplasmic reticulum), the "untwisting" or recoil of stored energy contributes to the diastolic "suction" that opens the mitral valve and accelerates atrial emptying along the LV inflow path. These important mechanics may be deranged under a wide variety of pathologic conditions,

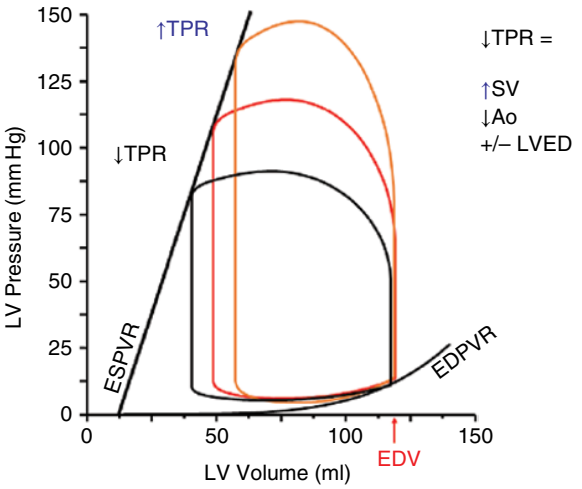

Figure 1.5 The effect of increasing afterload or total peripheral vascular resistance (TPR) decreases SV, increases aortic pressure, and minimally modifies LVEDP. (*See insert for color representation of the figure.*)

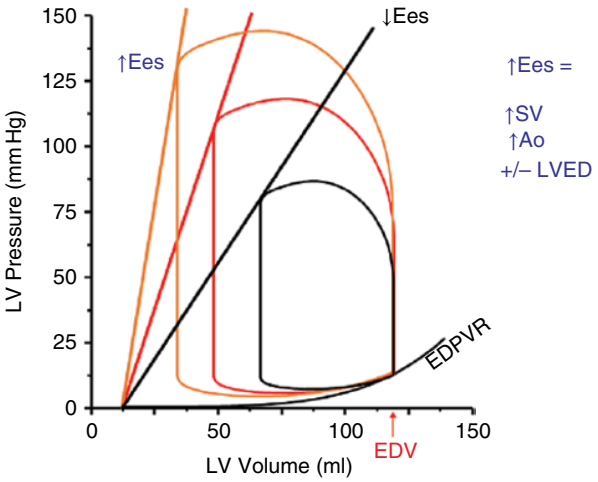

Figure 1.6 The effect of increasing contractility: the increasing slope of the line of end-systolic elastance (Ees) increases SV and aortic pressure, with minimal effect on LVEDP. (*See insert for color representation of the figure.*)

may be evident in hemodynamic traces, and contribute to clinical hemodynamic compromise.

Diastolic Performance and Cardiac Compliance

Diastolic function is the ability of a chamber to obtain its necessary preload at physiological filling pressures to generate CO under a variety of physiologic conditions, both at rest and during stress (exercise and metabolic stress such as infection, surgery, etc.). Diastole is not a passive process and is fundamentally influenced by various active factors. Diastole can be considered in four phases: isovolumic relaxation, early filling, diastasis, and atrial contraction. Isovolumic relaxation (lusitropic function) is a bit of a misnomer, for this is an active ATP-requiring process that untwists the LV, rapidly reducing ventricular pressure and through suction opening the mitral valve and initiating the rapid early filling phase. The majority of LV filling occurs here, through ventricular suction; this is followed by equilibration of LA and LV pressures and temporary cessation of flow (diastasis). Finally, active atrial contraction contributes the booster pump function, which delivers additional ventricular preload. This booster optimizes ventricular filling at a lower mean atrial pressure, and the end-diastolic "kick" elevates ventricular end-diastolic pressure (EDP) as the atria actively relax (X descent), thereby facilitating ventricular–atrial pressure reversal which initiates AV valve closure; in aggregate, these effects optimize LV preload while concomitantly minimizing the effects of ventricular diastolic pressure on the back tributaries of filling; that is, the lungs. These diastolic patterns are best illustrated not by invasive catheter interrogation, but rather by Doppler echocardiography under physiologic conditions. LV inflow velocity across the mitral valve is most rapid early, reflected as a predominant E wave on the transmitral Doppler echocardiogram. In normal anatomy, the preload contributed by atrial contraction is relatively small (in contrast to when the ventricle is stiff or the AV valve is obstructed), and therefore the velocity imparted by atrial contraction (the transmitral inflow A wave) is relatively low, thus the normal E/A wave ratio is greater than 1 but less than 2.

Functional preload is the amount of blood actually distending the cardiac chamber. This volume is reflected in filling pressure according to chamber compliance, the relationship between diastolic pressure and volume in any anatomic chamber (ventricle, atrium, pericardium, cranium, etc.). Cardiac chamber diastolic pressure is determined by the volume of blood in the chamber and its distensibility (compliance). In normal anatomy, optimal filling occurs at low filling pressures (Figures 1.2 and 1.7).

During diastole, the LV, left atrium, and pulmonary veins form a "common chamber," which is continuous with the pulmonary capillary bed; in the right heart a similar relationship exists. Diastolic dysfunction is defined as a functional abnormality of diastolic relaxation, filling, or distensibility, in which filling is limited by abnormal chamber stiffness (hypertrophy, ischemia, fibrosis, infiltration, extrinsic pericardial resistance). Increased stiffness dictates that at any given level of chamber filling, the filling pressure is disproportionately elevated (Figure 1.7). Diastolic dysfunction may occur in association with chamber dilation and related systolic dysfunction (e.g., ischemic cardiomyopathy), or with a small stiff chamber with an intact ejection fraction (e.g., hypertensive cardiomyopathy). Figure 1.2a is the classic Frank–Starling curve wherein end-diastolic volume (true preload) generates output (SV) dependent on the inotropic state. Pure diastolic pressure–volume relationships are illustrated in

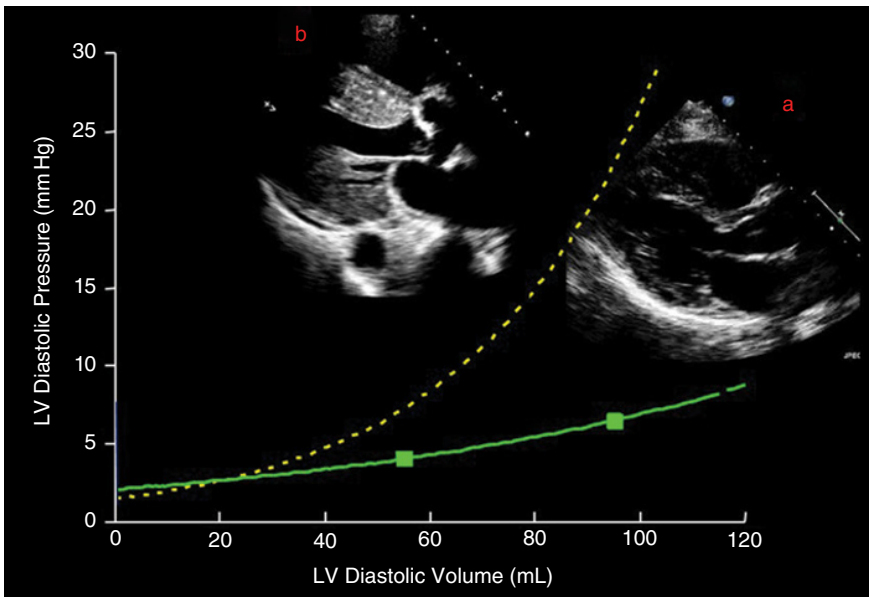

Figure 1.7 Left ventricular pressure–volume relationships demonstrating compliance curves in a normal LV (b) versus a thick stiff LV (a). (*See insert for color representation of the figure.*)

Figure 1.2b, wherein chamber compliance determines the actual distending pressure (and thus back pressure) for any given level of true preload (Figure 1.2c). What matters clinically is the diastolic pressure needed to generate a given SV. The compliant and contractile ventricle can accommodate a dramatically increased preload (i.e., stress or exercise) and generate high output at low filling pressures. In contrast, both types of heart failure, those with stiff hearts and preserved ejection fraction (HFPEF) and those with dilated hearts and reduced ejection fraction (HFREF), suffer elevated filling pressure and low output syndromes. Finally, consideration of these principles must also take into account the profound influence of excess afterload on ventricular performance (Figure 1.2c), which has disproportionate effects on SV in those with depressed ejection fraction (EF).

Differentiation of Cardiac Preload and Filling Pressures: Left Ventricular End-Diastolic Pressure Does Not Necessarily Reflect Left Ventricular Filling

Cardiac performance is optimal when SV is generated at low filling pressures. However, diastolic pressure generated by any given degree of filling (true preload) is a function of the compliance of the chamber, and therefore filling pressure reasonably reflects preload *only* if chamber compliance is normal.

Thus, impaired compliance attributable to intrinsic factors (hypertrophy, infiltration or ischemia, or primary pressure and volume overload) or extrinsic constraint (pericardial disease or ventricular interactions) distorts the relationship between filling pressure and true preload. This distortion may confound clinical and invasive hemodynamic assessment. Measurement of intracardiac filling pressures (for example, LVEDP) is used for two basic purposes: (i) to determine whether preload is adequate to generate SV (i.e., whether the patient is volume depleted); and (ii) to determine whether there is elevated pressure exerting adverse "backward" congestive effects.

With respect to assessing true preload in a patient with clinical low-output hypoperfusion, pulmonary capillary wedge pressure (PCWP) or LVEDP is a convenient surrogate for left-heart preload, although under noncompliant conditions (e.g., severe LV hypertrophy or cardiac tamponade) LV preload may be markedly reduced, but intracardiac pressures may be strikingly elevated. In fact, in some cases patients may be in pulmonary edema despite an LV with small cavity and intact contractility (e.g., restrictive cardiomyopathy). Conversely, chronic volume overload lesion such as aortic regurgitation may result in dramatically increased chamber volumes, but in those who are well compensated, intracardiac pressures are relatively normal as the chamber and pericardium dilate and become more compliant.

Cardiac Mechanics, Atrial Waveforms, and the Venous Circulations

A critical relationship exists among cardiac mechanics and atrial waveforms, the physiology of the venous circulations, and the dynamic effects of intrathoracic pressure (ITP) and respiratory motion on cardiovascular physiology, permitting a better interpretation of the waveforms to reflect pathophysiology.

Atrial Waveforms

Analysis of the atrial waveforms (Figure 1.8) yields insight into cardiac chamber and pericardial compliance. The atrial waveforms are constituted by two positive waves (A and V peaks) and two collapsing waves (X and Y descents). The atrial A wave is generated by atrial systole following the P wave on ECG. Atrial mechanics behave in a manner similar to that of ventricular muscle. The strength of atrial contraction is reflected in the rapidity of the A wave upstroke and peak amplitude. The X descent follows the A wave and is generated by two events: the initial decline in pressure reflecting active atrial relaxation, with a latter descent component reflecting pericardial emptying during ventricular systole (also called systolic intrapericardial depressurization, a condition that is exaggerated when pericardial space is compromised). The X descent's second component is affected by the pericardial space and changes when the ventricles are maximally emptied, therefore pericardial volume and intrapericardial pressure (IPP) are at their nadir.

During ventricular systole, venous return results in atrial filling and pressure which peak with the V wave, whose height reflects the atrial pressure–volume compliance characteristics. The subsequent diastolic Y descent represents atrial emptying and depressurization. The steepness of the Y descent is influenced by the volume and pressure in the atrium just prior to atrioventricular (AV) valve opening (height of the V wave) and resistance to atrial emptying (AV valve resistance and ventricular–pericardial compliance).

Venous Circulations and Respiratory Oscillations

Venous return to both atria is inversely proportional to the instantaneous atrial pressure, which is itself dependent on compliance. The lowest return occurs when each pressure is highest. Under physiologic conditions, venous return to both atria is biphasic, with a systolic peak determined by atrial relaxation (corresponding to

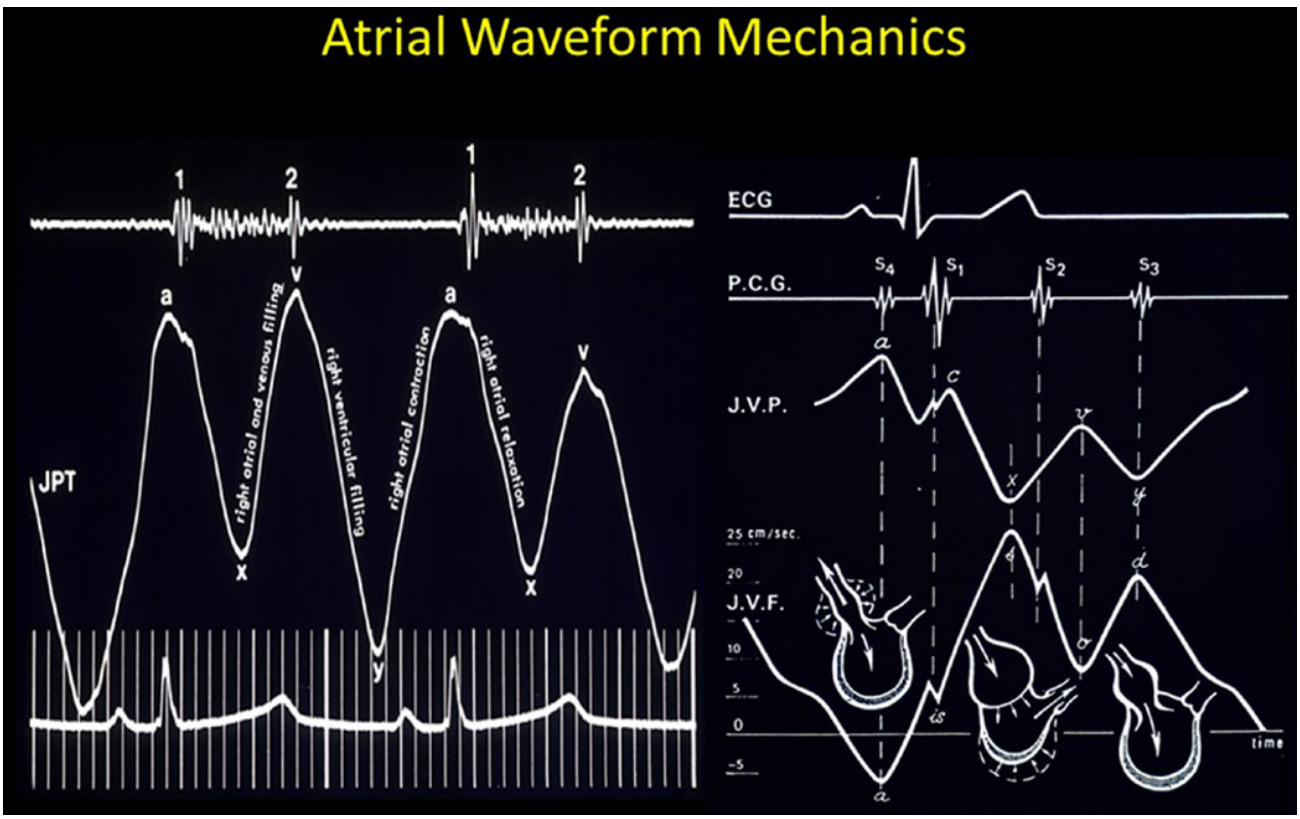

Figure 1.8 Atrial mechanical cycle. The upstroke and amplitude of the A wave reflect atrial contraction and the initial portion of the extra set reflects atrial relaxation, with the latter portion due to systolic intrapericardial pressurization. From the downslope of the latter portion of the extra set to the height of the V wave represents the peak period of atrial venous return filling (or regurgitant filling if the atrioventricular valve is incompetent), and therefore is a reflection of atrial compliance. The widest set reflects ventricular relaxation, opening of the AV valve, and subsequent atrial emptying. *Source:* Kalmanson 1971 [5]. Reproduced with permission of Oxford University Press.

the X descent of the atrial and jugular venous pressure [JVP] waveforms) and a diastolic peak determined by tricuspid valve (TV) resistance and RV compliance (corresponding to the Y descent of the atrial and JVP waveforms). It is essential to consider the relationship of IPP to atrial pressures and flows. Normal IPP is subatmospheric, and both approximates and varies with pleural pressure, decreasing dramatically during inspiration. IPP also tracks right atrial (RA) pressure and shows fluctuations that are associated with the cardiac cycle. In general, IPP increases when cardiac volumes are increased (peak ventricular filling, the V wave) and is lowest at peak ventricular emptying (the later portion of the X descent). It follows that inspiratory decrement in pleural pressure normally reduces pericardial, RA, RV, wedge, and systemic arterial pressures slightly. However, IPP decreases somewhat more than RA pressure, thereby augmenting right-heart filling and output.

Under physiologic conditions, respiratory oscillations exert complex effects on cardiac filling and dynamics since the respiratory effects on the right and the left heart are disparate, owing to differences in the venous return systems and the intrapleural space. The left heart and its tributary pulmonary veins are entirely within the intrathoracic space. In contrast, although both right-heart chambers are intrathoracic, the tributary systemic venous system is extrapleural. Normally, inspiration-induced decrements in ITP (from expiratory 5 to end-inspiratory 25–30 mm Hg) are transmitted through the pericardium to the cardiac chambers. In the right heart, these decrements in ITP enhance the filling gradient from the extrathoracic systemic veins to the right atrium, thereby increasing the caval–right atrial gradient and augmenting venous return flow by 50–60%, increasing right-heart filling and output.

In contrast, the left heart and its tributary pulmonary veins are entirely intrathoracic. Therefore, since pleural pressure changes are evenly distributed to the left heart and pulmonary veins, the pressure gradient from the pulmonary veins to the left ventricle shows minimal change with respiration. However, left-heart filling, stroke volume, and aortic systolic pressure normally decrease with inspiration (up to 10–12 mm Hg). The mechanisms responsible for this normal inspiratory oscillation in aortic pressure include variable ventricular volumes as each ventricle competes for its part of the entire cardiac volume constrained by the pericardium. This competition leads to leftward septal displacement due to augmented right-heart filling, increased LV "afterload," and inspiratory delay of augmented RV output through the lungs. This physiologic respiratory blood pressure oscillation phenomenon has somewhat confusingly been termed paradoxical pulse, but is normal when <10–12 mm Hg. The moniker pulsus paradoxus was bestowed by W. Kussmaul in 1898, describing the findings of cardiac tamponade in a patient who was tachycardic by auscultation but manifested "paradoxical" phasic dropout of radial pulse on palpation. Paradoxical pulse >12–15 mm Hg is abnormal and may reflect cardiac tamponade and other conditions of enhanced ventricular interaction with intact inspiratory venous return.

Hemodynamics and Exercise/Stress

Cardiac output increases to meet peripheral demands during exercise or metabolic stress (e.g., infection, surgery). Under physiologic conditions, increased CO is mediated by neuro-hormonal stimulated tachycardia together with increased stroke volume achieved by augmented increased contractility, as well as by peripheral vasodilation (primarily of skeletal muscle). The increased heart rate is associated with enhanced contractility (the systolic "force–frequency relationship"). In addition, no increase in CO can be achieved without a proportional increase in venous return to both sides of the heart. During exercise, venous return is enhanced by the pumping action of skeletal muscle, venous valves, inspiratory suction induced by enhanced respiratory effort which augments right-heart filling, and ventricular suction during diastole. The LV "suction" effect related to active relaxation and "untwisting" further facilitates an increased diastolic filling rate during exercise by rapidly and markedly decreasing LV pressure during early diastole. Normal LV distensibility allows increased end-diastolic volume with minimal change in mean filling pressure. These mechanisms are frequently deranged in various pathologic conditions.

Ventricular Interactions

The right and left hearts are connected "in series" across the lungs. The right heart is designed to pump blood through the lungs to deliver oxygenated preload to the left heart. (This observation was first appreciated by Sir William Harvey, who stated that "The purpose of the right heart is to pump blood through the lungs, not to nourish them" [6]). Optimal in-series performance is essential to maintain adequate CO at rest and increased CO under conditions of exercise or stress. This requires (i) adequate RV preload (inflow; i.e., systemic venous return); and (ii) optimal pulmonary blood flow through the lungs, which is influenced by RV contractility, the pulmonary valve, and pulmonary vascular resistance (pre-, intra-, and postcapillary). It therefore follows that derangements of any component may lead to in-series failure, which may be subcategorized as "forward failure"