Hemodynamic Physiology in Advanced Heart Failure and Cardiogenic Shock

Hoong Sern Lim

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Hoong Sern Lim
University Hospitals Birmingham NHS
Foundation Trust
Queen Elizabeth Hospital Birmingham
Birmingham, UK

Institute of Cardiovascular Sciences
University of Birmingham
Birmingham, UK

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Introduction: Physiology and Evidence-Based Medicine

It should be said at the outset, even if self-evident, that I am a strong proponent of randomized controlled trials (RCTs) and Guidelines. The value of good RCTs and Guidelines cannot be overstated. Randomized controlled trials are universally regarded as the pinnacle of evidence-based medicine, and International Guidelines promulgate the results of clinical trials and serve to raise the standards of clinical practice. However, adherence to the principles of evidence-based medicine does not mean blind or slavish devotion to RCTs as the only source of evidence. The single and only source of truth. To cite David Sackett, widely regarded as the pioneer of evidence-based medicine:

> Good doctors use both individual clinical expertise and the best available external evidence, and neither alone is enough. Without clinical expertise, practice risks becoming tyrannised by evidence, for even excellent external evidence may be inapplicable to or inappropriate for an individual patient.

Sackett's recognition of the tyranny of absolutes was prescient. Randomized controlled trials and Guidelines are dictating contemporary clinical practice, reducing uncertainties into absolutes, instilling certainty into our beliefs. Yet, "we are never in greater danger of error than when we are absolutely certain that we are absolutely right"—an aphorism we would do well to heed. Guidelines are rarely questioned or challenged. The risk of harm from Guidelines is an apparent impossibility. But uncertainties and possibilities are the very nature of clinical medicine. This vision of clinical medicine as absolutes is distorted, not evidence based.

If the likelihood of benefit of a drug or an intervention is Gaussian, RCTs depict the bulging centre as the absolute certainty, adopted by Guidelines and embraced by clinicians. But there are also the potentially fatal or lifesaving "tails"—statistically remote but clinically significant to the patient's outcome. These "tails" are simply ignored or disregarded because it is too difficult to identify and characterize with certainty. Understanding these "tails" requires clinical expertise. Evidence-based medicine was not conceived as a compilation of RCTs into a "cookbook", but an integration of patients' choices with the best external evidence and clinical expertise.

But what is clinical expertise? Clinical expertise is many things to many people, from a specific skill with a scalpel to the vagaries of "clinical acumen". At its heart, it is the application of physiology to determine how, why, and what external evidence is applied to which patient. Physiology, "the science of life" is the premise for good clinical trials and in conditions where RCTs "cannot be done" or good external evidence are lacking, physiology provides the basis for therapeutic interventions. Yet, physiology is increasingly marginalized, drowned out by "big data", "-omics", gleaming devices, unprecedented technological advances, and the draw of technical procedures, especially in Cardiology and Cardiac Surgery.

Cardiology and Cardiac Surgery disciplines target and treat specific diseases. Ablation of arrhythmias in electrophysiology, pacemakers in bradyarrhythmias, coronary stenting in acute coronary syndrome, and coronary artery bypass and valve surgery. The management of cardiogenic shock is the treatment of specific diseases and more. It is also the management of homeostasis of the whole person, a domain that is usually presided by Intensivists. Thus, cardiogenic shock is more than *just* Cardiology, Cardiac Surgery, or Intensive Care Medicine. It is confluence of these major medical/surgical disciplines. Physiology is the common thread. Physiology *is* the underpinning of cardiogenic shock management.

Analogous to Darwinian evolution, the sub-specialties of Critical Care Cardiology and Interventional (or invasive) Heart Failure have emerged, catalysed in no small part by the challenges of cardiogenic shock and developments in mechanical circulatory support. As a practitioner, implanter, and a clinician, it is easy for me to appreciate the technology of extracorporeal life support and mechanical circulatory support in cardiogenic shock and advanced heart failure. But Critical Care Cardiology and Interventional Heart Failure must be more than *just* about the technology. Indeed, clinical trials in cardiogenic shock must be more than *just* about the machines. These new sub-specialties must inspire and enable the clinician with expertise, founded on physiology to apply the most appropriate external evidence for the patient. It must be about evidence-based medicine.

People, ideas, machines—in that order.

This is the context for this book, this personal endeavour. This is not a book about the technology behind mechanical circulatory support devices, impressive as they are. This book will not dwell on cutting-edge "big data", proteomics, genomics, or other "-omics" or lofty theories or hypotheses that have yet to distil into clinical application. Instead, this book will revisit physiologic studies and concepts from the last two centuries and (re) contextualize these concepts in contemporary practices of temporary mechanical circulatory support in cardiogenic shock. This is a book about the physiology behind clinical expertise, upon which the foundation of evidence-based medicine in cardiogenic shock is built.

October 2023

Hoong Sern Lim
(For Mary, Eleanor and Theodore)

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Law of the Heart

1

Abstract

The 'Law of the Heart' as it is known—the volume of blood that is ejected by the heart is related to the initial filling of the heart (i.e., muscle length)—is widely attributed to Otto Frank and Ernest Starling, and eponymously known as the Frank-Starling Law of the Heart. However, the origin of this 'Law' owes much to the physiologists at the Carl Ludwig Physiological Institute at the University of Leipzig. This chapter will discuss the origin of this 'Law', the subsequent work by Guyton and colleagues, most notably the superimposition of the cardiac function and venous return curves (and the debates that followed), and to the elastance model that is widely adopted in contemporary depiction of cardiovascular physiology in the form of pressure–volume loops.

1.1 The Law of the Heart

Ernest Starling drew on skeletal muscle physiology to describe the relationship between the energy of muscle contraction and the initial length of the muscle fibre at his Linacre Lecture at the University of Cambridge in 1915 (published in 1918) (Katz 2002). Just over 10 years later, Starling and Visscher (1926) in 1926 wrote that "an isolated heart, beating with a constant rhythm and well supplied with blood, the larger the diastolic volume of the heart (within physiological limits) the greater is the energy of its contraction. It is this property which accounts for the marvellous adaptability of the heart, completely separated from the central nervous system, to varying load…." This description of the "regulation of the heartbeat" and "adaptability of the heart" became the immutable 'Law of the heart'.

Physiologists and clinicians have generally ascribed this 'Law' to both Otto Frank and Ernest Starling, now widely known as the Frank-Starling law of the heart. However, scientific and medical advances can rarely, if ever, be attributed to the work of one or even two individuals. In truth, the 'Law of the heart' was the

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culmination of decades of work by a number of physiologists, and much of the work can be traced back to Carl Ludwig's Physiological Institute at the University of Leipzig. Indeed, Carl Ludwig described the relationship between cardiac work and diastolic volume as early as 1856 "… a strong heart that is filled with blood empties itself more or less completely, in other words, [filling of the heart with blood] changes the extent of contractile power".

In 1866, Elias Cyon established an isolated perfused frog heart preparation at Carl Ludwig's Physiological Institute. Although this frog heart preparation was developed to study the effect of temperature, several investigators including Henry Bowditch and Joseph Coats noted the relationship between ventricular filling and the ejected volume from the heart (Who Discovered the Frank-Starling Mechanism 2002). Bowditch continued his work the physiology of the heart with the (modified) isolated frog heart, describing the refractory period of the heart and the Treppe phenomenon that bears his name. Charles Roy, with help from Kronecker (one of Ludwig's pupils), described the ability of the heart to vary its work with changes in venous pressure in his publication titled "On the influences which modify the work of the heart" (Roy 1879).

Otto Frank was an investigator at the Carl Ludwig's Physiological Institute in 1892–1893, before moving to Munich. His interest in the heart was stimulated by earlier studies of skeletal muscle contraction. Like Starling, Frank drew on the length-tension relationship in skeletal muscles, and using an improved frog heart preparation, Frank noted that increasing diastolic pressure by increasing filling of the frog ventricle increased the generation of isometric pressure (up to a certain point before a decrease in isometric pressure) (Fig. 1.1).

Starling had specific interest in the mammalian heart's ability to maintain constant cardiac output over a broad range of arterial pressures. Unlike earlier

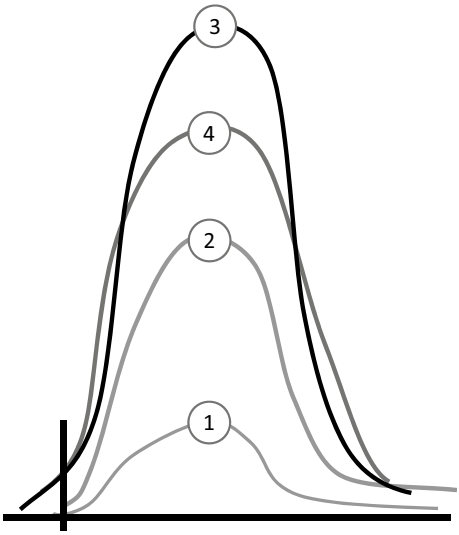

Fig. 1.1 Increasing filling of the isolated frog heart resulted in increase in isometric pressure, but the ventricular peak pressure declined beyond a certain point (point 4). Reproduced from reference (Coats 1869)

experiments, Starling used a dog heart–lung preparation to isolate the effects of venous return and peripheral resistance, and measure heart volume using a brass cardiometer. Starling was able to demonstrate that (i) an increase in venous inflow increased ventricular end-diastolic volume and stroke volume; and (ii) increase in peripheral resistance also led to an increase in ventricular diastolic volume, which maintained normal stroke volume (Patterson and Starling 1914). From these experiments, Markwalder and Starling wrote that "…. the rise of venous pressure [that accompanies increased demands on the heart] must be regarded as one of the mechanical means which are operative in enabling the heart to maintain an output corresponding to the blood it receives from the venous system" (Markwalder and Starling 1914), which led to the 'Law of the heart' a year later.

Starling also extrapolated from skeletal muscle energetics and the relatively new science of thermodynamics to describe the "New elastic body" theory of muscle excitation. This "New elastic body" theory is, of course incorrect, but the work on myocardial contraction and energy expenditure was a significant contribution to the 'Law of the heart'. Crucially, Patterson and Starling deduced that initial fibre length, and not initial tension was the major determinant of cardiac energy expenditure, because end-diastolic volume could increase with little change in pressure (Patterson et al. 1914); establishing the 'Law' as we know today. In his Harveian Oration (Starling 1923), the 'Law of the heart' was described as such: "The heart has thus the power of automatically increasing the chemical changes and the energy evolved at each contraction in proportion to the mechanical demands made upon it, behaving in this way almost like a sentient and intelligent creature."

Thus, the relationship between ventricular filling and amplitude of ventricular contraction was recognised decades before Starling's seminal Linacre Lecture, but this fact should not diminish Starling's contribution to the 'Law of the heart'. By connecting the dots, advancing and bringing together the different strands of cardiac physiology, Starling rightly deserves much of the credit for the 'Law'. Matt Ridley wrote about the process of innovation and highlighted the example of Thomas Edison—"Edison … may not have been the first inventor of most of the ingredients of a light bulb….he was none the less the first to bring everything together, to combine it with a system of generating and distributing electricity". Being the first to describe a phenomenon is neither a pre-requisite nor a fast-track to be an innovator; but Starling was an innovator in every definition of innovation.

1.2 The 'Law' and Cardiac Function Curves

As we are now aware of the denouement, it is easy to forget that the validity of this "Law of the heart" was questioned, quite rightly with a dose of healthy skepticism by the clinical community. Afterall, many questions were unanswered: (i) these experiments were performed in isolated heart and heart–lung preparation; (ii) the use of stroke volume did not reflect cardiac work (stroke work); (iii) right-sided filling pressure was used to correlate with left-sided stroke volume, and

crucially (iv) a single cardiac function curve failed to explain observations in clinical practice when the cardiovascular state was manipulated (e.g., with inotropes or change in loading conditions). Sarnoff and Berglund's studies of the cardiac function curves addressed these questions and the concepts deduced from their observations over 60 years ago remain valid today.

First, Sarnoff and Berglund reproduced the non-linear ventricular function curve (stroke volume plotted against filling pressure). The ventricular function curve shows a steep rise at lower filling pressure but reaches a plateau at higher filling pressures. This is in part related to the non-linear diastolic properties of the heart, i.e., the initial increase in volume could be accommodated with modest increase in filling pressures (increases in volume were initially accompanied by small increments in filling pressure), larger ventricular volume even in the absence of any change in the intrinsic diastolic 'stiffness' of the heart was associated with greater rise in filling pressure per unit increase in volume. Changes in myocardial diastolic properties (e.g., restrictive cardiomyopathy or pericardial constraint) resulted in an upward shift in the diastolic pressure–volume relationship, characterized by a larger pressure increase per unit increase in volume. Hence, a large increase in filling pressure from a modest increase in filling volume may result in minimal increase in stroke volume, thereby producing the flattening the of stroke volume-filling pressure curve.

Second, the left ventricular stroke work-left atrial pressure curve plateaued, but there was little or no decline at higher filling pressure (no descending limb) in the normal dogs. Stroke work has the correct dimensions of force × distance to describe external work:

$$\text{Stroke work} = \text{stroke volume} \times \text{mean aortic pressure},$$

The use of stroke work instead of stroke volume was appropriate:

(i) The term energy of contraction was frequently used by Starling; and
(ii) Aortic pressure was controlled in the heart–lung preparation used in the experiments, and stroke work taking this pressure load into account is valid.

A plateau was often not noted in the right ventricular stroke work-right atrial pressure curve, and a descending limb was almost never seen on the right side. The presence of the 'descending limb' of the cardiac function curve became a subject of debate. A 'descending limb' of the Frank-Starling left ventricular function curve has subsequently been demonstrated to be related to diastolic ventricular interaction and pericardial constraint (Moore et al. 2001), when filling pressure and filling volume became uncoupled (Fig. 1.2). This descending limb is not evident when stroke volume (or stroke work) is plotted against ventricular volume, instead of atrial pressure.

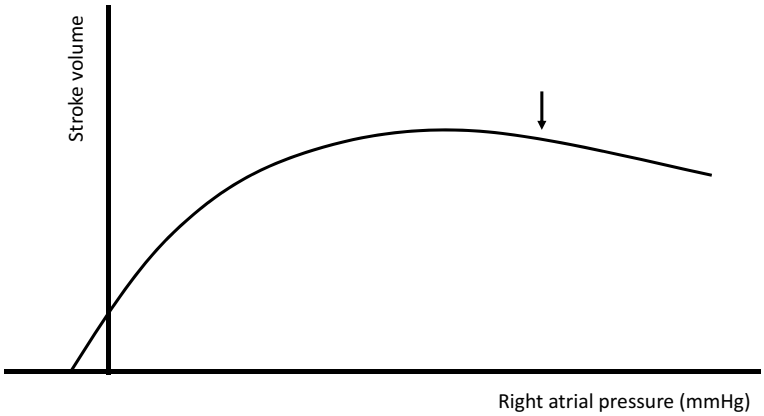

Fig. 1.2 The descending limb (downward arrow) of the cardiac function curve when stroke volume (or stroke work) is plotted against right atrial pressure, due to diastolic ventricular interaction and pericardial constraint. This descending limb is not present when stroke volume is plotted against ventricular volume

Third, significant changes in left atrial pressure were often accompanied only by modest changes in right atrial pressure, leading to discordance in right and left-sided filling pressures. These observations highlighted the importance of "homolateral correlation". Indeed, discordance between right and left-sided filling pressures is well-recognized in patients with heart failure, and the ratio of right and left atrial pressures used as a measure of right heart failure.

Fourth, cardiac tamponade reduced biventricular stroke work despite increase in apparent cardiac filling pressures. However, this suppression of the ventricular function curve was no longer evident when stroke work was plotted against the "effective" or transmural pressure (transmural pressure = intravascular pressure − external pressure). That stroke volume or stroke work is related to transmural pressure and not the apparent filling pressure is consistent with ventricular stretch as the determinant of preload, and indeed consistent with the 'Law of the heart'.

Box 1.1: Measured and Transmural Pressure

Pressure measurements are taken typically with a catheter in the vessel. The difference between the pressure inside the vessel versus pressure outside or surrounding the vessel is the distending or transmural pressure (Fig. 1.3):

In the case of the heart, the use of the measured intraluminal pressure (e.g., ventricular end-diastolic pressure or atrial pressure) and not the transmural pressure explains two 'peculiarities' of the cardiac function curve. Firstly, the descending limb at higher measured right atrial pressure can be explained by diastolic ventricular interaction and pericardial constraint, that simultaneously increases the intraluminal right atrial pressure (due to the

high external pericardial pressure) and reduces transmural pressure and ventricular filling (i.e., preload). This descending limb of the cardiac function curve is no longer evident when transmural pressure or ventricular end-diastolic volume is used on the x-axis, instead of the measured intraluminal right atrial pressure. Pericardial effusion and tamponade have similar effects on the cardiac function curve.

Secondly, the cardiac function curve, as displayed, intersects the x-axis at a pressure that is less than zero, which is counterintuitive as the venous system would be expected to collapse at sub-atmospheric pressure. However, the sub-atmospheric pressure reflects the negative intra-thoracic pressure surrounding the heart, which increases transmural pressure. This negative x-axis intercept is not evident when transmural pressure is used.

Finally, it is the transmural pressure and not the measured intraluminal pressure that determines wall stress, as follows:

The Law of La Place (also known as the surface tension law or the Law of Young-La Place):

$$\text{Wall tension} = \text{transmural pressure} \times \text{chamber radius}$$

The original Law of La Place pertains to thin-walled spheres (bubbles). For a cylindrical structure, the force that threatens to push the structure apart (circumferentially) is the pressure times the area, i.e., 2 × (transmural pressure/chamber radius). This circumferential force is counteracted by stress on the wall of the structure, which is $2 \times \sigma \times w$, where σ is wall stress and w is the wall thickness. As these forces are in equilibrium to maintain the structure:

$$2 \times (\text{transmural pressure/chamber radius}) = 2 \times \sigma \times w$$

Thus, circumferential wall stress, σ = transmural pressure × chamber radius/w for a cylindrical structure (Lame's equation).

For a spherical structure (e.g., simplified model of the heart chambers), the circumferential wall stress is equivalent to the longitudinal wall stress of a thin-walled cylinder.

As the circumferential wall stress is twice the longitudinal stress:

σ = transmural pressure × chamber radius/2w for a spherical structure, or

$$\sigma = T/2w$$

Hence, wall stress is related directly to transmural pressure and vessel radius (i.e., wall tension); and inversely with wall thickness.

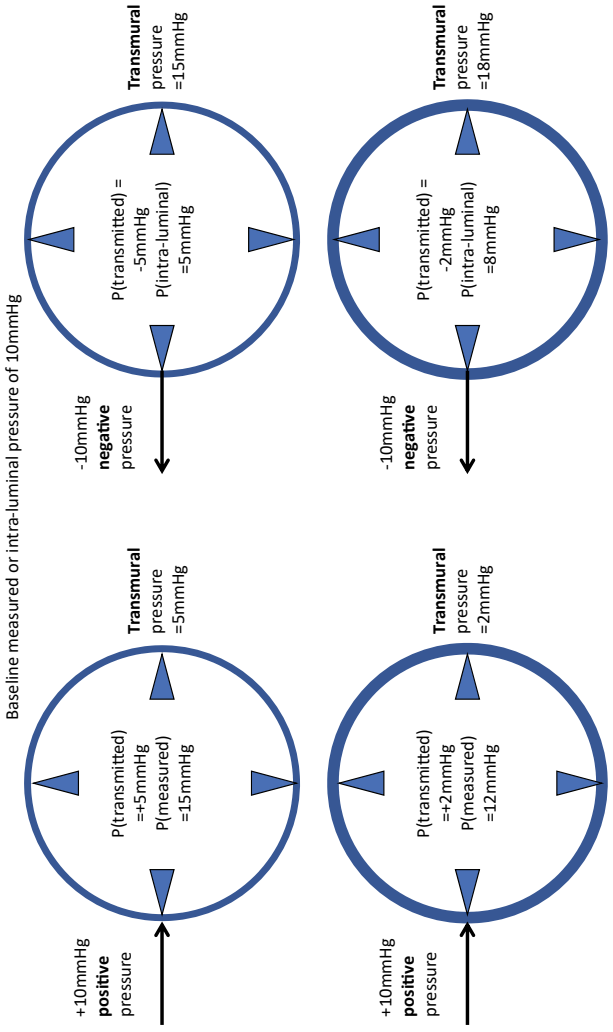

Fig. 1.3 Transmural pressure = intraluminal pressure − external pressure

Fifth, myocardial ischemia induced by restriction of left main coronary artery flow resulted in the expected depression in left ventricular stroke volume/stroke work-left atrial pressure curve, The right ventricular stroke volume-right atrial pressure curve was similarly depressed (even producing an apparent descending limb), but there was no change in the right ventricular stroke work-right atrial pressure curve, as the right ventricle generates lower stroke volume at the cost of more work due to the higher pulmonary artery pressures. Although not specifically studied by Sarnoff and Berglund at that time, this reduced efficiency is now recognized as right ventriculo-arterial uncoupling in the setting of left ventricular dysfunction and consequent elevation in left-sided filling pressure. Of note, although not specifically identified by Sarnoff and Berglund, left main coronary artery restriction resulted in both a downward and rightward displacement of the left ventricular stroke work-left atrial pressure curves. The rightward displacement of the curve (i.e., higher filling pressure at the equivalent stroke work) is indicative of diastolic filling abnormalities during myocardial ischemia.

Sixth, epinephrine increased right and left ventricular stroke work despite reduction in filling pressures; while increased aortic resistance resulted in reduced right and left ventricular stroke work at the same filling pressures under control conditions (i.e., downward and rightward displacement of the left ventricular function curve). These observations cannot be explained by movement of the operating point on a single cardiac function curve. Hence, Sarnoff and Berglund established the concept of a "family of ventricular function curves" depending on loading conditions and contractility (Fig. 1.4).

1.3 Guyton Cardiac and Venous Function Curves

Early studies by Frank, Starling and others deliberately separated the heart from the vascular system (isolated perfused hearts) to allow rigorous control of the experimental variables required to elucidate the basic mechanisms that control ventricular output. Following the description of the 'Law', it became evident that the vascular system interacts with, and dynamically control cardiac output.

In the 1950s, Guyton and colleagues performed a series of experiments that examined the relationship between right atrial pressure and pump flow, as a means of studying the behaviour of the systemic circulation on cardiac output. In their experimental set-up, Guyton and colleagues used a Starling resistor (collapsible tube) to vary the right atrial pressure. Varying the height of the Starling resistor also variably limited the inflow to the pump, i.e., venous return or cardiac output (an artificial pump with a flowmeter replaced the right ventricle that delivered flow from the right atrium to the pulmonary artery). At each level of the Starling resistor and right atrial pressure, Guyton and colleagues noted the pump flow after a brief period to achieve steady state. The steady-state experimental measurements of the pump output (=cardiac output) at each level of right atrial pressure produced a relatively linear relationship, plotted as the now well-known Guyton's venous return

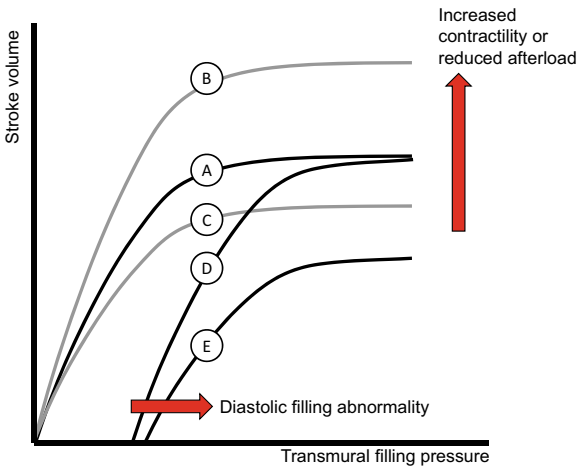

Fig. 1.4 The cardiac function curve represented as a family of curves depending on the loading conditions and contractile function. Note in this figure, the x-axis is the transmural filling pressure; as such, the intercepts of the curves do not drop below zero. Curve A indicates normal resting condition. The curve moves upwards, Curve B with increased contractility (e.g., due to sympathetic stimulation of exogenous catecholamines) or reduced afterload (e.g., vasodilatation), resulting in increased stroke volume at the same or even lower transmural filling pressure. Curve C indicates the opposite scenario (i.e., downward shift of the curve with reduced contractility or increased afterload). The rightward-shifted Curve D reflects diastolic or restrictive filling abnormality, with the same or lower stroke volume despite higher transmural filling pressure. A combination of reduced contractility and diastolic filling abnormality would move the curve rightwards and downwards (Curve E)

curve (or venous function curve). Guyton subsequently overlaid the venous function curve on the Frank-Starling cardiac function curve (Fig. 1.5), producing an input–output relationship (right atrial pressure-cardiac output and cardiac output-right atrial pressure) that determined the stability of the closed-loop cardiovascular system (via negative feedback interaction) (Guyton et al. 1957). Arguably, this this depiction of venous return (and cardiac output) and right atrial pressure relationship was Arthur Guyton's greatest contribution to our understanding of circulatory physiology.

Matthew Levy reproduced Guyton's venous return curve (or 'vascular function curve') with a right heart bypass model, without a Starling resistor (Levy 1979). Levy manually adjusted pump output and recorded the right atrial pressure at different pump output. In so doing, Levy, unlike Guyton effectively placed cardiac output as the independent variable, transposing Guyton's depiction of the cardiac and venous function curves (Fig. 1.6).

At this point, it is worth noting that while Guyton's depiction has become the widely-held interpretation of the right atrial pressure-cardiac output relationship, i.e., right atrial pressure, as preload determines cardiac output, with the intuitive

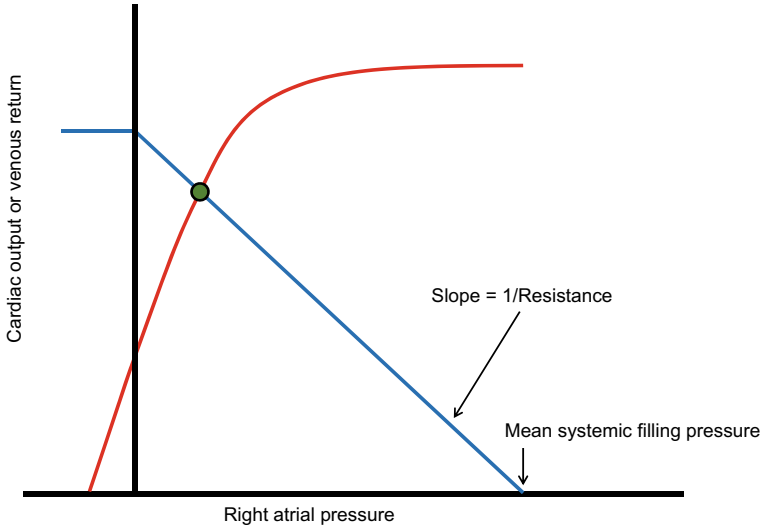

Fig. 1.5 The overlay of the venous function curve (blue) on the Franks-Starling cardiac function curve (red). The point of intersection between these two curves (green dot) is the 'equilibrium point' of the circulatory system

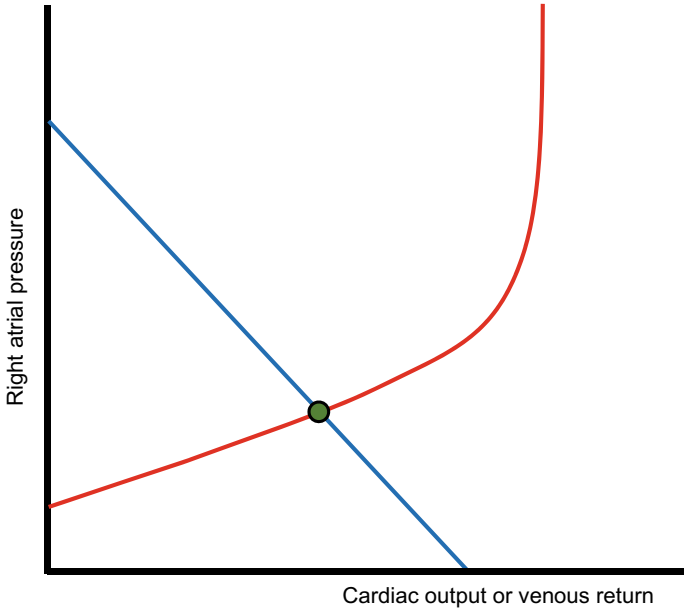

Fig. 1.6 The cardiac function and venous function curves depicted with right atrial pressure as the dependent variable on the y-axis

invocation of the already-established 'Law of the heart'. Guyton's depiction generated significant criticism and debate. Central to the debate is the overlaying of the two functional relationships, which in effect resulted in plotting one of them 'backwards' (i.e., the independent variable on the ordinate and the dependent variable on the abscissa) that called into question the 'true' independent variable. Many have argued that this depiction of right atrial pressure as back pressure against venous return and determinant of cardiac output is mechanistically and physiologically flawed (Brengelmann 2002); asserting that it is the rate of pump output (cardiac output) that determined right atrial pressure, based on the experiments by Levy and others. The point and counterpoint of the debate is beyond the scope of this chapter. Interested readers are referred to a series of publications related to this debate by Magder (2006), Brengelmann (2006) and others.

Guyton and others, in a series of experiments studied the venous return function extensively. Based on their work, the behaviour of the venous return curve can be interpreted as follows:

1. The intersection on the x-axis is the mean systemic filling pressure;
2. The slope of this venous function curve is related to the resistance to venous return;
3. The flattening of the venous return curve at low right atrial pressure is related to collapse of the central veins, analogous to Starling resistors.

The mean systemic filling pressure is the pressure that is equilibrated throughout the circulatory system when blood flow is stopped. Mean systemic filling pressure is related to the total volume of fluid within the circulatory system and the capacitance of the system (Box 1.2). The latter is determined largely by the venous capacitance, as venous capacitance is 40 times higher than the arterial capacitance. Venous capacitance in turn is dependent on vascular tone, with veno-constriction and dilatation reducing and increasing venous capacitance respectively.

Box 1.2: Volume, Pressure, Capacitance and Compliance

Capacitance describes the relationship between volume and pressure, and frequently used to describe the behaviour of biological structures, such as blood vessels, alveoli, pericardium and the heart. Vascular capacitance is the function of its connective tissue composition (relative elastin and collagen content). Capacitance is often expressed as the volume contained within the structure at a particular transmural pressure. Mathematically, capacitance = volume/transmural pressure. Plotting the pressure–volume relationship produces a non-linear relationship, steepening exponentially at larger volumes. Most vessels can accommodate a certain filling volume without an increase in pressure.

The unstressed volume, V0, refers to the maximum filling volume that does not produce a filling pressure (i.e., pressure remains zero). Further

increase in volume with continued filling will increase filling pressure; the volume above V0 is the stressed volume, Vs.

Compliance refers to the change in volume per unit change in pressure (i.e., delta volume/delta pressure). Compliance is the slope or tangent of the pressure–volume curve. For the same increase in volume, a more compliant vessel will have a smaller increase in pressure. Due to the non-linear pressure–volume relationship, vessel compliance decreases at higher vessel volume, with a greater increase in pressure for the same increase in volume (Fig. 1.7). Of note, a change in capacitance is not necessarily accompanied by a change in compliance, if the shape of the pressure–volume relationship is unchanged.

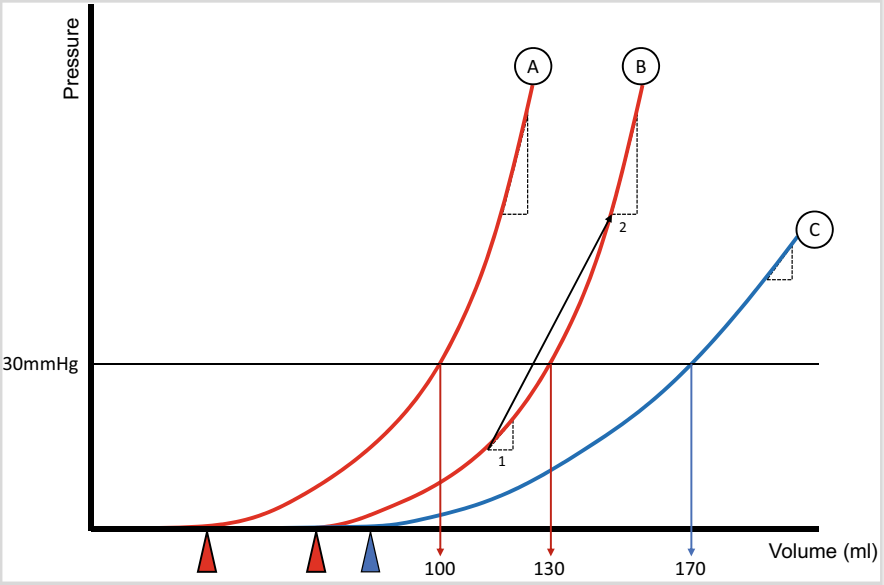

Fig. 1.7 Curve B has higher capacitance compared to curve A, as indicated by the higher volume at the same pressure of 30 mmHg (130 ml vs 100 ml), but note compliance is the same (parallel curves). Curve C has higher capacitance compared to both A and B (volume at 30 mmHg of 170 ml) and also higher compliance, as indicated by the smaller increase in pressure at the same increase in volume. Compliance decreases at higher volume, shown in curve B, with a larger increase in pressure for the same increase in volume (triangle 1 to triangle 2). The arrowheads below the x-axis are the V0 for curves A, B and C, volumes below these levels do not produce filling pressures

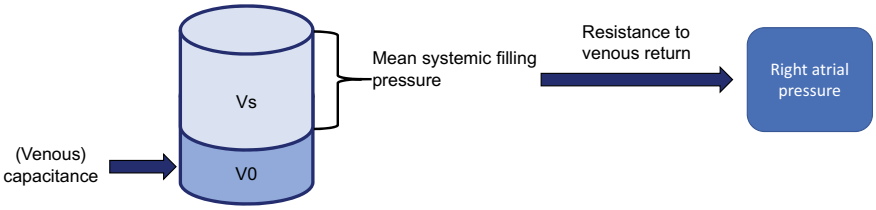

Fig. 1.8 Assuming total blood volume is constant, reduction in venous capacitance increases the mean systemic filling pressure by simultaneously increasing the stressed volume and reducing the unstressed volume, i.e., venous capacitance determines the unstressed volume. The stressed volume contributes to mean systemic filling pressure. The Guytonian depiction of venous return has led to the interpretation of mean systemic filling pressure as the 'driver' of venous return. Based on the Ohmic relationship, venous return (i.e., flow) is the ratio of the mean systemic filling pressure—right atrial pressure gradient to the resistance to venous return

Reducing venous capacitance and compliance with veno-constriction reduces the unstressed volume, V0; and simultaneously increase the stressed volume, Vs (Fig. 1.8). Thus, the venous pressure generated by Vs, i.e., the mean systemic filling pressure, is dependent on the venous capacitance, compliance and the filling volume:

$$\text{mean systemic filling pressure} = (\text{Vs} - \text{V0})/\text{venous capacitance}, \text{ or}$$

$$\text{Venous capacitance} = (\text{Vs} - \text{V0})/\text{mean systemic filling pressure}$$

The difference between right atrial pressure and mean systemic filling pressure determines the pressure gradient for venous return. Based on Ohm's Law, venous return (in L/min) is greater at the same mean systemic filling pressure-right atrial pressure gradient at low resistance to venous return, Rv:

$$\text{Venous return} = (\text{mean systemic filling pressure} - \text{right atrial pressure})/\text{Rv}$$

Graphically, lower Rv is evident as a steepening of the slope. Increased Rv is associated with a shallower slope. Increase and decrease in mean systemic filling pressure without concomitant changes in Rv shifts the venous return curve rightward and leftward respectively, without changing the slope (Fig. 1.9).

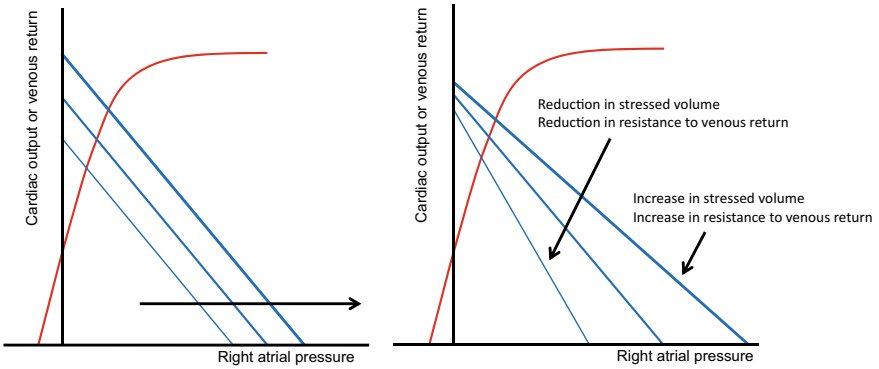

Fig. 1.9 Left—reduced venous capacitance or increased Vs shift the venous return curve to the right. The increased x-axis intercept indicates an increased mean systemic filling pressure. Right—increased resistance to venous return results in a shallower slope of the venous return curve and vice versa

Box 1.3: Central Venous Pressure

The point of intersection between the cardiac function and venous return curves determines the prevailing central venous pressure (or right atrial pressure). By extension, central venous pressure is a function of cardiac contractility, afterload, stressed volume and resistance to venous return. It is unsurprising, given this complex interaction that there are limitations to central venous pressure as a parameter to assess fluid responsiveness. Three points about the central venous pressure are noteworthy.

Firstly, the 'extremes' of central venous pressures may be more helpful to guide fluid administration. In a systematic review of 1148 patients from 51 studies, the overall predictive value of central venous pressure was poor. However, approximatively two thirds of the patients with central venous pressure < 8 mmHg but only one third of patients with central venous pressure > 12 mmHg responded to fluids (Eskesen et al. 2016). Coincidentally, Rivers et al. adopted a target central venous pressure of 8–12 mmHg, which has become a part of the 'standard' goal-directed therapy. This target range is reasonable as the majority of patients respond to fluids (increase stroke volume) when CVP is less than 8 mmHg, but only a minority of patients demonstrate an increase in stroke volume in response to fluid administration when CVP is > 12 mmHg (Magder and Bafaqeeh 2007).

Secondly, changes in central venous pressure must be interpreted with changes in cardiac output. Both cardiac output and CVP are determined by the intersection of the cardiac function and venous return curves. Without cardiac output measurements, the position of the operating point cannot be determined, and no conclusion can be drawn on the patient's response to fluid administration (Magder 2005).

Thirdly, central venous pressure is a measure of congestion. The 'renal tamponade' hypothesis implicates venous congestion in the pathophysiology of renal dysfunction. In patients with heart failure, higher central venous pressure is associated with worsening renal function (Mullens et al. 2009). Higher central venous pressure is also associated with worsening renal function in critically ill patients (Chen et al. 2016). A conservative fluid management strategy (almost neutral fluid balance over 7 days), resulting in lower central venous pressure shortens the duration of mechanical ventilation in patients with acute lung injury (National Heart and Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network 2006). Thus, the intensive care community have broadly embraced the strategy of conservative fluid management and lower CVP after stabilization of circulatory failure.

Thus, Guyton described the venous return function and overlaid it with the cardiac function curve. In so doing, Guyton built on Starling's 'Law of the heart' and presented a cardiovascular model for the regulation of cardiac output that is still shaping clinical practice today.

Box 1.4: Venous Blood Volume and Capacitance

It is estimated that 70–80% of the blood volume resides in the unstressed compartment under normal conditions. This is blood volume that does not contribute to filling pressure. Hence, for an adult of average size and under resting conditions, stressed volume can be estimated at approximately 1.0–1.5 L of blood (20–30% of 5.0 L), and this volume contributes to the mean systemic filling pressure. Mean systemic filling pressure has been measured at approximately 8–10 mmHg in normovolaemic humans, but may be increased two or threefold in fluid-overloaded patients with heart failure (Starr 1940). The capacitance of the human venular bed can thus be calculated at 0.100–0.1875 L.mmHg^{-1} (capacitance approximated as the ratio of stressed volume/mean systemic filling pressure, assuming negligible volume at zero pressure).

An acute mobilization of blood from the unstressed volume into stressed volume of one litre (e.g., vasoconstriction) would increase the mean systemic filling pressure from 8–10 to 13.3–20.0 mmHg. The capacitance of the venous system contrasts that of the arterial system (Fig. 1.10), which is characterized by significantly higher pressures with only a small fraction of the blood volume. The arterial blood pressure also rises more steeply with a small increase in volume compared to the venous system.

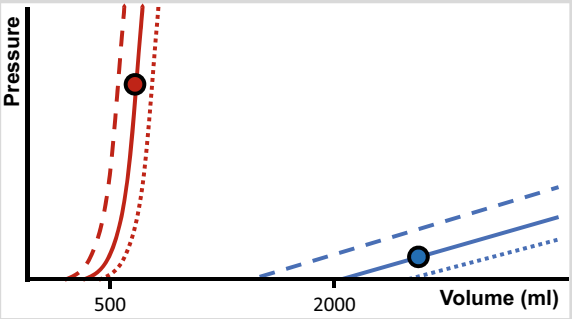

Fig. 1.10 The high capacitance of the venous system is evidenced by the shallow pressure–volume relationship compared to the steep pressure–volume relationship (low capacitance) of the systemic arterial system

A large proportion of the venous blood volume resides in the splanchnic circulation. The splanchnic capacitance veins hold 25% of the total blood volume under normal circumstances (Greenway and Lister 1974). The capacitance of the splanchnic veins directly regulate the stressed volume (and cardiac preload), by: (i) buffering excesses in circulating blood volume (an increase in blood volume of up to 65% in an euvolaemic circulation may be buffered in the splanchnic vasculature without systemic hemodynamic effects (Greenway 1983)), and (ii) 'auto-transfusing' blood into a hypovolaemic circulation. The latter is mediated by sympathetic stimulation. Splanchnic arterioles contain both α- and β_2-receptors that mediate vasoconstriction and vasodilation, respectively, but the capacitance veins contain predominantly α-receptors. Therefore, sympathetic stimulation through epinephrine and/or norepinephrine causes venoconstriction, reducing splanchnic capacitance (Gelman and Mushlin 2004), thereby transferring the blood volume into the stressed compartment and increasing effective circulatory volume. In heart failure, this sympathetic stimulation-mediated venoconstriction may similarly redistribute blood from the (splanchnic) venous capacitance beds to the effective circulatory volume, and contribute to venous congestion (Fallick et al. 2011). Splanchnic nerve modulation is now undergoing evaluation as a therapeutic intervention to relieve congestion in heart failure (Fudim et al. 2021).

The redistribution of blood from the capacitance veins into the circulation is determined by the resistance to venous return (R_v), which is represented as the slope on the venous function curve. Hence, the slope is steeper at lower R_v (i.e., much greater venous return per unit change in pressure) and shallower at higher R_v. Resistance to venous return is affected by:

- Vascular tone (e.g., increased with vasoconstrictors)
- Viscosity (e.g., increased in polycythaemia)

- Distribution of blood flow (e.g., increased with redistribution of blood flow from vascular beds with fast time constant, T_f to slow time constant, T_s)

The time constant of the vascular bed is a function of the volume of the vascular bed and flow through the bed. The venous vascular beds are highly heterogenous in volume and flow and have varied time constants. Low volume vascular beds with high flows (eg: renal venous bed) have a fast time constant. In contrast, large volume vascular bed with slow flow (eg: cutaneous venous plexus) have a slow time constant. Redistribution of blood from T_s to T_f vascular beds will reduce resistance to venous return.

1.4 From Guyton to Pressure–Volume Loops

Hiroyuki Suga started his research career in the late 1960s in Tokyo, Japan. He described the time-varying elastance to describe left ventricular contraction. To test this elastance model, Suga measured instantaneous volume from electromagnetically measured aortic flow and ejection fraction by an indicator dilution during the cardiac cycle in dogs. The result was the construction of the left ventricular pressure–volume (PV) loops under various end-diastolic volumes and aortic pressures (Suga 1969). Suga noted that a straight line connected the left-upper end-systolic corners of the multiple PV loops, which is the end-systolic PV relationship. Suga designated the slope of this end-systolic PV relationship as the maximum elastance (e_{max}) in 1969. He also noted that e_{max} changed with contractility (Suga 1970) (Fig. 1.11). With support from Professor Sagawa at Johns Hopkins University, Suga established e_{max} as an index of contractility. The term e_{max} was later capitalised to Emax on Professor Sagawa's advice (Suga and Sagawa 1972). The Emax is also known as the end-systolic elastance, Ees.

Suga and Sagawa continued their work into PV loops and about 10 years later, they postulated that the total mechanical energy of ventricular contraction could be deduced from the elastance model. Total mechanical energy of ventricular contraction is the combination of stored potential energy and the external mechanical work. As the PV loop area reflects external mechanical work, Suga demonstrated that the area under the end-systolic pressure–volume relation—the pressure–volume area—is related to myocardial oxygen consumption (Suga 1990). The slope of the myocardial oxygen consumption-PV area was defined as the oxygen cost of external mechanical work and the y-axis intercept is the oxygen cost of the fully unloaded ventricle (Fig. 1.12). The latter is related to Emax (Ees)—the higher the Emax, the higher the intercept (the heart consumes oxygen even when producing no external work to maintain basal cellular function). The slope of the myocardial oxygen consumption-PV loop area has a slope of about 30% (Suga et al. 1981),