Ernest Henry Starling, His Predecessors, and the "Law of the Heart"
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The discovery that end-diastolic volume regulates the work of the heart is generally credited to Ernest Henry Starling, who described this relationship in a series of papers between 1912 and 1914 and in his Linacre Lecture, which was given at Cambridge University in 1915 and published in 1918. In these papers, Starling and his collaborators acknowledged that they were not the first to describe this relationship; they cite the work of Blix7 and Evans and Hill8 on the length-dependence of energy release by skeletal muscle, Frank’s 1895 description of the influence of diastolic volume on the work of the frog ventricle,9 and contemporary descriptions in canine10 and feline hearts.11 The present article reviews evidence that what we now call “Starling’s Law of the Heart” or “The Frank-Starling Relationship” was widely appreciated by late 19th century physiologists.

The Length-Tension Relationship, Thermodynamics, and Muscle Energetics

Starling’s Law of the Heart is a manifestation of the length-tension relationship seen in skeletal muscle, which was well known to physiologists during the second half of the 19th century. This relationship was discovered in 1832 by Schwann; Needham, who described this history,13 stated that Schwann’s discovery “caused a great sensation among physiologists of the time,” in part because this discovery was made at a time when muscle performance was being analyzed in terms of the then new science of thermodynamics. That contracting muscles liberate energy as both work and heat was first noted by Helmholtz, whose 1848 description of heat production by muscle “...lighted a flame which...burnt brightly in Germany till the end of the [19th] century.”13 Recognition of the role of rest length in determining energy release by skeletal muscle led to studies of cardiac energetics during the second half of the 19th century.

Diastolic Volume and the Work of the Heart

Early German Contributions

Carl Ludwig seems to have been the first to describe the dependence of cardiac work on diastolic volume when, in 1856, he wrote, “...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.”14 Ludwig’s views had a major impact on cardiovascular physiology during the second half of the 19th century, in part because he had invented the kymograph, a device used to record physiological data for the next 100 years, and also because he had trained more than 200 scientists of all nationalities.15,16

Henry P. Bowditch,17 who, as a student in Ludwig’s laboratory, described the force-frequency relationship (“staircase phenomenon” or “treppe”), revealed his understanding of the role of diastolic volume in determining the work of the heart when he described how he overcame the depressant effect of muscarin by “filling the heart to a higher pressure than usual.” Julius Cohnheim, who spent the summer of 1869 with Ludwig, described the interplay between cardiac filling and ejection in his textbook on general pathology, translated into English in 1889. “With a heart of normal functional capacity...a diminution in the quantity of blood ejected during systole can only depend on a diminution in the quantity present in the ventricle at the commencement of the cardiac contraction; in other words, on a lessened flow into the chambers during diastole...[t]he work done by the heart...is determined by the quantity of blood reaching the ventricle during diastole, and the amount of resistance to be overcome by the heart in propelling it into the arteries.”18

British and American Contributions

Sir Michael Foster, a founder of the British Physiological Society,19 was trained by William Sharpey, 19th century Britain’s foremost teacher of physiology. Foster attested to Ludwig’s prominence when he wrote, “I remember very well when [Sharpey] was lecturing on blood pressure, and was describing to us the new results of Ludwig, endeavoring to explain to us the blood pressure curve, all he had to help him was his cylinder hat, which he put on the lecture table before him and with his finger, traced on the hat the course of the curve.”20 In the 1878 edition of his Text Book of Physiology,21 Foster echoed Ludwig’s view that increased filling of the heart increases ejection: “a full ventricle will, other things being equal, contract more vigorously than one less full.” Foster’s list of factors that regulate the heart beat is headed by “distension of the walls of the ventricular cavities.”21

In 1879, Charles Smart Roy, one of Foster’s pupils, described the dependence of the work of the frog heart on diastolic volume (Figure 1). His report, published the follow-
ing year,\textsuperscript{22} acknowledges a “debt of gratitude” to Kronecker, one of Ludwig’s pupils. Roy’s work showed that “at constant aortic pressure and heart rate, the work of the heart is capable of being varied within wide limits by variations in the venous pressure,” and concluded that “we must look to the quantity of blood arriving at the heart as the predominating factor in regulating the work done.” Roy implied that the relationship between diastolic volume and the work of the heart was well known when he wrote:

Physiologists seem pretty generally to agree in holding that the ventricle, in the normal condition, expels at each contraction the whole, or very nearly the whole, of its contents. If this be so, and there is every reason to believe in the truth of the generally accepted opinion (italics added), it follows that the quantity of blood thrown out at each systole will depend on the degree of distension assumed by the relaxed ventricle.\textsuperscript{22} A decade later, Roy and Adami,\textsuperscript{23,24} showed that the output of the mammalian heart increases when blood volume is increased and decreases when blood is removed from the circulation.\textsuperscript{24} They also observed that a rise in aortic pressure “does not change the amount of blood thrown out by the heart” because when aortic pressure is increased, the “size [of the heart] at the end of systole is greater than with normal arterial pressure.”\textsuperscript{23} This finding anticipated Starling’s later observation that stroke volume is maintained when aortic pressure is increased because a greater end-systolic (residual) volume increases end-diastolic volume.\textsuperscript{1,2} To validate their conclusion that the contracted ventricle contains a residual volume, which contradicted the then prevalent view that the ventricle empties completely during each systole, Roy and Adami inserted a finger into the apex of the contracting ventricle and found that although “the lower part of the ventricular cavity closes completely, the musculi papillares coming into contact with one another; the upper part of the cavity . . . does not become emptied.” They concluded, “It need hardly be said that the larger the quantity of blood which reaches the ventricles . . . the larger the quantity will be which it throws out.”\textsuperscript{23} In 1897, Starling\textsuperscript{25} mentioned Roy and Adami’s finding that end-diastolic volume is increased by a rise in arterial pressure or increased venous return, but did not cite Roy’s 1879 paper.\textsuperscript{22}

William Henry Howell and Frank Donaldson, Jr, who were trained at Johns Hopkins by one of Foster’s students, studied the regulation of stroke volume in the mammalian heart. In their 1884 paper,\textsuperscript{26} they reported that “the work done by the left ventricle at each systole increases with the venous pressure” (Figure 2). They concluded that “the most direct factor influencing the quantity of blood sent out from the ventricle, and hence the work done by the ventricle, is the intra-ventricular pressure by which the ventricle is distended during diastole.”

Later 19th Century German and French Contributions

Wilhelm Blasius, working in the Physiology Department at Würzburg (headed by Adolph Fick, one of Ludwig’s first students), demonstrated that, up to a limit, raising venous

\begin{figure}
\centering
\includegraphics[width=0.8\textwidth]{figure1.png}
\caption{A, Relationship between initial muscle length (lower portion of each deflection) and extent of shortening (amplitude of each deflection); curves are read from right to left. Numbers below abscissa are the height of the venous reservoir in cm H$_2$O. Modified from reference 22. B, Dependence of shortening on diastolic pressure. Data from reference 22.}
\end{figure}
pressure increased the pressure developed by the frog heart. Blasius also found that reducing diastolic volume by compressing the ventricle, a model that resembles tamponade, lowers developed pressure (Figure 3).

Étienne-Jules Marey, who was trained in Paris as a physiologist, included a "Starling curve" in his 1881 text *La Circulation du Sang* (Figure 4). He noted that "[o]n increasing venous pressure, one obtains an increase in the output of the heart, that is to say, in its work." Herrman Dreser, who is best known for his discovery of aspirin, worked in the Laboratory of Experimental Pharmacology in Strasbourg, which was then headed by Schmiedeberg, another of Ludwig’s pupils. To define optimal conditions for studying drug effects on the heart, Dreser quantified the role of increasing diastolic volume on stroke volume and found that ejection is maximal at a filling pressure of 20 to 30 cm H₂O (Figure 5).

Otto Frank, who studied with Ludwig from 1891 to 1893, was stimulated to study the heart by earlier thermodynamic analyses of skeletal muscle contraction. He wrote, "[t]he basic idea which guided my investigation was that the knowledge of the mechanical performance of cardiac muscle should be brought into relation, as far as possible, with what is already known concerning the mechanical performance of skeletal muscle." That led him to describe the dependence of peak isovolumic pressure on ventricular volume (Figure 6).

**Ernest Henry Starling**

Starling began his work on the mammalian heart to explain why cardiac output remains constant over a fairly broad range of arterial pressures, heart rates, and temperatures. In 1914, Markwalder and Starling stated 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." Later that year, Patterson and Starling examined the rela-

![Figure 2](image2.png)

**Figure 2.** Effects of increasing superior vena cava pressure (venous pressure) on cardiac output (○) and left ventricular work (●). Data from reference 26.

![Figure 3](image3.png)

**Figure 3.** Effect of pressure in a chamber surrounding a frog heart on developed pressure. Data from reference 27.

![Figure 4](image4.png)

**Figure 4.** Relationship between venous pressure (Charges) and ventricular output (Debit) in the frog ventricle. Modified from reference 28.

![Figure 5](image5.png)

**Figure 5.** Effect of increasing diastolic pressure, measured as the height of the inflow reservoir, on the output of two frog ventricles. Data from reference 29.
increased cardiac work causes energy utilization to increase, the heart is like a motorcycle which, when traveling on a flat surface, uses energy at a given rate. However, when “the road begins to mount [the rider] lets in more mixture of petrol and air, the chemical energy available for the explosion is thus increased, and the cycle mounts the hill at the same pace as it had before on the level.” To explain why energy expenditure increases when the heart performs more work, Starling suggested that increased fiber length exposes more active surfaces in the muscle such that “[a]ny increase in the extent of active surface increases the energy of change,” which he suggested explains why dilatation of the heart increases its ability to do work. Starling’s 1923 Harveian oration carried this concept further:

Proposed more than 30 years before the sliding filament model of muscle contraction, Starling’s model has many similarities to some older ultrastructural explanations of the length-tension relationship.

Starling concluded his Linacre lecture with the suggestion that heat failure occurs when “the concentration of active molecules per unit surface becomes less and less, so that this surface has to be continuously increased by dilatation of the heart.” In subsequent lectures to practitioners, published in the Lancet and British Medical Journal, he suggested that clinical heart failure occurs when the increased force of contraction made possible by dilatation can no longer compensate for progressive weakening of the heart muscle.

Is Dilatation Compensatory or Deleterious?

The significance of Starling’s Law of the Heart was immediately recognized by his clinical contemporaries. The initial response, however, was one of confusion because the ability of dilatation to increase the heart’s ability to do work seemed to contradict the 19th century view that dilatation weakens the failing heart. In his 1917 Lumleian Lectures presented to the Royal College of Physicians of London, Sutherland stated:

Dilatation of the heart...has long been recognized among the changes associated with valvular disease. The view taken was that was a sign of weakness, a sign that the heart was yielding to some stress or strain more than it could effectively deal with. [However, the] whole subject of dilatation...is admittedly one of great difficulty... On the physiological side Starling and his coworkers have recently promulgated some new views on this subject.”

Figure 6. A, Effect of varying the volume of two frog hearts on peak tension, expressed as pressure. B, Original curves showing the effects of diastolic pressure (increasing from curve 1 through curve 4) on developed pressure (ordinate). The abscissa is time. Modified from reference 9.
This contradiction was also noted by Sir James Mackenzie, whose first edition of Diseases of the Heart highlighted the disadvantages of dilatation: “[a] certain size of the heart is also necessary for the perfect performance of contractions, and if the chambers be dilated the contractile force is placed at a disadvantage, and exhaustion results.” In lectures given in 1917 at the London Hospital, however, Mackenzie began his discussion of “Dilatation of the heart” in Principles of Diagnosis and Treatment in Heart Afflictions.

The real meaning of dilatation of the heart has, so far, eluded recognition... The latest researches by Starling show that a dilatation of any of the chambers of the heart is produced when there is an increase in the pressure during diastole — the increase of pressure being due to a larger influx of blood. Starling shows that, when the heart is stimulated to greater effort, it dilates slightly, because a slight increase in size gives the best condition of the heart for increased effort. Cowan and Ritchie’s 1922 text on heart disease noted that, according to Starling, dilatation is “determined entirely by the venous inflow, rather than by loss of diastolic tone”; these authors went on to state that increasing diastolic volume increases the work of the heart when “within physiological limits.” In 1925, Poulton distinguished between “compensatory dilatation,” which occurs when a “particular chamber of the heart has to accommodate an extra quantity of blood,” and the dilatation that “spells the onset of cardiac failure.”

Noting that “Starling’s experiments suggest that [dilatation], too, may be a compensatory mechanism, enabling the heart to beat more forcibly... this is called Starling’s ‘Law of the Heart.’” Whether dilatation of the heart is good or bad was addressed by Vaquez in the 1924 translation of his Diseases of the Heart, which describes the late 19th century view that dilatation is “a reaction of distress testifying to the heart’s inability to provide for an excess of work or even for the normal needs of the circulation.” After noting that Starling’s papers describe “the occasional providential or compensatory role of dilatation,” however, Vaquez asked, “Is [dilatation] merely an exaggeration of that which normally follows exertion?... Physiologists, notably Starling, have reached the conclusion that dilatation is one of the principal means of adaptation of the heart to the needs of the organism.” Vaquez resolved these apparently contradictory effects by proposing two types of dilatation: physiological dilatation, which is “essential for the heart’s ability to respond to the various demands made on it in normal existence,” and pathological (or passive) dilatation, which “coincides with loss of energy of the cardiac systole.” Causes for the latter, according to Vauez, include infectious, toxic, rheumatic, and alcoholic myocarditis.

A “modern” way to resolve this apparent contradiction is to view Starling’s Law of the Heart as a short-term adaptive functional response in which dilatation increases the work of the heart, whereas the dilatation of the failing heart described by the great clinical pathologists of 19th century results from a long-term maladaptive architectural response caused by abnormal proliferative (transcriptional) signaling (Table).

### The Impact of World War I

One reason that British clinicians were quick to accept the importance of Starling’s Law was World War I, which unified British physiology and medicine at a time they were cut off from the stronger programs in Germany. Five months after the November 1918 armistice, Allbutt described a Meeting of the British Medical Association as “a gathering of physicians of commonwealths, dominions, colonies, and allied and friendly nations,” stating that medicine had come to a “new birth,” which represents “nothing less than its enlargement from an art of observation and empiricism to an applied science founded on research.” World War I also increased the impact of basic science on therapeutics because the pharmaceutical industry had received a major stimulus from both the medical demands of the war and weakening of international trade agreements. The prominence of British physiology continued to increase as the influence of German science diminished in the aftermath of World War I.

Starling noted the lack of understanding of science by British leaders that was revealed at the start of World War I when he described “[t]he astounding and disastrous ignorance of the most elementary scientific facts displayed by members of the Government and administration in the early days of the war.” He added, “The Government adopted the traditional method ofoultering the sore place in public opinion by the appointment of two committees.”

### Changing British Medical Education at the Beginning of the 20th Century

Throughout most of the 19th century, students who sought to learn the scientific basis of medicine generally studied in Continental Europe, notably in Germany. At that time, medical science in Britain was usually taught in facilities that lacked the financial support and equipment of the German institutions. Although Foster at Cambridge, Burdon-Sanderson at Oxford, and T.H. Huxley at University College in London established strong physiology departments in which well-equipped laboratories replaced the hat used by Sharpey to simulate Ludwig’s smoked drum kymograph, few British medical students had contact with highly trained scientists. This system did develop several outstanding clinical investigators, such as Sir James Mackenzie and Sir Thomas Lewis, but British medical students and physicians at the beginning of the 20th century were rarely encouraged to...
participate in clinical research, and there were no academic clinical departments.\textsuperscript{49} Contrasting British and German medicine at the end of the first decade of the 20th century, Flexner wrote “[t]he German clinician is a trained, often a productive physiologist, but English physiology has not yet conquered English medicine.”\textsuperscript{45}

Starling strongly advocated a role for university-based basic science in the medical curriculum. In his testimony to the Royal Commission on University Education, chaired by Viscount Haldane, Starling characterized London medical schools as “trade schools” in which “[t]he teachers of science with whom [the medical student] comes in immediate contact, in many cases not of marked ability, are in all cases in a position of inferiority to the clinical staff, whose servants they are. The work of these scientific teachers is to get the students under them as quickly as possible through the various examinations, so that they may be passed on to the clinical work of the wards.”\textsuperscript{46}

Starling recommended that Universities be given “direct control of the first two and a half years of the medical curriculum” to expose students to the “University spirit,” which is “…not simply diagnosing the patient and deciding what we can do for him in order to earn our fee, but what we can get out of this case in order to do better next time; how we can get some knowledge out of this patient in order to have more power when we have another man in the same condition.”\textsuperscript{46} Starling’s testimony had a major impact on the final report of the Haldane Commission,\textsuperscript{47} many of whose recommendations, although shelved during World War I, were implemented over the following decade.\textsuperscript{48} In 1918, Starling wrote in The British Medical Journal:

We do not want the medical man or student entering the wards to have at the tip of his tongue the properties and atomic weights of all of the elements, or to be prepared to give a historical account of the views concerning the origin of the heart beat. We do want, however, that the student shall have dipped so deeply into the sciences of chemistry and physiology that he has become imbued with the scientific spirit, and that he knows where to turn to refresh his knowledge on any matter germane to the problems which concern him on the wards.\textsuperscript{49}

\section*{Conclusions}

There is abundant evidence showing that the role of end-diastolic volume in determining the work of the heart was widely known to physiologists during the latter half of the 19th century, decades before Starling described the Law of the Heart that bears his name. For this reason, the credit generally given to Starling for discovering this law cannot be attributed to the originality of his findings. Instead, Starling’s preeminence probably reflects his ability to describe the role of end-diastolic volume in terms of muscle biochemistry and biophysics and the physiology of circulatory control in health and disease, along with his ability to communicate all this to the practicing physician. Starling’s commitment to what he referred to as the “University spirit,” what today might be called dedication to scientific medicine, is seen in our growing ability to analyze human disease in terms of fundamental causes and to tailor therapy to pathophysiology. Starling described the importance of science to medicine when, paraphrasing Leonardo da Vinci, he wrote, “Those who are enamoured of practice without science are like a pilot who comes into a ship without rudder or compass and never has any certainty where he is going.”\textsuperscript{49}

\section*{Note Added in Proof}

After submission of this article, a paper was published by H.G. Zimmer (Who discovered the frank-starling mechanism? News Physiol Sci. 2002;17:181–184.) that describes the contributions of three of Carl Ludwig’s pupils to our knowledge of Starling’s Law of the Heart. These are Elias Cyon, who in 1866 described the influence of diastolic filling on stroke volume, and Joseph Coats, who in 1869 cited data obtained by H.P. Bowditch that described the effect of filling pressure on the amplitude of contraction.

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