Who Discovered the Frank-Starling Mechanism?

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In 1866 at Carl Ludwig's Physiological Institute at Leipzig, Elias Cyon described the influence of diastolic filling of the isolated perfused frog heart on ejection volume. A study performed at the institute of the effect of filling pressure on contraction amplitude was published in 1869 by Joseph Coats, based on a recording made by Henry P. Bowditch.

In their 1926 publication, E. H. Starling and M. B. Visscher wrote

> Experiments carried out in this laboratory have shown that in 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 marvelous adaptability of the heart, completely separated from the central nervous system, to varying load.... (11)

This view was adopted by the subsequent generations of physiologists and still prevails in modern textbooks of physiology, which describe

> the Frank-Starling law of the heart as the principal mechanism by which the heart adapts to changing inflow of blood. When the cardiac muscle becomes stretched an extra amount, as it does when extra amounts of blood enter the heart chambers, the stretched muscle contracts with a greatly increased force, thereby automatically pumping the extra blood into the arteries. (6)

In this review, I will show that neither Otto Frank nor Ernest H. Starling made the first observations on the effect of filling pressure on heart function. I will present evidence that the essential features of this mechanism were discovered at Carl Ludwig's Physiological Institute at the University of Leipzig in the course of the first experiments on the isolated perfused frog heart long before Otto Frank and Ernest H. Starling started their own work. Their work will be compared with these early findings.

The first observation and recording at Carl Ludwig's Physiological Institute

This phenomenon could only be discovered and studied on the isolated perfused heart. The first preparation was established at the institute by Elias Cyon in 1866. The aorta of the isolated frog heart was connected to an artificial circulation. A side arm was inserted to enable pressure measurements with a manometer. It was a working heart preparation with recirculation. The primary aim was to study the effect of temperature on the frequency and contraction of the heart. It was observed that a certain degree of filling of the ventricle was necessary for the heart to produce a sufficient ejection volume (3). No records of the phenomenon were made. However, it can be assumed that the experience was passed on to the subsequent young investigators who came to Leipzig to work in what was then the newly built and most modern physiological institute.

One of these was Joseph Coats from Glasgow, Scotland. To investigate the effects of the stimulation of the vagus, he did experiments in which this nerve was exposed from the spinal cord to the heart. The preparation was a closed, nonrecirculating system in which the heart pumped the serum with which it was filled into a manometer. The regular and consistent excursions of the mercury reflected the force developed by the heart (2). In control experiments, the effect of filling pressure on the amplitude of contractions was examined. The reference pressure was obtained when the heart was filled from a reservoir with serum before a clamp was closed. This line, labeled gg (Fig. 1), represented the balance between the floating rod on top of the mercury column, the mercury, and the serum. When the filling pressure was increased up to the diastolic pressure H, the amplitude of contraction was high (h^{I}). When the filling pressure was reduced to the diastolic pressure H', the amplitude was lower (h^{II}). With each further reduction in filling pressure, the excursions decreased in amplitude (h^{III}, h^{IV}, h^{V}). When the original filling pressure was restored, the previous amplitude of contraction (h^{VI}) was reestablished (Fig. 1). This recording was made by Henry P. Bowditch, as acknowledged in a note in Coats' paper (2). Furthermore, it was observed, but not recorded, that the excursions became smaller in amplitude when the filling pressure was excessively elevated. Bowditch (1840–1911) continued the work on another modification of the isolated frog heart and discovered the staircase ("Treppe") phenomenon, the all-or-none law of the heart, and the absolute refractory period (1).

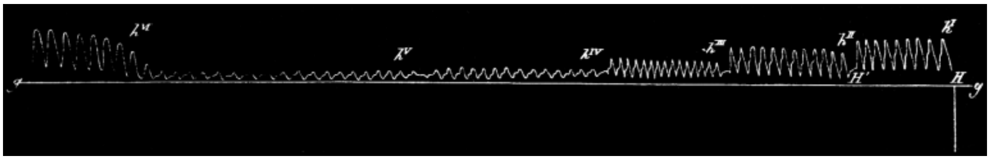

FIGURE 1. Effect of lowering the filling pressure on diastolic pressure (H) and amplitude of contraction (h) of the isolated frog heart. Restoration of amplitude when original filling pressure was applied (from *right* to *left*) is shown. Recording made by H. P. Bowditch. Reprinted from Ref. 2.

The experiments of Otto Frank

Otto Frank (1865–1944) did most of his experiments in 1892–3 at Carl Ludwig's Physiological Institute, where the first observations had been made. He moved then from Leipzig to Munich, where he continued his studies in 1894 and published the results in 1895 (4), the same year in which Carl Ludwig (1816–1895) died. He looked at the heart from the viewpoint of skeletal muscle mechanics, substituting volume and pressure for length and tension. Using an improved frog heart preparation, he inserted several valves, stopcocks, and manometers in the perfusion line, which enabled him to measure isovolumetric and isotonic contractions. With increasing filling of the frog ventricle, diastolic pressure was elevated at each step. Also, the maximal isovolumetric pressure increased (*contractions 1–6*; Fig. 2, *left*). Beyond a certain filling pressure, it decreased (*contraction 4*; Fig. 2, *right*). Otto Frank compiled all of the data in the pressure-volume diagram that resulted in the diastolic pressure curve as well as in the curves of the isovolumetric and isotonic maxima. Subsequently, he was more concerned with methodological problems, such as the construction of manometers and the careful mathematical analysis of pressure curves recorded in the cardiovascular system (5). Carl Wiggers, who visited Otto Frank in 1911, was so impressed by his methods that he adopted and transferred them to the U.S. (12).

The experimental studies of Ernest Henry Starling, leading to the "law of the heart"

Clearly, it was Ernest H. Starling (1866–1927) who did most of the experimental work relating cardiac output to ventricular filling pressure. He used the dog heart-lung preparation in which peripheral resistance could be regulated independently of venous inflow. First, he determined the effect of peripheral resistance and venous pressure on cardiac output (9). As a new parameter, heart volume was measured by inserting the heart hermetically into a brass cardiometer (8). When venous inflow was increased by elevating venous pressure (*bottom* curve; Fig. 3, *left*), diastolic heart volume and stroke volume increased (*upper* record; Fig. 3, *left*). Thus the heart was able to eject the increased volume against an unchanged peripheral resistance with only a slight increase in blood pressure (*middle* tracing; Fig. 3, *left*). When peripheral resistance was elevated (increase in arterial pressure; *middle* tracing; Fig. 3, *right*), there was also an increase in diastolic volume that enabled the heart to eject a normal stroke volume (*upper* recording; Fig. 3, *right*). In both cases, diastolic fiber length was increased. In a subsequent paper, it was shown that oxygen consumption of the isolated heart is determined by its diastolic volume and therefore by the initial length of its muscular fibers (the "law of the heart") (11).

Comments

The influence of diastolic filling on contraction amplitude (2) and cardiac output (3) was observed almost 30 years before Otto Frank and almost 50 years before Ernest H. Starling by young scientists working in the Carl Ludwig's Physiological Institute. Although other observations obtained there from the isolated frog heart such as the absolute refractory period and the Treppe phenomenon (1) were recognized, the

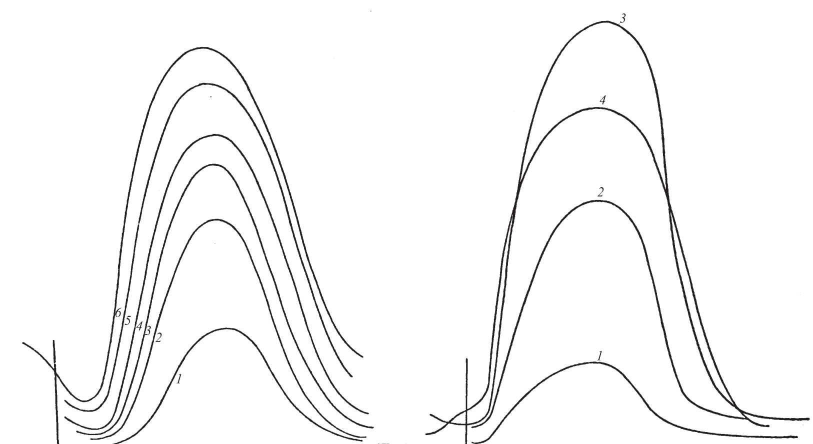

FIGURE 2. Effect of increasing initial filling of the frog heart on the isometric pressure curve. The peaks of the isometric pressure curves obtained in the ventricle rose with increasing initial filling (*left*). Beyond a certain level of filling, the ventricular pressure peak declined (*curve 4*, *right*). Reprinted from Ref. 4.

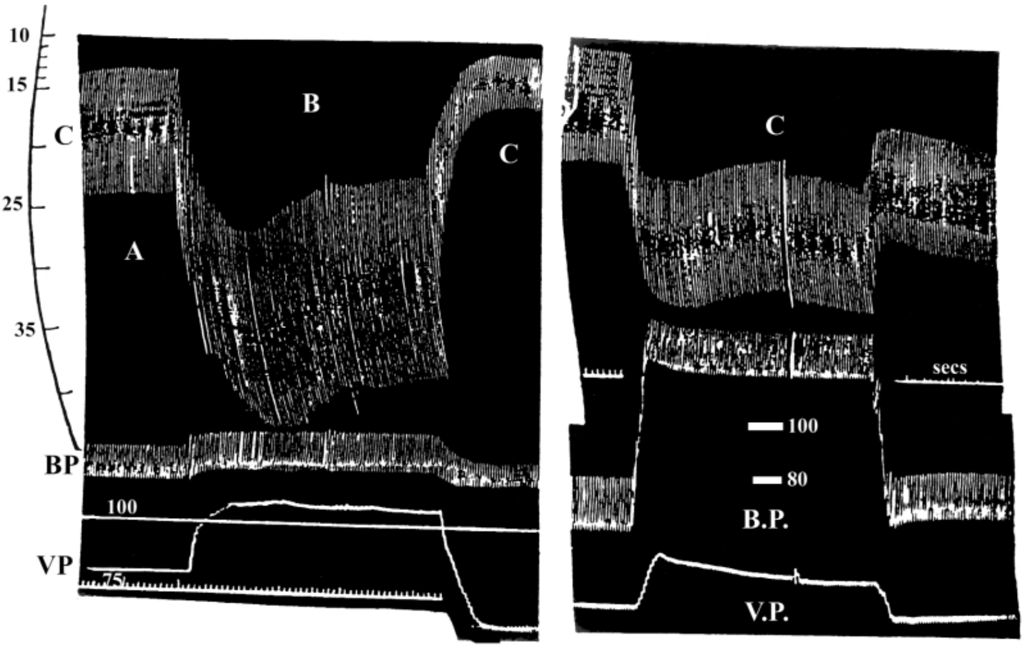

FIGURE 3. Changes in ventricular volume (*upper* recording) when the venous inflow (B, *left*) or the peripheral resistance was suddenly raised (C, *right*) in the dog heart-lung preparation. BP, arterial pressure; VP, venous pressure. Increase in ventricular volume (ml) as measured by the cardiometer is registered as a downward deflection of the *upper* recording (from *left* to *right*). Reprinted from Ref. 8.

effect of filling pressure on heart function was not even mentioned by the subsequent investigators. One reason may be that the young investigators of the institute had only touched on the subject in control experiments. They did not pursue the phenomenon in more detail (Table 1). Nevertheless, it was recorded (2) and described to some extent (2, 3).

Otto Frank discounted this early work as irrelevant for methodological reasons, since the modified frog heart on which Coats and Bowditch had worked was directly connected to the manometer and pumped the serum into it in a closed system (4). Obviously, he was well aware of these results (Fig. 1) (2, 3) obtained at the same institute at which he

TABLE 1. Comparison of the experimental studies describing the effect of filling of the heart on contraction and ejection

	Carl Ludwig	Otto Frank	Ernest H. Starling
Year of publication	1886 (3); 1869 (2)	1895 (4); 1898 (5)	1914 (8, 9); 1926 (11)
Performed at	Leipzig, Germany	Leipzig, Germany; Munich, Germany	London, England
Animal used	Frog	Frog	Dog
Heart preparation	Working, recirculating (3); Closed system pumping into manometer (2)	Working heart dependent on preload and afterload	Heart-lung preparation
Parameters measured	Pressure (2)	Pressure and volume	Pressure, cardiac output, and heart volume
Aim of study	Effect of temperature (3); Vagus stimulation (2)	Heart as muscle and reliable pressure recording	Application to the mammalian heart
New finding	Ejection (3) and contraction amplitude dependent on filling (2)	Curves of isovolumetric and isotonic maxima (5)	Regulation of heart volume and output by preload and afterload
Effect	described (3); recorded (2)	quantified and visualized as a graph (5)	designated "the law of the heart" (11)
Continued research focusing on the mechanism?	No	No	Yes

Numbers in parentheses are references.

did most of his experiments. When comparing Fig. 1, in which the contractions are recorded successively, with Fig. 2, *left*, in which the contractions are reproduced on top of each other, essentially the same phenomenon is shown. However, Otto Frank never made reference to this similarity. It seems that he was so convinced of the superiority of his improved frog heart preparation that he felt justified in disregarding the results of the earlier work.

The heart-lung preparation was the basis of the experiments that led Ernest H. Starling to formulate as the law of the heart that "the total energy liberated at each heartbeat is determined by the diastolic volume of the heart and therefore by the muscle fiber length at the beginning of contraction" (11). However, subsequent studies showed that oxygen consumption of the heart is determined by more factors, such as heart rate, the total tension developed by the myocardium (tension-time index; Ref. 10), peak wall stress, and peak developed tension (7).

From the comparison of the studies done by the group of Carl Ludwig, by Otto Frank, and by Ernest H. Starling and his associates (Table 1), it can be seen that the methodology became successively more refined so that more relevant parameters could be measured. Furthermore, the research changed from general to focused topics. The early results at Carl Ludwig's Physiological Institute were obtained while defining the control conditions in the original and in a modified isolated frog heart preparation (13). Otto Frank extended muscle physiology to the heart and subsequently became more interested in methodological problems of pressure recording. Ernest H. Starling, however, focused his research on all possible physiological aspects of the effect of diastolic fiber length on heart function, culminating in the formulation of the law of the heart (11). However, the original contributions of Elias Cyon (3), Joseph Coats (2), and Henry P. Bowditch (2) while they were working at the Leipzig Physiological Institute should also be recognized and acknowledged to put the scientific and historical record straight.

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