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Review article

Rediscovery of Otto Frank's contribution to science

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ABSTRACT

In the late 19th century, German physiologist Otto Frank (1865–1944) embarked on a near life-long research program of laying down the mathematical, methodological, and theoretical foundations in order to understand and define the performance of the heart and circulatory system in all their complexity. The existence of the "Frank-Starling law" testifies to this. Two of his seminal publications have been translated into English previously, introducing Frank's research on the dynamics of the heart and the arterial pulse to a wider audience. It is likely that there are a host of other comparable achievements and publications of Frank that are still unknown to the international scientific (cardiological and physiological) community. However, their influence can still be felt and seen in modern cardiology and cardio-physiology, such as in the development of modern interactive simulating and teaching programs. We have translated and commented on ten of these papers, which can be read in parallel with the German originals. These publications show a wealth of theoretical assumptions and projections regarding the importance of the sarcomere, the development of models of contraction, thermo-dynamical considerations for muscular activity, differences between cardiac and skeletal muscles, problems related to methodology and measurement, and the first pressure-volume diagram (published 120 years ago). These topics were envisioned by Frank long before they became a focus of subsequent modern research. Nowadays, frequent measurements of pressure-volume relationships are made in research using the pressure-volume conductance catheter technique. In commenting Frank's scientific topics, we try to show how interconnected his thinking was, and thus how it enabled him to cover such a wide range of subjects.

1. Introduction

Researchers and clinicians invariably refer to the "Frank-Starling law" when referencing a fundamental principle of cardiac mechanics [1–3], namely that an increase in blood volume in the heart (often somewhat incorrectly [2] called preload) prompts an immediate increase in stroke volume or pressure development. The underlying molecular mechanisms, which involve myofilament length-dependent muscle activation, are a topic of contemporary research [4]. Otto Frank (1865–1944), the first namesake of the law, was a German physiologist who discovered and formulated theoretical principles of cardiovascular and muscle physiology more than 100 years ago. Many of Frank's concepts were validated both experimentally and morphologically over the following decades [2]. Frank combined experimental physiological research with physical and mathematical analyses, and continually strived to optimise instrumentation. His wide-ranging knowledge in natural sciences allowed him to address thermodynamic problems, devise complex equipment, and comment critically on both methodological and epistemological questions, as well as explore issues of physiology. The interrelated areas of scientific interest form the essential building blocks of Frank's oeuvre [5]. The scientific merits of Ernest Henry Starling (1866–1927), the second namesake of the Law, are widely acknowledged in the field of physiology and cardiology [6–10].

Frank's research has modern-day relevance. One example is the very recent development of devices that simulate complex pressure, flow, and volume data of the cardiovascular system, which relies to a great extent on Frank's mechanistic concepts [11–14]. These devices are not only valuable tools in understanding and teaching cardiovascular physiology, but can also predict the potential beneficial effects of cardiac assist systems and other cardiological interventions, meaning that they are of practical clinical value. Perhaps Frank had such simulations

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in mind when he, based on measurements of pressure and volume from experiments with frog hearts [15], began to develop mathematical models of the cardiovascular system in 1899 [16].

From Frank's 133 publications (see supplementary material for a bibliography), we have chosen twelve articles that represent the core of his work on cardiac mechanics and measuring methods [15–26]. Two articles have been translated and commented on previously, namely the 1895 paper “On the dynamics of cardiac muscle” [15, see supplementary material] by Chapman and Wasserman in 1959, and the 1899 article “The basic shape of the arterial pulse” by Sagawa et al. in 1999 [16, see supplementary material]. These papers proved to be quite influential in furthering the understanding of cardiovascular physiology. To the best of our knowledge, no other articles of Frank have yet been translated. To cover the breadth of his far-sighted scientific approach, we thought it necessary to translate ten additional publications [17–26] from his very creative period between 1894 and 1914. These translations can be accessed as supplementary material and are edited so that one can compare Frank's original German text and our translation line by line. We have enriched and complemented each translation with translators' notes (including comments, reference lists, figures) so that cross-linkages between Frank's different topics can be established.

2. Short biography

Otto Frank was born in Gross-Umstadt (Odenwald, Germany) on June 21, 1865. He attended grammar school in Darmstadt, where he gained a higher education entrance qualification in 1884. He went on to study medicine in Munich and in Kiel, and completed his studies with a license to practice medicine in 1889. Frank continued to study natural sciences (physics, mathematics, chemistry, zoology) and anatomy at Heidelberg, Munich, Glasgow, and Strassburg [27–29]. Later he wrote in his curriculum vitae that he had used available time alongside his studies to teach himself higher mathematical analysis and analytical mechanics [30]. His career as a physiologist began in 1891 at Carl Ludwig's renowned laboratory in the chemical department of the Institute of Physiology in Leipzig, where he wrote an experimental doctoral thesis on the resorption of fatty acids [31]. Frank moved to the laboratory of Carl von Voit at the Ludwig-Maximilians-Universität in Munich in 1892, where he submitted his habilitation thesis “On the dynamics of cardiac muscle”, which was published in 1895 [15]. A habilitation thesis is more or less equivalent to a postdoctoral thesis, and is a requirement in Germany for becoming a professor. Frank's thesis marked his profound interest in analysis of the cardiovascular system using physical and mathematical principles, and initiated what would be a long series of related articles [27]. Frank was appointed professor of physiology in Giessen in 1905, but returned to Munich as von Voit's successor in 1908. He remained there as a professor until 1934, when he was compelled by the Nazi regime to accept emeritus status. Frank died in Munich on November 12, 1944.

3. Topics of Otto Frank's research

The ten papers that we have translated ([17–26], supplementary material) illustrate some perhaps lesser known aspects of Frank's immense scientific work. Their topics range from the effects of vagal nerve stimulation and digitalis glycosides on the heart to technical issues such as the design of high quality manometers, and the principles of graphic recording. The pressure-volume diagram and cardiac work are, of course, central topics. There are unifying themes in this diverse array of topics; Frank always strove to understand the cardiovascular system through sound theoretical analysis, and by developing methods of measurement to be as exact as possible. Some highlights will be presented.

3.1. Autonomic nervous system

Frank was interested in the effects of the autonomic nervous system on the heart [17,19]. He reports that the most consistent effect of vagal nerve stimulation is a decrease in atrial contraction strength, as indicated by lower maxima of isovolumetric and isotonic contractions (pages 37–39 in [19]). This decrease is observed regularly and occurs even in the absence of bradycardia. Since the effects of vagal nerve stimulation depend on the strength and timing of the stimulation in the cardiac cycle, Frank infers that the nerve influences “energy development” in cardiac muscle. Thus he predicted negative inotropic effects of acetylcholine, which was not yet known at that time. Referring to experiments with frog hearts, he reports that stimulation of the N. vagus does not increase distensibility of the cardiac ventricle, because the filling curve (“distension curve of isovolumetric minima”, see page 38 in [19]) of the resting heart is not altered. He contrasts this with assumptions from contemporary researchers, who report a decrease in muscle tone. Concerning cardiac rhythm, Frank states that vagal nerve stimulation usually leads to bradycardia and eventually to atrial arrest, while the ventricle is able to maintain an escape rhythm. Stimulation of the sympathetic N. accelerans does not, according to Frank, change the curves of the isovolumetric minima and maxima (page 39 in [19]). A positive inotropic effect is not mentioned. The acceleration of the heart rate is, however, reported quantitatively (pages 61–63 in [17]).

But what happens when vagal and sympathetic nerves are activated at the same time? To tackle this question, Frank experimented with artificially ventilated and curarized dogs in which he had strongly activated the vagal nerves by inducing asphyxia, which led to profound bradycardia. He then electrically stimulated the exposed sympathetic Nervus accelerans. This counteracted the vagal effects and accelerated the heart rate during asphyxia. Frank concludes that the effects of both nerves on the heart rate can counterbalance each other when the stimulation strength is adjusted appropriately, and postulates that both nerves influence the activity of the heart's movement “at different points” (synapses, neurotransmitters and receptors were not known yet). He assumes that stimulation of the vagal nerve exclusively prolongs the diastole without changing the length of the systole, whereas stimulation of the sympathetic N. accelerans shortens both periods. Combined simultaneous activation of both nerves may therefore result in a third (unphysiological) effect, namely a constant duration of the diastole and a shortened systole (pages 64–67 in [17]). Frank could not provide suitable ECG data because the equipment was not available to him. Decades later, Manning and Cotton reported that stimulation of the diencephalon can evoke arrhythmia, which possibly results from the interplay of simultaneous sympathetic and parasympathetic effects on the heart [32]. Recently Oppenheimer discussed how proarrhythmic shifts in sympathovagal balance can occur following brain lesions in human patients [33].

3.2. The pressure-volume diagram and cardiac work

The translated article titled “The effect of digitalis (helleborein) on the heart” contains the first-ever version of Otto Frank's famous pressure-volume diagram (page 16 of [19]), which was later reproduced with some alterations in many German physiology textbooks [34–38]. For the sake of clarity we have schematized Frank's diagram and rotated it, so that the pressure axis points upwards and the volume axis to the right (Fig. 1). Experimenting with isolated frog hearts, Frank studied different types of contractions of the cardiac ventricle, systematically adjusting the initial filling. All contractions start from the distension curve of the minima (Frank's term), i.e., the filling curve that characterises the end-diastolic pressure-volume relation EDPVR (curve 1 in Fig. 1). The hydrostatic pressure acting on the chamber wall remains constant during isotonic contractions, so that only volume changes [21]. Ventricular volume remains constant during isometric contractions, so only pressure increases [21]; we prefer the more common term

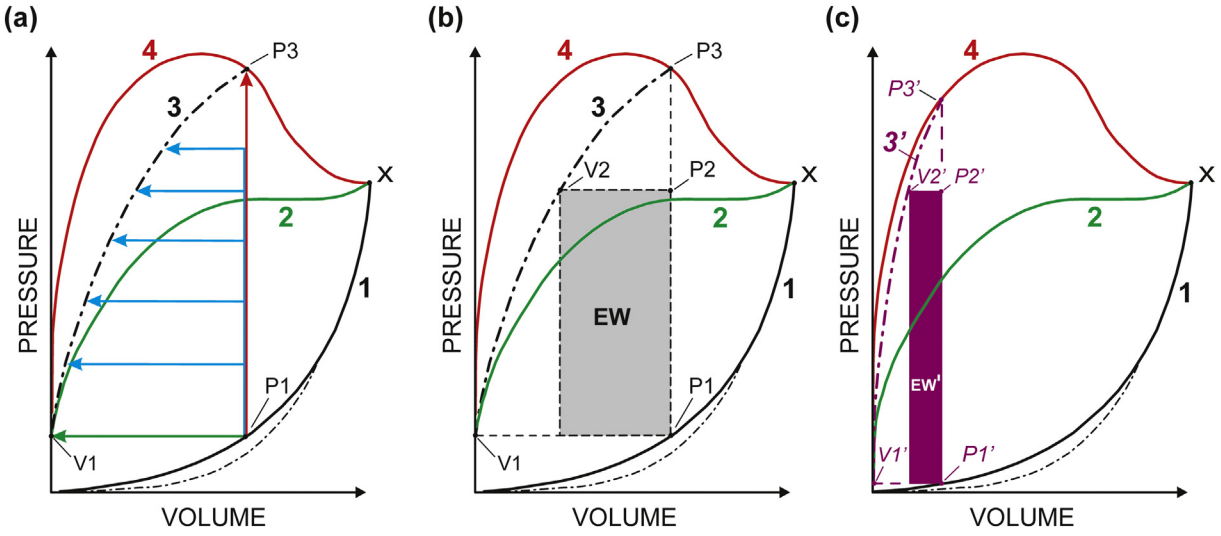

Fig. 1. Pressure-volume diagram. Modified schemes of Frank's original figure (see page 16 of translated paper [19]).
(a) Four curves are shown: (1) filling (distension) curve, which represents the end-diastolic pressure-volume relation (EDPVR). Frank depicts two slightly diverging distension curves, whose shape depends on the type of preceding contraction (see Section 3.3). (2) Curve of the maxima of isotonic contractions (green). (3) Curve of the maxima of afterloaded contractions (broken line) for the given preload P1. This curve connects intraventricular volume V1 (at the end of an isotonic contraction) and pressure P3 (peak pressure of an isovolumetric contraction). (4) Curve of the maxima of isovolumetric contractions (red). Arrows denote an isotonic contraction (green, P1 → V1), an isovolumetric contraction (red, P1 → P3) and five afterloaded contractions (light blue arrows). These afterloaded contractions all start isovolumetrically from P1 to continue isotonically once the (variable) load is overcome, and end on curve 3 (maxima of the afterloaded contractions). Curves 1, 2 and 4 meet at a point X, where contractions are no longer possible.
(b) The external work of the heart during a natural contraction is proportional to the shaded area EW according to Frank (see page 22 in [19]). P1 → P2 represents the increase in pressure generated by the contraction of the ventricle, P2 → V2 the ejected volume.
(c) Example of a low enddiastolic filling, as given by point P1' on the filling (distension) curve. Cardiac performance is now delimited by the newly constructed curve 3′ (magenta) of the maxima of afterloaded contractions (see page 20 in [19]). Curve 3′ is drawn as an arc between the points of the isotonic (V1') and isovolumetric (P3') contraction maxima that can be reached from P1'. Stroke volume (P2' → V2') and external work EW' are reduced at this low preload, so that Starling's 'Law of the Heart' is inherent in Frank's diagram. The magenta lines and area EW' have been inscribed into Frank's schematised diagram by the authors. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

isovolumetric contraction. From each starting point (preload) on the filling curve, Frank determines the maxima of isotonic and isovolumetric contractions and, by connecting them, draws the corresponding curves (curves 2 and 4 in Fig. 1). He states that isotonic and isovolumetric contractions represent boundary conditions, which in the pressure-volume diagram define the range of other contractions that are possible at a given end-diastolic volume, i.e., the range of afterloaded contractions ("*Unterstützungszuckungen*"). An afterloaded contraction is defined as beginning with an isovolumetric contraction that continues isotonically once the pressure is great enough to overcome the load, so that a stroke volume is expelled (pages 15 in [19], also pages 18/19 in [21]). Frank argues that the systolic contraction of a ventricle in the living organism (the "natural contraction of the cardiac muscle") is essentially equivalent to an afterloaded contraction (page 22 in [19]). When different afterloaded contractions start from the same end-diastolic volume (i.e., same preload), the ejected volumes will decrease more and more as the amplitude of the initial isovolumetric rise in pressure increases. This is evident from the decreasing length of the horizontal blue arrows in Fig. 1a. These arrows end on a curve of the afterloaded maxima (curve 3 in Fig. 1a), which is specific for the given preload (page 20 in [19]).

Frank defines the external work performed during a cardiac cycle as the area within the pressure-volume loop, which he represents as a rectangle in his diagram (EW in Fig. 1b). Pressure-volume loops that start at a certain end-diastolic volume (e.g., from point P1 in Fig. 1) cannot go beyond curve 3, which thus delimits all possible afterloaded contractions at a given preload. Frank introduces time as a third variable, which would graphically result in three-dimensional pressure-volume-time loops – an idea that was later implemented by Straub [39], Jacob and Kissling [40]. Considering changes in heart rate, Frank also defines cardiac power ("*Effect*") as work per unit of time (page 23 in [19]).

The curves of Frank's pressure-volume diagram implicitly convey the Frank-Starling law, as shown by Fig. 1b and c: With a sufficient end-diastolic filling (Fig. 1b), afterloaded contractions of the ventricle start at point P1 of the filling (distension) curve. P1 → P2 represents the increase in pressure, P2 → V2 the ejected stroke volume, and area EW the external work of the ventricle. When the end-diastolic filling is reduced (Fig. 1c), all contractions will start at point P1' of the filling curve. Isotonic contractions reach volume V1', isovolumetric contractions reach pressure P3'. Pressure-volume loops are now delimited by curve 3′ of the afterloaded maxima, which forms an arc connecting V1' and P3'. Due to the low preload, the stroke volume is small (P2' → V2') and the external work (EW') reduced below baseline values (compare Fig. 1c and b). A moderate increase in the end-diastolic volume, i.e., moving to the right along the filling curve, would again result in higher amplitudes of the isovolumetric and isotonic contractions, i.e., increased pressure development and/or stroke volume. The ability of an isolated ventricle to contract more forcefully and to eject a higher stroke volume when inflow is augmented has been referred to as (heterometric) autoregulation of the heart [41]. Over-distension of the ventricle will, however, ultimately decrease the amplitudes of all contractions to zero (at point X in Fig. 1).

Frank's nomenclature may be confusing for today's readers, as the terms have changed with time. His distension curves of the (isovolumetric and isotonic, see Section 3.3) minima correspond to the end-diastolic pressure-volume relationship (EDPVR), as described by Noble et al. [42] and Suga and Sagawa [43] decades later for the canine heart. Frank's curves of the afterloaded maxima ("*Maxima der Unterstützungszuckungen*") connect the points of the isovolumetric and isotonic maxima, which the heart can reach from a given (starting) point on the filling curve. Each time the preload changes, a

corresponding new curve of the afterloaded maxima has to be constructed; curves 3 (Fig. 1a,b) and 3′ (Fig. 1c) are examples. Frank's concept that there is a family of curves of afterloaded maxima depending on the end-diastolic state has prevailed for a long time in European literature and in German physiology textbooks [40]. In contrast, the newer diagrams of Suga and colleagues [43–46], obtained from experiments with canine hearts, show just a single end-systolic pressure volume relationship (ESPVR) as long as the contractility of the ventricle remains constant. The ESPVR is often simplified as a straight line that connects the 'top-left corners' of pressure-volume loops obtained at different preloads. Curves of isovolumetric (and isotonic) maxima are not shown in these newer diagrams [43–46], possibly because Suga and Yamakoshi found that the isolated canine ventricle reaches similar maximal pressures during isovolumetric and ejecting contractions [47]. The maxima of isovolumetric and afterloaded (ejecting) contractions of the frog heart, however, diverge considerably, as shown by Frank's curves 3 and 4 (Fig. 1), and which was later confirmed by others [48]. Details of the different concepts and diagrams of Frank, Starling and Suga have recently been discussed elsewhere [49].

Frank's article "On the basic shape of the arterial pulse" [16] provides a detailed calculation of the work of the contracting cardiac ventricle, namely an equation with seven variables representing potential and kinetic energy, energy to overcome frictional resistances, inner mechanical energy creating tension in the ventricular wall, and heat production (page 511 in [16]). Frank states that pressure-volume work, which reflects potential energy transmitted to the blood from the activity of the ventricle, is most important. But is it possible to directly visualize the pressure-volume work of the beating heart? For this Frank invented and described the heart-indicator (translated article [20]), a device that measures ventricular volume and pressure simultaneously, and which converts the signals into movements of a ray of light recorded onto photographic film. The principle is comparable to an instrument that records the work of a steam engine (page 150 in [20]). Movements of the light ray in one direction indicate volume changes, while simultaneous movements in an orthogonal direction indicate pressure changes. Referring to a coordinate system with the volume axis pointing downward and the pressure axis pointing to the right, Otto Frank explains the changes in pressure and volume that take place during the filling, isovolumetric contraction, ejection, and relaxation phases of a cardiac cycle. He states that the light ray would move along a closed loop in the pressure-volume plane, the area of which corresponds to the external (i.e. pressure-volume) work of the heart (page 153 in [20]). Decades later, Suga and colleagues [43–46] recorded pressure-volume loops of canine hearts. A close correlation between the pressure-volume area — a composite of Frank's loop plus the area of remaining potential energy — and myocardial oxygen consumption was found [44–46]. Recently, Burkhoff and colleagues have been using pressure-volume diagrams of the human left ventricle to determine its oxygen consumption, and have developed tools to simulate pressure-volume loops that help predict and understand the effects of cardiac assist devices [12–14].

3.3. The effects of digitalis on the heart

As a physician, Otto Frank aimed to quantify the effects that agents such as atropine, muscarin, caffeine and digitalis glycosides have on the heart. In his article on the effects of digitalis [19] he argues that recording the curves of the pressure-volume diagram satisfactorily describes the mechanical function of the heart (page 24). Such recordings should therefore be performed before and after the administration of a drug or a nerve stimulation to measure the effect of the intervention. Frank felt compelled to publish preliminary data in order to be acknowledged (pages 14–15 in [19]): "Since the complete study has been conceived according to a far reaching plan, and because during its execution there will always pop up new points of view, a summarising extensive publication is postponed for a longer period of time; I had to choose this way of making it public if I would not have risked that my contribution to this new method would have slowly gone into the hands of other scientists." His observations are summarized on pages 39 to 43 of paper [19]. Frank assumes that digitalis can increase the maxima of isovolumetric and afterloaded contractions. Such increases would indicate a higher contractility [35–38]. Examining pressure-volume diagrams of canine hearts, Wu and colleagues confirmed Frank's assumption approximately 90 years later [50]. They found that the glycoside ouabaine increases the contractility index E_{max}, the incline of the ESPVR. The curves and the diagrams have changed with time, but the essential finding remained the same.

Frank points out that digitalis does not increase the distensibility of the resting heart muscle, unlike other researchers had assumed (page 40 in [19]). He argues that one has to consider that the distension of the ventricle depends on the type of preceding contraction [19,21]: After an isotonic ejection of the stroke volume, filling of the cardiac ventricle proceeds slowly especially when the filling pressure is low. It is therefore often not yet complete at the onset of the next heartbeat (see pages 18–20 and translators' notes in [21]). Conversely, distension proceeds faster after an isovolumetric contraction, so that a lower intraventricular pressure is reached at the onset of the next heartbeat. To account for this difference, Frank depicts two slightly different filling (distension) curves in his pressure-volume diagram, namely one for the isotonic minima and another one for the isovolumetric minima (Fig. 1). Lack of familiarity with these variations has, according to Frank, led to the incorrect conclusion that digitalis causes a greater distensibility of the heart.

Frank describes the slowing of the heart rate that occurs after administration of digitalis and the appearance of double beats that can merge with each other (pages 41/42 in [19]). He indicates that the bradycardia induced by digitalis will increase the ventricular filling due to a prolonged diastole, thus altering the mechanical conditions. How such a change in heart rate can influence blood pressure is discussed extensively in a theoretical approach (translated paper [22]). On the one hand, a longer diastole will increase ventricular filling and increase stroke volume. Yet fewer stroke volumes are ejected per unit of time (e.g., per minute), so the net effect on cardiac output is not clear. Frank implicitly assumes that changes in cardiac output are paralleled by changes in blood pressure, which would only be true with constant peripheral resistance. To assess the relationship between heart rate and cardiac output, he introduces the concept of a "pure" change of the heart rate, where only the time intervals between the heartbeats change, while the contractions themselves remain unaltered. He illustrates a curve that characterises a typical change in ventricular volume over time, the "Normal Volume Curve" (Fig. 1 on page 4 in [22]). The increasing segment of the curve represents the ventricle being emptied during ejection of the stroke volume; the decreasing segment indicates the ventricle being filled. The shape of each "Normal Volume Curve" is assumed to remain stable during a "pure" change of the heart rate. When there are long pauses between beats, stroke volume is high. With shorter pauses between the beats (i.e. higher frequency), diastolic filling of the ventricle remains incomplete, so that the stroke volume is diminished.

Taking a mathematical approach, Frank then calculates possible changes to cardiac output that result from placing volume-time curves at different heart rates. Variable shapes of these curves are also considered. The author concludes that moderate changes in heart rate will not alter blood pressure substantially. However, blood pressure will decrease below baseline at unphysiologically fast heart rates, at very slow heart rates, and when contractions occur irregularly (arrhythmia). Frank infers that the slowing of heart rate induced by digitalis can increase blood pressure, provided that the initial rhythm of the heart was very fast or irregular.

This theoretical approach is based, in modern terms, on mathematical modeling (like a computer simulation). From hypothetical shapes of volume-time curves and the concept of a "pure" change in heart rate,

Frank extrapolates changes in cardiac output and the parallel changes blood pressure that may occur in vivo. Related experiments were later performed later by Noble and colleagues [51,52]. In the intact dog, end-diastolic and stroke volume fall when the heart rate is increased by an implanted pacemaker; cardiac output increases slightly and then declines (see page 9 and translators' note 5 in [22]). Confirming effects of heart rate on blood pressure, cardiac pacing can reduce elevated systolic pressures in patients where bradycardia is associated with hypertension [53]. Frank had commented upon consequences and causes of arrhythmia on cardiac performance already in his habilitation thesis (page 389 in [15]): His figure 9 shows a sequence of contractions that can be interpreted as an early observation of mechanically-induced extrasystoles of the frog heart [54].

3.4. Forces of the muscle element (sarcomere)

Drawing parallels between skeletal and cardiac muscle, Otto Frank suggests that the pressure-volume diagram of the frog heart matches the tension-length diagram of the skeletal muscle [19,21]. Likewise, he discusses how changes in the initial length influence contractions in both musculature types in a similar way [16,21]. His 1901 paper “Isometry and isotony of the heart muscle” [21] describes isometric and isotonic contractions that Fick had previously defined for skeletal muscle [55]. Muscle length stays constant during an isometric contraction, while tension increases. During an isotonic contraction the specific tension, namely the force per cross section of the muscle, should ideally remain constant. Perfectly isotonic contractions are, however, difficult to achieve, since even the skeletal muscle usually becomes thicker while shortening, so that its cross-sectional area enlarges. This situation is even more complicated for the heart, where the largely unknown architecture of the cardiac muscle fibres renders a calculation of their tension impossible (page 16 in [21]). To circumvent this problem, Frank introduces practical definitions of isovolumetric, isotonic and afterloaded contractions of the heart, as outlined above in Section 3.2. He estimates that the tension of the ventricular wall will generally decrease during the so-called isotonic contraction (page 26 of [21]), which is in line with the Law of Laplace.

In a line of theoretical argumentation, Frank then postulates that core results of experiments performed with the whole organ (frog heart) can also be transferred to the muscle elements – in other words, to a microscopic level (pages 24–27 in [21]). He does not use the term sarcomere, although it had been introduced by E.A. Schäfer in 1891 [56], but rather refers to the cross-striation, with the longitudinal direction of the muscle elements being orthogonal to the striation. In an abstract model, he reduces the geometry of the muscle element to two points, one of which is fixed, the other of which is movable (pages 31–34 in [21]). The distance between these two points corresponds to the length of the muscle element (sarcomere length). Frank defines the following five forces that act on and between the two points (pages 31–33 in [21]): (i) A contractile force that varies in time and depends on the distance between the points, decreasing with growing distance. The typical relationship between sarcomere length and contractile force [57–61] was not known to Frank at that time. (ii) An elastic force that increases with growing distance. (iii) An additional force that explains delayed distension phenomena and represents a kind of inner friction. (iv) An external force that acts on the movable point. This force remains constant during isotonic contractions, and is equivalent to the tension of an unyielding spring during isometric contractions. (v) An inert force. Frank assumes that the five forces are superimposed and formulates an equation with five terms representing them (page 33 in [21]). He envisions the functions of structures such as the interaction of actin and myosin (contractile force) and the elastic force of titin, which was discovered eight decades later [62–64]. Also the concept of parallel-elastic and series-elastic components of the muscle [65–68] can be traced back to Frank's work. Towards the end of his paper [21], Frank proposes a mathematical model of the circulatory system that combines the aforementioned equation of the five muscular forces with two further equations describing the mechanical properties of vessels: these latter equations had been presented in his earlier (1899) article on the arterial pulse [16]. Such a mathematical model can be regarded as a forerunner of modern-day computer simulations of cardiovascular functions [13].

3.5. Understanding and improving instrumentation

At the end of the 19th century, Frank was confronted with a large and as yet largely unexplored field of research full of unsolved problems about how to design, build, and assess the quality of instruments used to record cardio-vascular functions, based on analyses from physics. Frank already began to highlight the challenges of recording methods in his habilitation thesis on the dynamics of cardiac muscle (1895), discussing artefactual oscillations that distort arterial pressure curves when inadequate elastic manometers are used (pages 305–307 in [15]). Like other renowned scientists at that time [5], he developed and perfected devices to improve precision of measurements. Thus, many of his following publications, including four of the freshly translated papers [18,23–25], address aspects of physics and the methodology of instruments. Frank was convinced that: “one just [cannot] penetrate into the mysteries of nature without levers and screws […] The method really has to be made to serve research […] even if those who drift in the currents of fashion choose to regard such kinds of research [developing a theory of the methodology of instruments] as petty carping.” (pages 1–3 in [69]).

In a critique concerning the pressure curves of the ventricle, published in 1897 [18], Frank argues that a large part of the so-called systolic pressure waves of the cardiac chamber described in the contemporary literature can be ascribed to measurement artefacts caused by vibrations of the moving masses. To solve this problem, he describes a device consisting of three parallel tubes with stopcocks and adjustable valves, which will reduce such errors. Using this instrument, one segment of the true ventricular pressure curve can be recorded in one trial. After appropriate adjustment of the valves, the following segment is recorded in the next trial, and so on: in this way the complete pressure curve can ultimately be accurately reconstructed from data recorded in different trials. Frank references a publication by Porter [70], who invented a functioning, but more complicated device for the same purpose. In a 1901 article [23] Frank emphasises the necessity of recording curves of motion processes in daylight, since bright illumination is indispensable during complicated animal experiments. He describes a device that can photographically record movements e.g., of fluid menisci being observed through a microscope. Through a system of lamps and lenses, a ray of light is projected onto photographic film moving at constant velocity. The device is reported to be nearly as convenient as recording curves on smoked paper, a common method at that time. Frank's “Principles of graphic recordings”, published in 1910 [24], deal with the technical principles of instruments that record movement or force. Here he lays out details of the dynamics of signal transmission and attenuation, as well as of measuring sensitivity, and explains how resonance phenomena can produce artefacts. Another paper published in the same year [25] sets out to provide evidence that Frank's mirror manometer is the optimal construction for recording pressure curves. The author reports oscillation frequencies, volume-elasticity coefficients, masses, and other technical details of membrane manometers connected to a mirror reflecting a light beam. He concludes that the quality of his device surpasses e.g., the quality of the instruments used by Bayliss and Starling (page 553 in [25]). Original pressure curves recorded with the different manometers are, however, not shown. Taken together, the newly translated technical articles [18,23–25] reveal Frank's wide-ranging knowledge of mechanics, physics, and mathematics, and demonstrate his endeavour to develop optimal instruments for cardiovascular research.

3.6. Experimenting with the hearts of warm-blooded animals

Otto Frank's renowned pressure-volume diagram (Fig. 1) is based on studies of the excised frog heart (page 26 in [19]), which does not possess coronary arteries. Frank was familiar with this approach and argued that it allows for larger and more systematic changes in mechanical conditions than would be possible during experiments where a heart was connected to the vessels in situ (pages 14/15 in [21]). He was skeptical about extrapolating insights gained from the frog heart to the mammalian heart [21,71]. It is thus not well-known that Frank studied various preparations of hearts of warm-blooded animals. His early (1897) study of the effects of vagal and sympathetic nerve stimulations in dogs [17] is one example (see Section 3.1). Seventeen years later Frank and his assistant Ritter von Skramlik published results of further experiments conducted with various preparations of excised mammalian hearts, which we have translated [26].

In section A of that article, Frank and von Skramlik refer to the Langendorff preparation of hearts in cats and guinea pigs, where they study the effects of oxygen tension and perfusion pressure (pages 1–5 in [26]). In section B they describe an artificial circulation with a preparation of the hedgehog heart: fluid enters the left atrium, flows into the left ventricle and is ejected into the aorta (pages 5–9 in [26]). The amount of ventricular filling is varied. Frank and von Skramlik aim to confirm that stroke volume depends on the initial tension (preload) of the ventricle and on the pressure developed during afterloaded contractions (page 7 in [26]). They state, yet without providing quantitative data, that “there is no doubt that these relationships correspond to those in the frog heart”. Insufficient filling of the ventricle of the hedgehog impedes its activity, and the authors refer to the dissertation of Frank's student Kurt Gross [72], who obtained similar results for the frog heart. Frank and von Skramlik do not show a pressure-volume diagram of the hedgehog (or another mammalian) heart. Instead, they discuss arterial pressure curves and results gained from another preparation, where nutritive fluid entered the aorta, passed through the coronary vessels, then reached the right atrium and right ventricle, which expelled it into the pulmonary artery (pages 7–11 in [26]). The stroke volume of the right ventricle depends on the pressure in the coronary arteries. Frank and von Skramlik also mention the influence of different nutritive fluids at different temperatures, and stimulations of the N. vagus and N. accelerans.

Due to the variety of preparations used and the multiple research questions that are touched upon, the article on experiments with mammalian heart preparations [26] is somewhat difficult to follow. The problems that the authors apparently encountered may explain Frank's critical attitude towards Hermann Straub's habilitation thesis [71]. Straub had utilized Starling's heart-lung preparation to study the dynamics of the mammalian heart [39,73]. Frank and von Skramlik did not systematically reinvestigate the pressure-volume diagram to validate the “Frank-Starling law” for hearts of warm-blooded animals. The well-known studies of Starling and colleagues, published between 1914 and 1918, would confirm that increased filling causes more blood to be ejected [74,75]. These led to Starling's formulation of the “Law of the Heart” in his Linacre Lecture in 1918 [76]; Frank's earlier pressure-volume diagram, meanwhile, began to fade into oblivion after World War I, at least outside of Germany [27].

4. Concluding remarks

During their investigations about a half a century ago, the American cardiologists Carleton B. Chapman and Eugene Wasserman stumbled across Frank's 1895 habilitation thesis “On the dynamics of cardiac muscle” [15]. They discovered a wealth of thought-provoking ideas and thought it worthwhile to translate and introduce this work to the English-speaking scientific world (see supplementary material). They summarized the significance of Frank's article in their translators' note: “The so called ‘Law of the Heart’ is implicit in Frank's work on cardiac dynamics, which Starling rediscovered ten years later than Frank for the warm-blooded heart, and which is linked with Starling's name especially in the English literature. Frank's observations constitute the transitional link between work on skeletal muscle and that on cardiac muscle… He equates change in length of skeletal muscle with change in ventricular volume … he indicates that the same relationship exists between initial ventricular tension and ejected volume … He leaves little doubt that end-diastolic filling, and hence volume, is the significant item …” (page 283 in [15]). Frank demonstrated that the amplitudes of isovolumetric and isotonic contractions in an isolated frog ventricle depend on the end-diastolic filling. The same principle applies to atrial contractions. He discussed atrial, ventricular and arterial pressure curves in relation to the phases of the cardiac cycle, explaining how changes in filling and pressure load (equated with preload and afterload of skeletal muscle) influence these curves [15]. In the related 1899 paper “The basic shape of the arterial pulse” [16], Otto Frank showed how changes in vascular elasticity and resistance influence the pulse curves. He introduced new concepts, e.g., setting up an isolated heart connected to an artificial circulatory system in order to develop mathematical models; provided detailed calculations of cardiac work and mean arterial pressure; and estimated stroke volume from the arterial pressure pulse curve. Thus he laid theoretical foundations for non-invasive measurement of cardiovascular variables from pulse wave analysis [77–79].

In order to understand cardiovascular physiology, Frank considered it indispensable to look at the complex interaction between the heart and the system of arteries and veins as a whole. For him, the most important way to reach this holistic view was through mathematical analysis. He aimed to build a mathematical model of the entire circulatory system by combining results and models for the isolated heart with similar data for the vessels [15,16,21]. His hemodynamic models were an application of fluid mechanics to the cardiovascular system. He was able to rely on the work of physicists who had established the foundations of fluid mechanics; in a 1913 textbook chapter on hemodynamics [69] Otto Frank refers to Poiseuille, Bernoulli, Helmholtz and to a model of the circulation described by E.H. Weber.

Frank thought that mathematical methods and mechanical models could be applied to the entirety of the cardio-vascular system. He considered mathematical descriptions a rational tool and the best means of expressing explanations of physiological relations: “[…] the nature of analytical mathematical formulations, […] guarantees that they do not become a straight-jacket for further research, on the contrary allowing it the greatest scope possible.” (page 446 in [80]). Thus he deemed theoretical arguments and mathematical models very valuable. Article [22] focuses on “modeling” without providing original pressure and volume curves, and articles [20,21] also report little quantitative physiological data. The distinction between experimental measurements and theoretical assumptions is not always clear. The axes of his pressure-volume diagram [19] lack units and numbers. The shape of the curves of the afterloaded maxima is, according to Frank, based on experimental observation (page 21 in [19]); on the other hand, however, the curves' convergence at point X (Fig. 1) is hypothetical (statement 25 on page 35 in [19]). Unfortunately Frank's laboratory notebooks, which might have provided direct access to further experimental results and observations that go beyond his publications, were lost during reorganization of the Institute of Physiology in Munich in 1960 (annotation 85 in [27]).

On the basis of the translated articles, it is clear what process Frank used in his scientific work: he was already envisioning a broad-based research project in his first big publication, his habilitation thesis [15] “On the dynamics of cardiac muscle” (1895). On the one hand, he incorporates his published results entirely within new articles and assumes that the reader has gathered the necessary information about them. It seems like an unremitting dialog with a well-informed reader. He also discusses papers from other authors but frequently only with vague citations. On the other hand, he already plans tasks for further

research, pointing out which problems he wants to tackle in the near future – or rather, which ones will have to be tackled in order to be able to get clear and verifiable results. Otto Frank contributed to the theoretical basis for modern cardiovascular physiology and his concepts, not just the “Frank-Starling law”, have remained valid and relevant over the course of time.

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Appendix A. Supplementary data

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