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Research Article

The pioneer in hemodynamics and pulse-wave analysis, Otto Frank

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Abstract

Arterial pulse-wave velocity is a noninvasive index of arterial distensibility now generally advocated to assess cardiovascular health above-and-beyond merely measuring blood pressure. A host of recent findings supports its use. This evidence draws attention to the fact that vascular stiffness precedes the increase in blood pressure with age and that even nonpharmacological lifestyle interventions can improve distensibility independent of blood pressure. Where do these ingeniously modern ideas come from, and who defined the principles we embrace today? A worthwhile lesson in physiology and exercise in humility is the effort to revisit the origins of these concepts and the man to whom gratitude should be directed. J Am Soc Hypertens 2016;10(4):290–296. © 2016 American Society of Hypertension. All rights reserved.

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Introduction

Medical students, at least in the English-speaking realm, encounter the term ''Frank'' as a part of the ''Frank-Starling'' principle. The more erudite students will realize that this was not Starling's first name, which was ''Ernest.'' The mechanism states that the stroke volume of the heart increases in response to an increase in the volume of blood filling the heart (the end diastolic volume) when all other factors remain the same. Otto Frank's (1865–1944) contribution to that idea was seminal; however, students of hypertension should remember the name of this Munich physiologist for other reasons.[1,2] Frank studied the basic concepts of the arterial pulse, the periodically oscillating pressure wave, and its propagation from the heart to the organs via the arteries.[3–6] In 1904, his essay entitled ''The arterial pulse'' he described the pulse wave, its reflection in the aorta, and a pulse-wave velocity of 7 m/s in the dog.[5] Later, he formulated a mathematical relationship between pulse-wave velocity and arterial stiffness.[2] Hence, more than 100 years ago, Otto Frank was describing important phenomena and parameters that form the basis for modern pulse-wave analysis (PWA) today. Nowadays, measurement of the elasticity or stiffness of the arteries is part of routine clinical practice. Already in 1863, the French physiologist Étienne-Jules Marey used a ''sphygmograph'' to record the pulse curve, which enabled distinguishing ''young'' and ''old'' arteries.[7] This device used a mechanical pressure transducer to convert the pulse to a written line on moving graph paper. However, with the technological development of indirect blood pressure measurement, assessment of the entire pulse curve was afforded less and less interest. Concentration on just two extreme pressure values (systolic and diastolic blood pressure) actually represented a step backward in assessing vascular physiology. Nonetheless, Marey and Frank continued to focus on blood pressure curves as a holistic assessment of vascular physiology. Only as modern methods of measurement were developed and new scientific data came to light, did we again pay attention to the entire pulse wave. Today's sphygmographs have much fancier trade names such as SphygmoCor, Arteriograph, Complior, or Mobilograph. These names would have amused Otto Frank; however, he would have been familiar with all these devices.

Pathophysiologically speaking, the methods are all based on the experimental findings of Otto Frank, shown in Figure 1. Pulse-wave velocity determinations, as first described by Frank in the dog,[5] are recommended in the 2007 Guidelines of the European Society for Cardiology and Hypertension as a (new!) biomarker for vascular

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Figure 1. Portrait Otto Frank. Figure reproduced with permission from Ref. 8.

health.[9] Frank was an exceptional physiologist and systematist with an extensive knowledge of physics and mathematics and tremendous talent for methodological and instrumental innovations. He was one of the greatest pioneers in physiology at the beginning of the last century.

About Otto Frank

Friedrich Wilhelm Ferdinand Otto Frank was born on June 21, 1865 in Gross-Umstadt im Odenwald (not too far away from Heidelberg), Germany, the son of medical practitioner Doctor Georg Frank and Mathilde Lindenborn. Young Otto studied medicine in Kiel and Munich between 1884 and 1889 and obtained his license to practice medicine on April 5, 1889 in Munich. Determined to complete his training in natural sciences, he next studied chemistry and mathematics in Heidelberg during the summer term of 1889 and in Glasgow during the winter term in 1889/1890. He spent the next summer term of 1890 in Munich studying chemistry and anatomy, and the winter term of 1890/1891 in Strasbourg studying physics, mathematics, and zoology. Thus, Otto Frank acquired the depth and foundation necessary for conducting his animal studies and working on his mathematical calculations.

From January 1, 1892 to the end of 1894, Frank worked as an assistant to Carl Ludwig in Leipzig at the Physiological Institute (the European investigative powerhouse of the time), where he completed his doctoral thesis (PhD equivalent) in 1892. On April 1, 1894, Frank began working as assistant to Carl von Voit at the Physiological Institute in Munich. Voit was also the publisher of the *Journal of Biology* (Oldenbourg Verlag, Munich and Leipzig) together with Wilhelm Kühne (Heidelberg), in which Frank published his groundbreaking articles on cardiovascular dynamics. This work included investigations on the function of cardiac muscle[1] with which he achieved faculty rank in 1895. On December 30, 1902, he was awarded the title of Extra-ordinary Professor. Frank was indeed extraordinary; however, the title in this case denotes the equivalent of an associate professorship. In June 1905, he took up the position, Physiology Department Chairman, at Giessen University. However, the departure of Carl von Void as Chairman in Munich allowed Otto Frank to return to Munich in 1908 as Voit's successor to direct the Physiological Institute. This decision must have been a difficult one because he would have known that managing such a large institute at one of the most illustrious universities would consume a considerable amount of the energy that he could otherwise invest in his original calling as a researcher.[8] Nonetheless, he remained loyal to Munich until his enforced retirement in 1934 because of his scathing criticism of the National Socialist regime, both in his student lectures and on a wider, more public scale. Otto Frank died on November 12, 1944 at the age of nearly 80 years. Two months thereafter, heavy bombing has destroyed his institute.

On the Dynamics of the Myocardium

Otto Frank performed a seminal work entitled: *On the Dynamics of the Cardiac Muscle*.[1] Building on the mechanisms of the skeletal musculature as described by Fick and von Kries, Frank's aim was to research the mechanical performance of the cardiac muscle. His experimental setup is illustrated in Figure 2. Using this method, Frank succeeded brilliantly in characterizing the dynamics of the heart under specific working conditions using an isolated-perfused heart model. Frank's experiments not only examined the isometric tension and isotonic contraction curves behavior of the atrium and ventricle depending on initial filling, wall tension, and overload but also provided a fundamental explanation of the elastic resistance arising in the connected artificial circulation and its impact on the pressure-and-volume ratios of the heart and the arterial system under variable conditions of filling and overload.[8] Investigators will immediately recognize the pressure-volume loops used in animal models today. The original illustration of the pressure-volume relationship is presented in Figure 3. It was here that the equilibrium curves of the heart (resting tension curve, curve of isotonic, isometric, and supporting maxima) were first described in the pressure-volume coordinate system, based on measurements from a poikilothermic heart.[8] These curves permitted insight, at a glance, into all the possible changes in the condition and activities of the heart in mechanical terms.[8] They later became the basis for evaluating a change in the performance of an exhausted,[10] aging,[11] or failing[12] heart and are still used today for this very same purpose.