Journal of the American Society of Hypertension 10(4) (2016) 290–296

Research Article

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

Martin Middeke, MD*

Hypertension Center-Munich, A European Society of Hypertension (ESH) Center of Excellence, Munich, Germany

Manuscript received January 17, 2016 and accepted January 22, 2016

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.

Keywords: Pulse-wave analysis; Otto Frank.

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

*Corresponding author: Martin Middeke, MD, Hypertoniezentrum München, Herzzentrum Alter Hof, Dienerstr. 12, 80331 München, Germany. Tel: 089-36103947; Fax: 089-36104026.

E-mail: Martin.Middeke@gmx.de

1933-1711/$ - see front matter
http://dx.doi.org/10.1016/j.jash.2016.01.022

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.

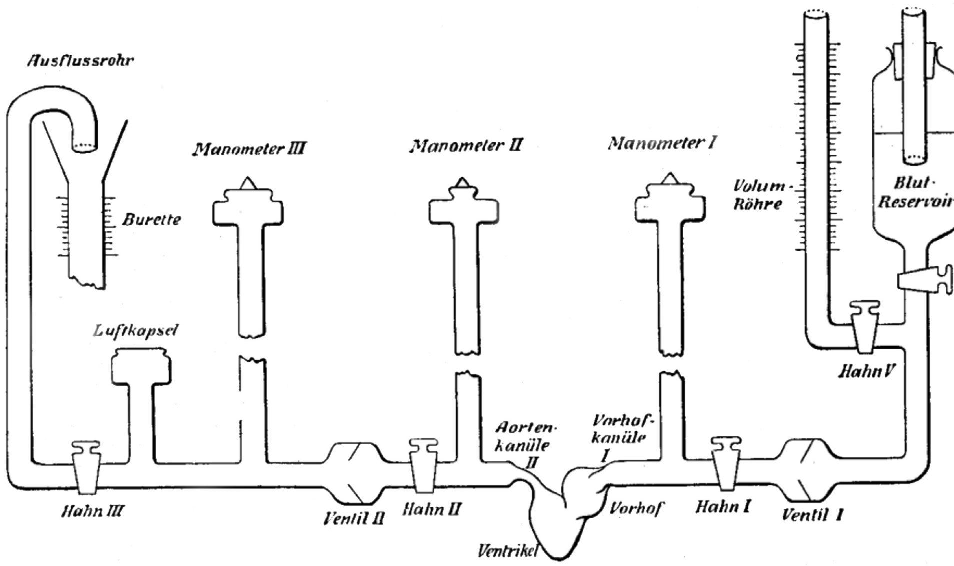


Figure 2. Experimental setting for the studying of the cardiac dynamics. Figure reproduced with permission from Ref. 3.

The English physiologist, Ernest Henry Starling (born 1866 in London, died 1927 in Jamaica), later (1915) also described the same pressure-volume ratio based on studies of a heart and lung model (whole animal rather than isolated-perfused heart). Hermann Straub, senior physician in internal medicine of the First Medical Clinic in Munich, made an important contribution with his postdoctoral thesis on the subject of the *Dynamics of the Mammalian Heart*. Hence, the concept can also be referred to as the Frank-Straub-Starling mechanism.

Neither Otto Frank nor Ernest H. Starling made the first observations on the effect of filling pressure on heart function. The essential features of this mechanism were discovered at Carl Ludwig's Physiological Institute at the University of Leipzig during the course of the first experiments on the isolated-perfused frog heart by three young investigators who came to Leipzig, namely Elias Cyon, Joseph Coats, and Henry P. Bowditch.[13] However, good ideas commonly occur to several people simultaneously. Dario Maestrini published similar experiments in 1914,

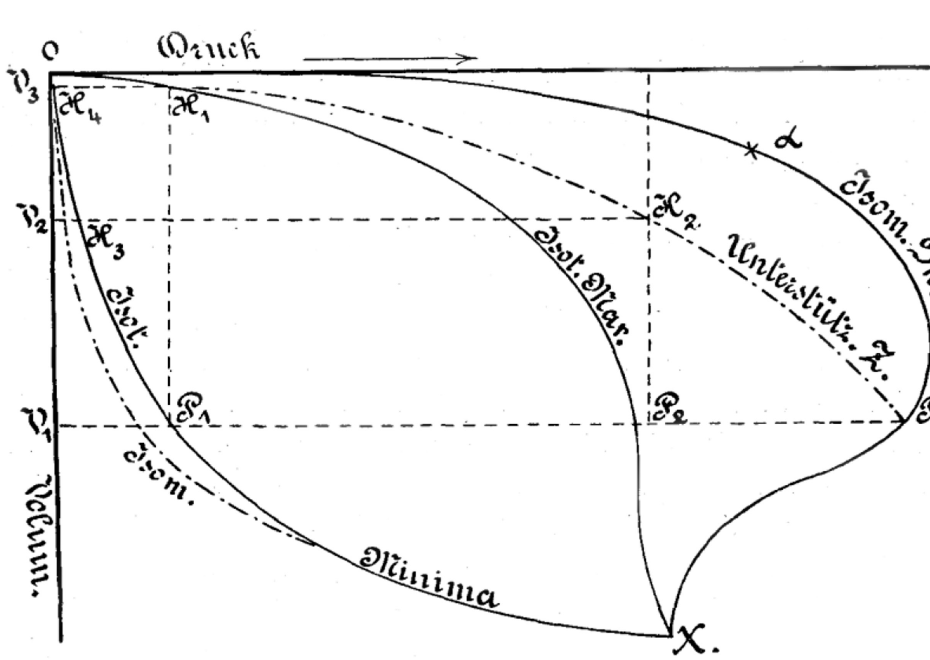


Figure 3. Otto Frank's drawing of the pressure-volume relationship. Figure reproduced with permission from Ref. 3.

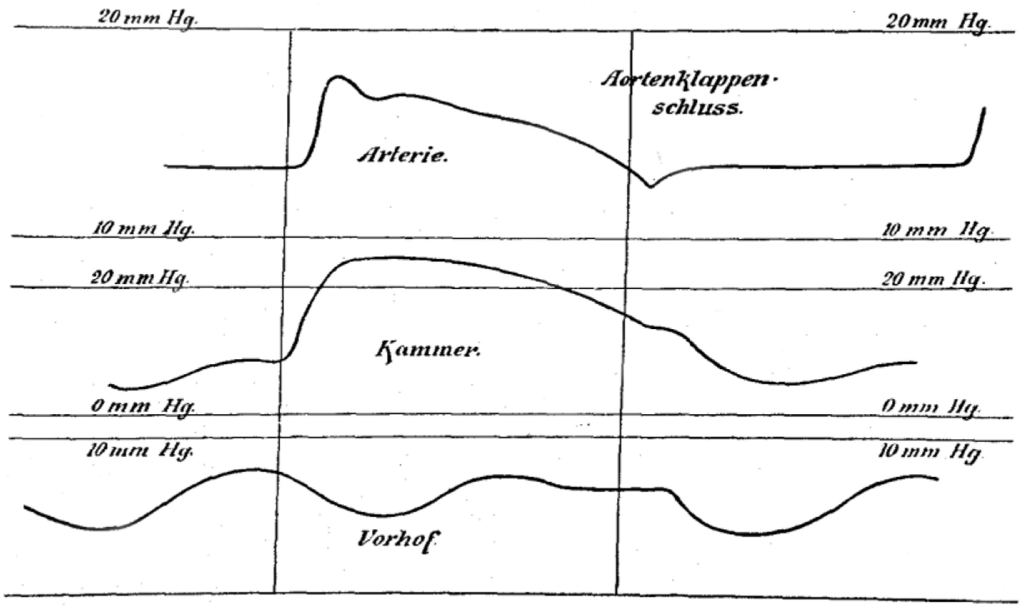


Figure 4. Pressure curves of atrium (Vorhof), ventricle (Kammer), and artery (Arterie). Figure reproduced with permission from Ref. 5.

termed ''legge del cuore'' by our Italian friends. Otto Frank also studied the progression of the pressure into the arteries and arterial dynamics very closely, including the mechanism of increasing filling pressure (paramount to defining heart failure), as shown in Figures 4 and 5.

On the Dynamics of the Arteries

The description of the basic concepts of the arterial pulse,[3] registration of the pulse with a mirror-sphygmomanometer,[4] discourses on elasticity of the arteries,[2] and the theory of the pulse wave[6] are the fundamental contributions made by Otto Frank to explain the physiology of the great arteries. All four contributions are still of vital importance to modern vascular medicine today. Frank described the location of pulse-wave reflection, as well as calculating the first measurements of pulse-wave velocity ever performed. These phenomena are important and form the parameters that are the basis for modern PWA used in vascular medicine today.[14–19] The prerequisite for these revolutionary experiments was a perfectly designed method for physiological registration,[8] one that Frank himself would continue to develop and further discuss in articles such as his 168-page ''Critique of the elastic manometer'' in 1903.[20] Only in such a way, could optimal pressure curves be registered and used to derive appropriate algorithms. And so in 1904, he published the article, ''The arterial pulse,''[5] in which the correct picture of the aortic pulse, with its typical characteristics of fluctuations, sharp increases, initial oscillation, and incisura, was described, as outlined in Figure 6. Otto Frank writes ''*The question concerning the pattern of pressure fluctuations in the various parts of the arterial system has finally been answered by this work. This achievement is primarily down to the principle of the instruments*.'' Further articles concentrate on the elasticity of the arteries and the theory of pulse waves, such

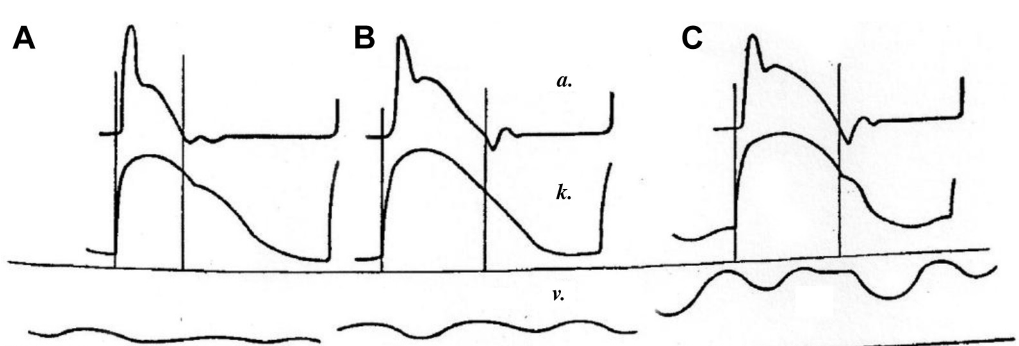
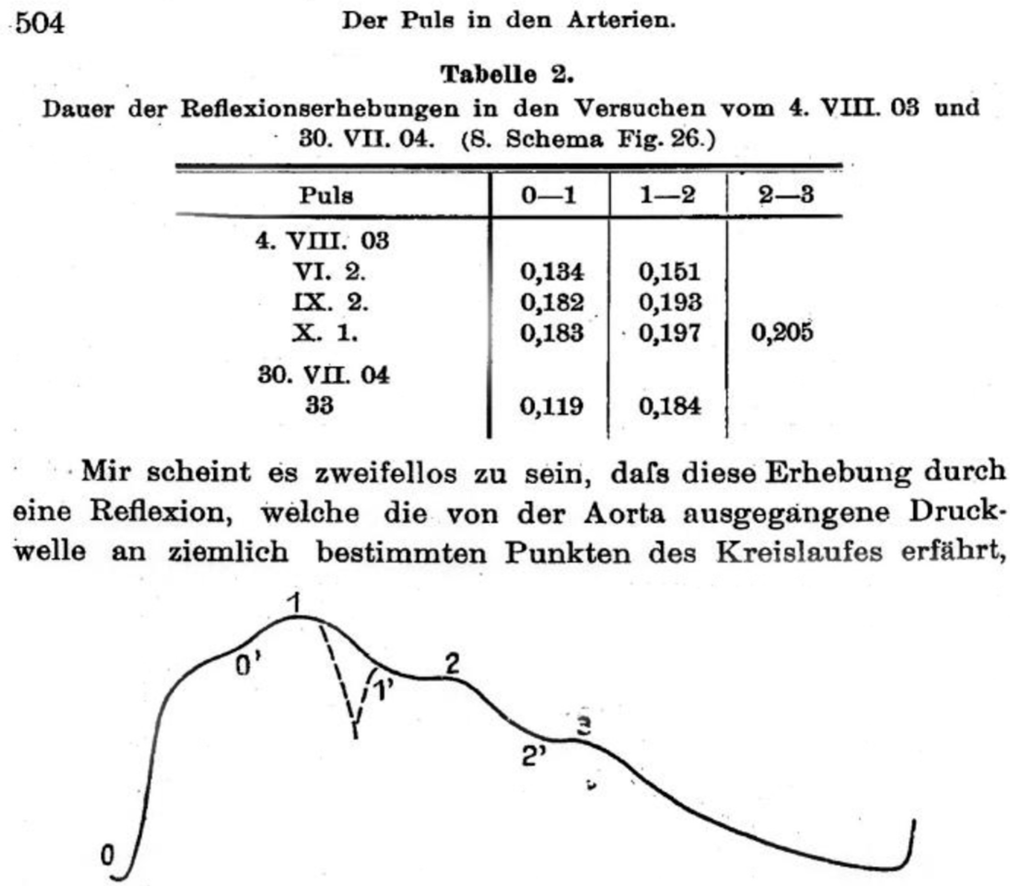


Figure 5. (A–C) Pressure curves of atrium (v), ventricle (k), and artery (a) with increasing filling pressures. Figure reproduced with permission from Ref. 1.



504 **Der Puls in den Arterien.**

Tabelle 2.

Dauer der Reflexionserhebungen in den Versuchen vom 4. VIII. 03 und 30. VII. 04. (S. Schema Fig. 26.)

Puls	0—1	1—2	2—3
4. VIII. 03			
VI. 2.	0,134	0,151	
IX. 2.	0,182	0,193	
X. 1.	0,183	0,197	0,205
30. VII. 04			
33	0,119	0,184	

Mir scheint es zweifellos zu sein, dafs diese Erhebung durch eine Reflexion, welche die von der Aorta ausgegangene Druckwelle an ziemlich bestimmten Punkten des Kreislaufes erfährt,

Figure 6. Pressure curve of the aorta. Figure reproduced with permission from Ref. 5.

as in "The elasticity of the arteries."[2] Therein, Frank addresses the theory of infinite distension and ultimately the practical method for determining the stroke volume in humans and animals based on the *Windkessel* and wave theories.

Windkessel, when loosely translated from German to English, means "air chamber." However, when used in vascular medicine, the term is generally taken to imply an elastic reservoir. The walls of large elastic arteries, such as the aorta, common carotid artery, subclavian artery, pulmonary arteries, and their larger branches contain elastic fibers, rich in elastin. The arteries distend when the blood pressure rises during systole and recoil when the blood pressure falls during diastole. Because the rate of blood entering these elastic arteries exceeds the rate leaving the arterial tree due to the peripheral vascular resistance, a net storage of blood occurs during systole which discharges during diastole. The distensibility of the large elastic arteries therefore functions as a capacitor, or *Windkessel*.

The generated pulse wave is similar to an acoustic wave in terms of frequency, amplitude, amplification, dampening (*Windkessel* function), and reflection (arterial stiffness). Frank also noted the significance of heart rate to the blood pressure level. He stated "The influence of the frequency of the heartbeat on the blood pressure and volume curve of the heart is generally such that at a certain average frequency the greatest volume of blood is ejected in the measured time unit, thus achieving maximum blood pressure at this frequency."[21] In the 1950s, McDonald[22] conducted fundamental research on the correlation of pulsatile pressure and arterial blood flow, revealing that the optimal frequency for ventricular-arterial coupling and conduction of the blood flow through the greater arteries is achieved at 60 bpm (1 Hz). At such a frequency, the pulse wave carries the blood in diastole, and the flow and pulse wave are optimally synchronized, thereby running in parallel. More recent data reveal that there is a close inverse relationship between the heart rate and reflection of the pressure wave: the reflection increases as the heart rate drops.[23] In modern methods of PWA, therefore, the influence of the heart rate must be taken into account when determining the pulse-wave velocity and augmentation index. Standardization to a heart rate of 75 bpm is recommended.

These examples aim to illustrate the fundamental importance of Otto Frank's research on the pulse wave and the significance it has today.

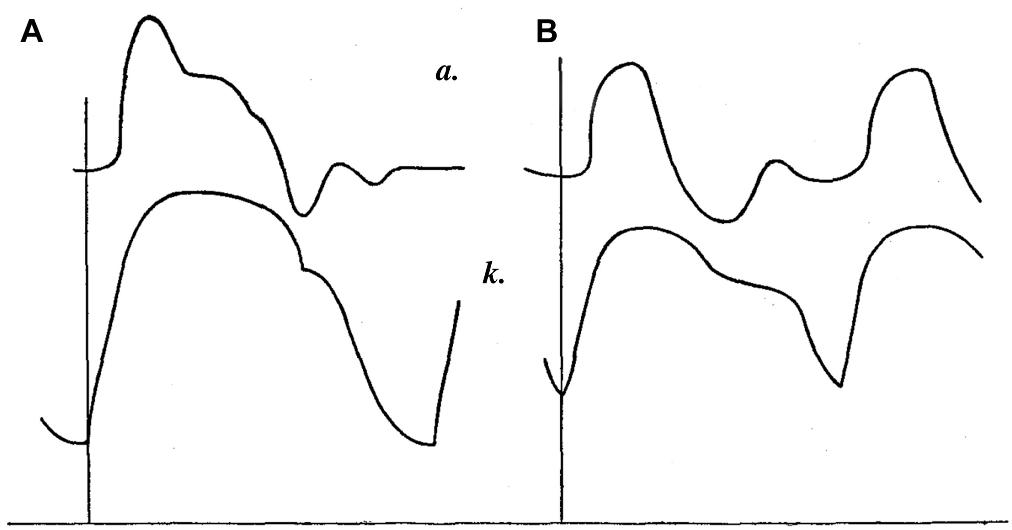


Figure 7. Pressure curves of ventricle (k) and artery (a) in a stiff artery (A) and in a free swinging artery (B). Figure reproduced with permission from Ref. 2.

Frank's studies and the theories he conceived as a result ultimately also enabled clinicians at that time to interpret blood pressure values correctly and evaluate the factors such as stroke volume, pulse rate, peripheral flow resistance, and total elastic resistance of the arteries that influence systolic and diastolic blood pressure. As Wezler[8] puts it, "Due to our deeper understanding, the times of indiscriminately attributing an increase in blood pressure to a rise in peripheral arterial resistance and so to vasoconstriction are—or at least should be!—over." And so, we find ourselves at the heart of modern medicine once more. Only recently, it was shown conclusively that the development of systolic hypertension is in fact preceded by the development of arterial stiffness.[14] This common form of hypertension in the elderly is not actually characterized by increased peripheral resistance. Otto Frank had already described the features of the pressure curve of a stiff artery, as shown in Figure 7.

Pulse-Wave Analysis Today

PWA is the easiest method available to us today for examining arterial function noninvasively. The recording and analysis of the pulse wave in an artery using modern systems allows conclusions to be made on pressure ratios and arterial elasticity.[24] It is possible to determine important clinical parameters such as the augmentation index or pulse-wave velocity, which are directly related to vascular elasticity. Standard values for pulse-wave velocity have now been derived from large populations. Accordingly, arterial stiffness is to be presumed at a velocity of $\geq$11 m/s.[25] The central (aortic) blood pressure calculated from PWA is regarded as an essential parameter for antihypertensive therapy, for example, and is more closely associated with the cardiovascular risk than the pressure in the brachial artery. At a younger age and with healthy blood vessels, the aortic pressure measured in the upper arm is overestimated. The reverse is true in old age and with rigid arteries. Arterial stiffness can be influenced in different ways by different antihypertensive substances and can be attenuated by nonpharmacological approaches.

Our pathophysiological concepts and therapeutic choices today are based on the experimental findings of the Munich physiologist Otto Frank at the beginning of the previous century.[26] Otto Frank was the first to describe pulse-wave velocity, a parameter, which today is of utmost importance with respect to arterial stiffness and will in the years to come play an essential role in preventive medicine. Aside from the conventional vascular risk factors, years of consuming increased quantities of salt along with a phenomenon that is very common here, namely vitamin D deficiency, are two important factors that lead to premature vascular aging and stiffness.[27–29] A healthy lifestyle can delay such developments and so prevent the emergence of (isolated) late-onset systolic hypertension.[30,31]

References

1. Frank O. Zur Dynamik des Herzmuskels. In: Zeitschrift für Biologie. Band 32, 1895, S. 370.
2. Frank O. Die Elastizität der Blutgefäße. Z Biol 1920; 71:255–72.
3. Frank O. Die Grundform des arteriellen Pulses. In: Zeitschrift für Biologie. Band 37, 1899, S. 483.
4. Frank O. Die Registrierung des Pulses durch einen Spiegelsphygmographen. Münchener Med Wochenschr. Band 1903;42:1809–10.

5. Frank O. Der Puls in den Arterien. Z Biol 1904;46: 441–53.
6. Frank O. Die Theorie der Pulswelle. Z Biol 1926;84: 91–130.
7. Marey EJ. Physiologie Medicale du Sang. Paris: A.Delahaye; 1863.
8. Wezler K. Otto Frank zum Gedächtnis. Z Biol 1950; 103:92–122.
9. Mancia G, De Backer G, Dominiczak A, Cifkova R, Fagard R, Germano G, et al. Guidelines for the management of arterial hypertension. J Hypertens 2007;25:1105–18.
10. Broemser Ph. Verh Dtsch Gesel Kreislaufforschung 1939;12:297.
11. Wezler K. Ztschr Altersforschung 1942;III:199.
12. Reindell H, Delius L. Klinische Beobachtungen über die Herzdynamik beim gesunden Menschen. [In German]. Delius Dtsch Arch Klin Med 1948;193:639.
13. Zimmer HG. Who discovered the Frank-Starling Mechanisms? News Physiol Sci 2002;17:181–4.
14. Kaess B, Rong J, Larson MG, Hamburg NM, Vita JA, Levy D, et al. Aortic stiffness, blood pressure progression, and incident hypertension. JAMA 2012;308(9): 875–81.
15. Laurent S, Katsahian S, Fassot C, Tropeano A-I, Gautier I, Laloux B, et al. Aortic stiffness is an independent predictor of fatal stroke in essential hypertension. Stroke 2003;34:1203–6.
16. McEniery CM, Cockcroft JR, Roman MJ, Franklin SS, Wilkinson IB. Central blood pressure: current evidence and clinical importance. Eur Heart J 2014;35:1719–25.
17. Vlachopoulos C, Aznaouridis K, O'Rourke MF, Safar ME, Baou K, Stefanadis C. Prediction of cardiovascular events and all-cause mortality with central hemodynamics: a systematic review and meta-analysis. Eur Heart J 2010;31:1865–71.
18. Weber T, Auer J, O'Rourke MF, Kvas E, Lassnig E, Berent R, et al. Arterial stiffness, wave reflections, and the risk of coronary artery disease. Circulation 2004;109:184–9.
19. Williams B, Lacy PS, Thom SM, Cruickshank K, Stanton A, Collier D, et al. Differential impact of blood pressure-lowering drugs on central aortic pressure and clinical outcomes: principal results of the Conduit Artery Function Evaluation (CAFE) study. Circulation 2006;113:1213–25.
20. Frank O. Kritik der elastischen Manometer. Z Biol 1903;44:445.
21. Frank O. Schätzung des Schlagvolumens des menschlichen Herzens auf Grund der Wellen- und Windkesseltheorie. Z Biol 1930;90:405.
22. McDonald DA. The relation of pulsatile pressure to flow in arteries. J Physiol 1955;127:533–52.
23. Williams B, Lacy PS. Impact of heart rate on central aortic pressures and hemodynamics: analysis from the CAFE study: CAFE Heart Rate. J Am Coll Cardiol 2009;54(8):705–13.
24. Weber T, Wassertheurer S, Rammer M, Maurer E, Hametner B, Mayer CC, et al. Validation of a brachial cuff-based method for estimating central systolic blood pressure. Hypertension 2011;58:825–32.
25. The Reference values for Arterial Stiffness Collaboration. Determinants of pulse wave velocity in healthy people and in the presence of cardiovascular risk factors: establishing normal and reference values. Eur Heart J 2012;31:2338–50.
26. Middeke M. Otto Frank der Dynamiker. Dtsch Med Wochenschr 2012;137:2706–11.
27. Avolio AP, Clyde KM, Beard TC, Cooke HM, Ho KK, O'Rourke MF. Improved arterial distensibility in normotensive subjects on a low salt diet. Arteriosclerosis 1986;6:166–9.
28. Mayer O Jr, Filipovský J, Seidlerová J, Vaněk J, Dolejšová M, Vrzalová J, et al. The association between low 25-hydroxyvitamin D and increased aortic stiffness. J Hum Hypertens 2012;26:650–5.
29. Webb DR, Khunti K, Lacy P, Gray LJ, Mostafa S, Talbot D. Conduit vessel stiffness in British south Asians of Indian descent relates to 25-hydroxyvitamin D status. J Hypertens 2012;30:1588–96.
30. Papamichael CM, Karatzis EN, Papaioannou TG, Karatzis EN, Katsichti P, Sideris V, et al. Acute combined effects of olive oil and wine on pressure wave reflections: another beneficial influence of the Mediterranean diet antioxidants? J Hypertens 2008; 26:223–9.
31. Schmidt-Trucksäss AS, Grathwohl D, Frey I, Schmid A, Boragk R, Upmeier C, et al. Relation of leisure-time physical activity to structural and functional arterial properties of the common carotid artery in male subjects. Atherosclerosis 1999;145(1): 107–14.