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The Nature of Waves in the Arteries In Memoriam: Nico Westerhof and John Tyberg

Kim H Parker^{1*}, Pieter de Tombe², Jolanda van der Velden³ and Berend E Westerhof⁴

Abstract

This memorial remembers the lives of two distinguished researchers who made major contributions to cardiovascular physiology; Nico Westerhof (1937-2022) and John Tyberg (1938-2022). It is a joint memorial not because they collaborated closely but because they held very different views about the nature of waves in the arteries. Their papers and particularly their lively discussions at many scientific meetings stimulated interest in the subject. Both were thoughtful and articulate about their views and the debates were polite and dignified. They never resolved their differences and, after outlining what these differences were, we will suggest that perhaps there is no resolution.

The authors of this memorial were close to one or the other protagonist; a son, a son-in-law and two close collaborators. We all have different views about the nature of waves in the arteries but we all share great respect for both men and felt that a joint memorial was a fitting way to remember them and their many contributions. All of the authors knew the subjects of this memorial as 'Nico' and 'John' and we will use these informal names throughout.

Brief Curricula Vitae

Nicolaas Westerhof

Born: 4 May 1937; De Bilt

Died: 25 April 2022; Amsterdam

Education: PhD 1969, University of Pennsylvania; Supervisor, Abraham Noordergraaf.

Academic: 1969-2022 Department of Physiology, and 2002-2022 Department of Pulmonary Medicine, Vrije Universiteit, Amsterdam, Netherlands



Nico Westerhof

John Tyberg

John Victor Tyberg

Born: 4 May 1938; Grantsburg WI, USA

Died: 10 April 2022; Calgary

Education: PhD 1967, MD 1972, University of Minnesota

Postdoctoral: 1968-1969 Harvard University;

Academic: 1969-1971 University of California, San Francisco;

1971-1973 Ceders-Sinai Medical Center, Los Angeles;

1973-1981 University of California, San Francisco

1981-2022 Cardiac Sciences, Physiology and Pharmacology, University of Calgary, Alberta, Canada

1 Introduction to Haemodynamics

One of the strengths of science is that it builds upon the achievements of previous scientists. Before a paper is published in a scientific journal it is screened by an editor and several referees to see if it is compatible with what is already known about the subject. This process ensures that the quality of the science is maintained but it also contributes a certain amount of inertia that impedes the acceptance of radically new ideas. The popular idea that scientists who have an eureka moment are instantly lauded when they publish their work is very mistaken. It is far more difficult to publish a radical new idea, no matter how correct

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it is, than to publish an incremental improvement of an already accepted idea. For example, it is said that not a single professor of physics who held their chair in 1905 ever accepted Einstein's theory of relativity during their tenure. Einstein's ideas were taken up by young physicists who eventually succeeded their professors and only then did relativity become accepted dogma in physics.

Quantitative arterial mechanics emerged relatively recently. The first in vivo measurements of arterial pressure and flow that can be considered high-fidelity by today's standards were made in the decades following World War II. The quasi-periodic nature of these data inevitably resulted in the use of methods based on Fourier's theorem that any continuous periodic function can be decomposed into sinusoidal wavetrains with different frequencies, amplitudes, and phases. Calculating the Fourier components for measured data involved calculating the integrals of complex functions by hand and it could take several days to calculate 16 harmonics for both the pressure and the flow. Needless to say, there were very few published results until the introduction of the modern computer and, significantly, the publication of the Fast Fourier Transform algorithm by Cooley and Tukey in 1965. In this setting, Nico and John initiated their scientific careers.

Although their contributions may not compare to Einstein's, Nico and John had similar experiences with the difficulty of publishing their novel ideas. Nico's work on aortic input impedance was extremely difficult to publish before finally appearing in *Circulation* in 1980. [1] It has since been cited well over 1000 times. Similarly, John's original work on what became known as the reservoir-wave hypothesis was rejected repeatedly before being published in *Am. J. Physiol* in 2003. [2] It has been cited over 300 times. It is this hypothesis that formed the basis for the controversies between Nico and John which provides the framework for this memorial.

1.1 Nico's scientific contributions

During Nico's PhD the application of Fourier methods to arterial haemodynamics, generally called impedance analysis, developed rapidly. Nico contributed significantly to this emerging field in his PhD thesis (1968) and by the time of his appointment to the staff of the Department of Physiology, Vrije Universiteit, Amsterdam (1969) he was recognised as one of the leading lights in the subject. He made many significant contributions during his long career; some of the most important are listed.

Based in impedance analysis, Nico introduced the 3-element Windkessel into modelling the cardiovascu-

the resistor-capacitor model introduced by Otto Frank (1899) significantly improved the performance of the model. Because the characteristic impedance is a property of the waves in the artery, this simple modification introduced an element of waves into the 0-D Windkessel model. [3] [4]

Nico created an analogue model of the systemic arterial circulation in man, assembling data from many sources that described the properties of the major arteries. [5] Although analogue computing has gone out of fashion, his model has been used by many researchers using 1-D computational fluid dynamics (CFD) to model arterial flow. The model has now been extended to include many more arteries, but Nico's model remains as the core of these extended models. (see [6] and references therein).

Another engineering concept introduced by Nico to cardiovascular practice is the pump function graph, traditionally used to characterise the performance of mechanical pumps such as ventricular assist devices where mean ventricular pressure is plotted versus cardiac output (or stroke volume, taking heart rate into account). The pump function graph follows a parabolic shape that intersects the pressure axis at the pressure generated by an isovolumetrically contracting heart and the cardiac output axis at the output for a heart ejecting against zero pressure.

The pump function graph is related in a straightforward manner to the well-known pressure-volume loops analysis as proposed by Sagawa. [7] While for the pressure-volume loops analysis simultaneous ventricular pressure and volume are required, for the pump function graph we need simultaneous ventricular pressure and cardiac output, which is sometimes more readily available. An increase in ventricular preload or an increase in heart rate will move the pump function graph outward (to the right and up). An increase in contractility causes the pump function graph to become steeper, hinging around its intersection with the cardiac output axis. This mirrors the rotation of the end-systolic pressure-volume relation, which rotates around its intersection with the volume axis (" V_0 ").

Perhaps Nico's main contribution, certainly in the context of the present overview, is realising that the measured pressure and flow waveforms in an artery can be separated into their forward and backward components if the local characteristic impedance is known. [8] This greatly increased our understanding of arterial haemodynamics, making it possible in principle to separate proximal effects (the heart) from distal (vascular) effects.

Nico was also active experimentally, measuring the effect of chronic occlusions at different locations in

aorta. His high-fidelity measurements in open-chested dogs are one of the classical experiments in arterial haemodynamics. [9] The results were used to illustrate the utility of the separation of backward and forward waves. They also demonstrated the complexity of cardiovascular haemodynamics; demonstrating, for example, the highly non-intuitive result that complete acute occlusion of the aorta at the aorto-iliac bifurcation made no observable effect on flow in the ascending aorta.

By the 1980s impedance analysis, originally controversial, effectively took over as the standard method for analysing arterial flow. McDonald's Blood Flow in Arteries, now in its 6th edition and written by Vlachopoulos, Nichols and O'Rourke [10], and Milnor's Hemodynamics [11] are now the standard textbooks about arterial flow. Both are based almost exclusively on impedance analysis.

After his retirement in 2002, Nico wrote a book on haemodynamics, appearing in 2004, and now in its 3rd edition [12] and a review on coronary circulation [13] With these two publications, he considered his scientific work well-documented, however, around that time he was asked by Anton Vonk Noordegraaf to come and support the research in the department of Pulmonary Medicine. Nico tremendously enjoyed his new career, bringing his vast knowledge about cardiovascular physiology on the "other side".

1.2 John's scientific contributions

John started work at the University of California, San Francisco on his first major scientific interest in cardiovascular physiology: the impact of external mechanical constraint on ventricular pump function. [14] This scientific interest continued upon John's recruitment (1981) to the University of Calgary, Alberta, Canada, the institution at which he was active, well beyond the his "official" retirement in 2011.

The work on external mechanical constraint of the heart led to a major shift in clinical practise with regards to the interpretation of end-diastolic pressure as an indicator of cardiac preload. Preload, in the days before portable ultrasound imaging was widely available at the bed-side, was a critical parameter to be obtained in patients with reduced cardiac output.

End-diastolic pressure was traditionally measured, importantly at the bedside and without radiographic imaging, with the aid of the Swan-Ganz catheter, which measures pulmonary wedge pressure that is a fairly accurate measurement of end-diastolic left ventricular pressure. A high wedge pressure in the face of low cardiac output indicates weak cardiac pump function or diastolic cardiac abnormalities preventing proper filling of the heart, while a low wedge pressure

indicates an effective low blood volume status (e.g. major blood loss due to external or internal bleeding or, alternatively, e.g. anaphylactic shock).

John's large body of work on this topic clearly demonstrated that end-diastolic pressure is not an unambiguous measure of cardiac preload because the mechanical constraints imposed by the pericardium and the lungs will, under certain conditions, impose a significant "extra" pressure to the cardiac cavity that is not transmitted to the cardiac sarcomeres to form the passive myofilament stretching force. As a result, sarcomeres are not stretched in proportion to diastolic pressure, and a limitation of cardiac output results due to the operation of the Frank-Starling Law of the heart, which itself is driven by myofilament length dependent activation. (see references in [15])

This work also explained why indiscriminate volume loading of patients with low cardiac output can be counterproductive and potentially lethal. [16] Moreover, subsequent extensive work within the Tyberg lab demonstrated that by taking into account right-atrial pressure (which is easily measured during the wedge-pressure procedure), a much more accurate "true" measurement of cardiac pre-load can be obtained to help guide the critical care clinical decision processes. [17]

Starting in the 1990's, John embarked on a new scientific topic of interest, the coupling of the heart to the circulatory system and the physiological properties of that system with regard to periodic pressures and waves. As a visiting Professor at Imperial College, London (1996, 2012) John actively pursued this interest in collaboration with one of the co-authors of this article.

In about 1990 Parker and his colleagues introduced wave intensity analysis into arterial haemodynamics using his background in gas dynamics (see [18]). Instead of the sinusoidal wavetrains that form the basis of impedance analysis, the elemental basis of wave intensity analysis are wavelets; discrete wave fronts. Any waveform, periodic or not, can be built up by successive wavelets of the appropriate magnitude. Its main advantage is that the analysis is carried out in the time domain instead of the frequency domain which makes it easier to relate specific features of the results of the analysis to events happening at specific times in the cardiac cycle. Another advantage is that it can be applied to non-periodic events, such as ectopic beats.

John became one of the leading proponents of wave intensity analysis; bringing his experience of cardiovascular mechanics and formidable experimental methods to the problem (see e.g [19]). Like impedance analysis before it, wave intensity analysis was very controversial for more than a decade, but it is now accepted widely

as an alternative method for the analysis of arterial haemodynamics.

The fact that both sinusoidal waves and wavelets can be shown to be solutions to the hyperbolic conservation equations that govern fluid mechanics has played a part in the relatively rapid acceptance of wave intensity analysis.

In 2003 John and his colleagues introduced the reservoir-wave hypothesis that it might be useful to decompose the arterial pressure into a 'reservoir' pressure that is uniform throughout the arterial network and an 'excess' pressure that is defined as the difference between the measured pressure and the reservoir pressure. [2] The reservoir pressure was inspired by the Windkessel pressure (in fact, in the first paper it was called the Windkessel pressure, but it quickly became obvious from John's simultaneous measurements at different sites down the aorta that the reservoir pressure was propagating down the aorta with the local wave speed).

1.3 The controversy between Nico and John

The reservoir-wave hypothesis was and remains controversial. Nico and John soon became key proponents of the different schools of arterial mechanics and their exchanges of views in various meetings and conferences had a very stimulating effect on the field. Their contributions to the "Crosstalk" series in *J Physiol* provides an excellent taste of these debates. [20] [21]

The reservoir-wave hypothesis remains heuristic; there is still no rigorous analysis leading to this separation of arterial pressure. However, a number of retrospective clinical trials have shown that various parameters describing the reservoir pressure are significant predictors of future cardiovascular events, independent of other risk factors.

Both Nico and John were key speakers at the 2016 Workshop at University College London on Arterial Hemodynamics: Past, Present and Future which was organised to resolve this controversy. Agreement was reached on some points but it is safe to say that the controversy was not resolved. [22]

John presented experimental results that showed that the backward waves calculated from the measured pressure were propagating in the forward direction. Nico pointed out that this can happen in complex wave packets under certain conditions (technically the difference between group velocity and phase velocity; prosaically the reason that stagecoach wheels sometimes appear to be rotating backwards in old western films).

Nico pointed out that the reservoir pressure during diastole was just twice the backward wave and speculated that this was also true during systole. John suggested that this was unlikely because there is always

port time at the start of systole when the outflow in the arteries still exceeds the inflow from the heart causing the reservoir pressure to continue to fall during that period. Nico noted that this inversion of the backward wave in the early phase has been observed and it tends to be dependent on the characteristic impedance that is used for the separation.

These discussions between such distinguished researchers were an inspiration for anyone who was fortunate enough to hear them.

Possible resolution of the controversy and general conclusions

The authors of this memorial believe that some of the controversy between impedance analysis and wave intensity analysis may be irresolvable and that it has a normal relationship to the particle-wave duality in modern physics. Simply stated, this says that any elementary particle such as an electron can behave as a wave in some cases and as a particle in others. The earlier components of impedance analysis are obviously analogous to the waves and the discontinuous nature of the wavelet is analogous to the particle. There is a quote attributed to John von Neumann referring to the method of characteristic, the foundation of wave intensity analysis: 'In mathematics you don't understand things. You just get used to them'.

If this analogy is true then the resolution of the long-standing controversy between Nico and John may be that both of them are right. Depending on the circumstances, waves in the arteries can be considered to be either sinusoidal wave trains or discontinuous wavelets. What is incontrovertible, however, is that both Nico and John independently and through their interactions with each other shed an enormous amount of light onto cardiovascular physiology.

Competing interests

The authors declare that they have no competing interests. (bmc-mathphys, vancouver, spbasic).

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