Bridging cardiovascular physics, physiology, and clinical practice: Karel H. Wesseling, pioneer of continuous noninvasive hemodynamic monitoring

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KAREL HENDRIK WESSELING (Fig. 1), emeritus professor of biomedical instrumentation, was born in The Hague, The Netherlands, on April 23, 1935. He studied electrical engineering, in his words, from 1950 on, and since 1953 at the Delft University of Technology (DUT) from which he graduated with honors in 1960. Subsequently, he worked at the DUT, did military service at the Dutch Air Force, and returned to the DUT to work in active networks. After that, he worked in radio astronomy, first in a European project and later in the United States at the National Radio Astronomy Observatory in Green Bank, WV; Charlottesville, VA; and Tucson, AZ; eventually as head of the mm-wave laboratory. In 1969, he moved back to The Netherlands “to marry a Dutch girl,” as he put it. Indeed, he married Hanny Gommers in 1971. He started working in the TNO Institute of Medical Physics in Utrecht with Professors Dick H. Bekkering and Jan E. W. Beneken and became head of the Cardiovascular Physics group in 1976. Here he developed several computational models of physiological systems, laying the basis for his later work on baroreflex, calculation of cardiac stroke volume from arterial pressure and of pressure transfer functions. His special interest was to obtain physiological parameters in a noninvasive manner. In 1984, he brought his group, now called TNO Biomedical Instrumentation, to the Academic Medical Center of the University of Amsterdam. In 1990, he was appointed professor in the Faculty of Electrical Engineering of the Eindhoven University of Technology.

In this editorial, a few researchers who knew him well briefly review some of the important contributions that Karel made to their field and how it helped in advancing science. (B.E.W.)

Innovation at the Basis of New Medical Devices

Karel’s motto in his professional life was “helping clinicians in their care for patients by providing them innovative, noninvasive concepts, methods and tools.” As physicist, engineer, and innovator, he realized that to achieve a situation where tools would actually be widely available to clinicians, major investments in research and development (R&D) and product development would be required, which would only be achieved with commercial, corporate involvement, which in turn would require intellectual property and patent protection. Karel’s innovations and patents span more than four decades.

In the 1970s, the development of his extensive model of the human circulation among other things led to the first method and algorithm for the beat-to-beat computation of cardiac output from the pressure waveform, the so-called Wesseling cZ method (39), which was patented, commercially licensed, and implemented in a patient monitor.

In the 1980s, research on continuous, noninvasive finger blood pressure, building on the original volume clamp principle patent of Jan Peñaž (33), led to a series of broad physiology and technology innovations and patents (34), including the ones on the Physiocal set point (35) for the volume clamp.

Fig. 1. Professor Karel H. Wesseling.
principle, finger cuff, method of calibration, proportional pneumatic control valve, and electronic light-emitting diode driver. This unique set of intellectual property and patents again led to a commercial license and development of the Finapres 2300 patient monitor.

The major limitation of Finapres, measuring blood pressure at the finger, was solved by R&D in the 1990s, and the development of brachial blood pressure waveform reconstruction (5, 11), licensed and implemented in Finometer and with a further R&D development, was also used in the Nexfin and ClearSight patient monitor.

The R&D efforts in this period also resulted in a battery-operated, ambulatory, 24-h blood pressure device, called Por-tapres, which was provided to many research groups around the world but also was the basis for a series of contracts with space agencies (Deutschen Zentrum für Luft- und Raumfahrt, Centre National d’Études Spatiales, European Space Agency and National Aeronautics and Space Administration) for the development of several generations of space-qualified “specials” which were used in space shuttle missions, aboard the Russian space station Mir, and now, with Cardiopres, in routine use on the International Space Station.

Further R&D in this period led to a new concept of modeling the real-time flow waveform from pressure, resulting in the second generation method and algorithm for the beat-to-beat computation of cardiac output from the pressure waveform, the so-called Modelflow method (36), which was patented, commercially licensed and implemented in several patient monitors. More recently, the two generations formed the basis for the calculation of cardiac output from finger pressure. The first step was derivation of proximal aortic pressure wave shape and magnitude from finger pressure (23). The second step was the calculation of cardiac output from pressure, using the windkessel parameters. Under his supervision, an extensive study was carried out in our laboratory for physiology to obtain data on aortic stiffness in aging (22). These data on human post-mortem aortas gave quantitative information of two important windkessel parameters, namely characteristic impedance and aortic stiffness. Knowing these parameters as a function of age allows estimation of aortic flow wave shape and cardiac output from the calculated proximal aortic pressure (27, 36). Additionally, methods were developed to calculate the sensitivity of the baroreflex acting on heart rate and on vascular resistance (3). All taken together, this resulted in practical methods, from the Finapres to the present-day Nexfin and ClearSight monitors. Karel has shown that the use of basic information on arterial function (transfer of pressure waves and arterial stiffness) can lead to the practical use of noninvasive pressure and flow monitoring. I have lost a very intelligent and wonderful personal friend. (N.W.)

Waveform Filtering

The shape of the arterial pressure wave changes on its way to the periphery due to pulse wave reflections, pulse wave distortions, and resistance to pressure. During the development of Finapres, Karel realized at an early stage that peripheral and, especially, finger pressure measurements are sensitive to such effects (4, 23, 38). At the level of the finger high-frequency components, i.e., the systolic upstroke, are amplified, and low-frequency components, i.e., the diastolic pressure, are attenuated. These distortions may limit the clinical use of finger pressure measurements. They can be corrected for by using a frequency-dependent transfer function, the inverse of the formula describing the amplification toward the periphery. Waveform filtering with generalized transfer functions is most often used to reconstitute aortic pressure waves from radial artery pressure recordings (15). Karel and coworkers (5, 10) applied the technique to successfully reconstruct brachial and aortic pressure waves from finger pressure registrations, thus enabling physicians to use upper arm pressures and physiologists to study the effect of blood pressure on the heart with aortic pressures. In later years, Karel worked on further improvements of the technique by investigating ways to individualize the generalized waveform filter (41).

Karel was a physicist with a keen eye for the needs of physicians and physiologists. Across institutional borders, he collected a group of professionals consisting of physicists interested in physiology and medicine, and physicians and physiologists with a sense for physics. It has been a delight to participate under the guidance of Karel Wesseling. (W.J.W.B.)

From Arterial Modeling to Practical Pressure Measurement

When we learned to know each other in 1969, Karel and I were both interested in the physical basis of arterial function. We discussed about the arterial windkessel model (42), where Karel was especially interested in its practical use. At that time, the quantitative measurement of arterial pressure using the finger came around: the Peñáz method (33). Karel’s objective was to develop a method to continuously and noninvasively measure cardiac output from finger pressure. The first step was derivation of proximal aortic pressure wave shape and magnitude from finger pressure (23). The second step was the calculation of cardiac output from pressure, using the windkessel parameters. Under his supervision, an extensive study was carried out in our laboratory for physiology to obtain data on aortic stiffness in aging (22). These data on human post-mortem aortas gave quantitative information of two important windkessel parameters, namely characteristic impedance and aortic stiffness. Knowing these parameters as a function of age allows estimation of aortic flow wave shape and cardiac output from the calculated proximal aortic pressure (27, 36). Additionally, methods were developed to calculate the sensitivity of the baroreflex acting on heart rate and on vascular resistance (3). All taken together, this resulted in practical methods, from the Finapres to the present-day Nexfin and ClearSight monitors. Karel has shown that the use of basic information on arterial function (transfer of pressure waves and arterial stiffness) can lead to the practical use of noninvasive pressure and flow monitoring. I have lost a very intelligent and wonderful personal friend. (N.W.)

Cardiovascular Variability

Blood pressure has long been known to rise because of emotions or physical exercise and to drop during rest. With the advent of a method to measure blood pressure noninvasively on a beat-to-beat basis during daily life, this variability itself has become the subject of much research.

Earlier analysis of cardiovascular variability was restricted to that of heart rate (HRV) (16). It was demonstrated (1) that HRV virtually disappears after vagal blockade not only at the respiratory but also at the lower frequencies, thus proving that even these are not due to oscillations in sympathetic outflow. Computer modeling demonstrated that the 0.1-Hz rhythm most probably originates from blood pressure oscillations due to delays in the baroreflex-systemic resistance feedback loop (6), HRV at the same frequency being due to heart rate reflexly “riding” on blood pressure changes. The combination of such data led Malliani et al. (24) to promote the use of the LF-to-HF ratio in heart rate (LF: variance in the LF = 0.1 Hz, and HF variance at the respiratory rate) as a measure of sympathovagal balance in autonomic nervous outflow.
How can blood pressure be regulated and still exhibit the extent of variability that is observed during a normal day? Wesseling proposed the “baromodulation” hypothesis (20, 37) to explain this phenomenon. This assumes the transfer of baroreceptor input information to autonomic output itself being modulated by events outside the baroreflex. Measurement of baroreflex sensitivity on a continuous basis, a technique he developed to be used in conjunction with Finapres recordings (40), supports this hypothesis.

It was a pleasure and a privilege to have known Karel for some 35 years, in particular sharing his years at the Academic Medical Center. When he showed his experimental finger-pressure set-up with loudspeaker magnet, I never dreamed it would ever fly as high as it did, eventually. (J.M.K.)

Autonomic Function Testing

Knowledge of the physiological mechanisms underlying disturbances in cardiovascular control mechanisms is of direct relevance for clinicians: it is the key to taking an intelligent history and understanding the appropriate emphasis for the physical examination. Only then is the doctor able to diagnose the condition and reassure a worried patient by explaining it in lay terminology. In addition, mechanistic insight is a crucial factor for the design and the evaluation of therapeutic measures.

In this context, the Finapres or volume clamp method developed by Peñáz and Wesseling (33, 35) with its ability to measure the arterial pressure in the finger noninvasively and continuously has been an enormous step forward in the evaluation of autonomic cardiovascular control (43). Monitoring of finger arterial pressure enables a clinician to study the dynamics of circulatory responses in detail. A further refinement was the calculation of beat-to-beat changes in stroke volume from the pulse wave with Modelflow (36). This allows the clinician to evaluate the hemodynamics underlying observed changes in blood pressure in terms of cardiac output and total peripheral resistance (43). This has opened new avenues of investigation in the laboratory, like the evaluation of the hemodynamic mechanisms underlying tilt table-induced syncope (32) and the effects of physical counterpressure maneuvers on a low standing blood pressure, such as leg crossing and squatting (21).

I had the good fortune to cooperate with Karel Wesseling in the Finapres evaluation studies since the early 1980s (17), the close interactions between Karel as a biomedical engineer and me as a clinician studying initial orthostatic hypotension (26), fainting in young healthy subjects (7, 8), and unusual circulatory responses in patients have been fruitful (28, 30, 31). In the process we became good friends. (W.W.)

The Volume Clamp Method in the Epidemiologist’s Tool Kit

Karel Wesseling’s contributions to cardiovascular physiology are immensely important and wide ranging. He will be remembered by innumerable physiologists, anesthesiologists, autonomic nervous function specialists, and most recently, a growing number of cardiovascular epidemiologists. Karel’s development of the volume clamp method for noninvasive finger arterial blood pressure measurement into a true cardiovascular “leatherman” tool has opened the field of population studies for serial hemodynamic observations. Given the gap in cardiovascular health between the wealthy and the poor, and more intriguingly between various ethnicities in the world, there is a genuine need to study the origins, for example, of the impressive differences in stroke prevalence between white and black people, or the devastating coronary atherosclerosis in people of Asian descent. Understandably, conventional risk factor analysis has been monopolizing field studies for decades. Karel has now enriched our tool kit with reproducible arterial blood pressure curves that closely follow changes in blood pressure during simple circulatory challenges, and pulse contour-derived stroke volume and vascular resistance. Systemic hemodynamics can now easily be estimated outside the laboratory and related to rates of conventional risk factors to better detect and follow these inequalities from their early start. For instance, preliminary findings in our ongoing population survey in Dutch Suriname comparing healthy Creole and Hindustani subjects show interesting differences in blood pressure regulation during changing posture: in the face of similar rises in blood pressure, in Creole subjects, resistance increases more than in Hindustani subjects, while left ventricular contractility does not change, whereas contractility drops in Hindustani subjects (F.S. Diemer, G. P. Oehlers, J. Q. Aartman, S. M. Baldew, F. A. Karamat, A. V. Jarbandhan, G. van Monfrans, L. M. Brewster, unpublished observations).

More accurate cardiovascular risk profiling, made possible by Karel’s gentle, probing, independent mind, should ultimately broaden the evidence we need to obtain better-focused guidelines for those who suffer disproportionally. (G.A.v.M.)

Noninvasive Hemodynamics in Clinical Practice

Interpretation of the heart rate and arterial pressure response to a reduced central blood volume is complex, and properly diagnosing hypovolemic shock continues to challenge the clinician since the Second World War (12, 25). Loss of 1 liter of blood or fluid does not affect arterial pressure, making it an imprecise parameter to recognize central hypovolemia (14). The blood volume is characterized not only by its size but also by its function as preload to the heart. From that perspective, a functional definition of “normovolemia” as a reference for volume treatment is by its ability to provide the heart with an appropriate central blood volume (i.e., the cardiac preload that maintains cardiac output) (13). The measurement of blood flow is so complicated that arterial pressure remains to be the monitored variable although according to Jarisch (18) more than 80 years ago “die meisten Organe gar nicht Druck, sondern Stromvolumen brauchen [most organs don’t need pressure but flow]." By modeling aortic flow from pressure, Wesseling and coworkers (19, 36) provided clinicians with continuous information on cardiac output extracted from noninvasive arterial pressure (29). This major contribution to cardiovascular monitoring makes it possible to introduce titration of fluid administration as the cornerstone of goal-directed fluid treatment into clinical practice.

Karel was my inspiring teacher in biomedical signal analysis and my older, wise friend and companion in research in Oslo, Copenhagen, Amsterdam, and at home in The Hague with his beloved Hanny. (J.J.v.L.)

Conclusion. Professor Wesseling passed away on September 4, 2014, in The Hague, The Netherlands. He leaves behind his wife Hanny, their three children, and a grandson whom he unfortunately did not live to see. While we are thankful to have had the opportunity to work with Karel for so many years, we are saddened by the loss.
We will miss his original way of thinking, his wit, and his friendship. His intellectual heritage in the field of physiology and noninvasive hemodynamic monitoring will live on. (B.E.W.)

DISCLOSURES

B. E. Westerhof and J. J. Settels are employed by Edwards Lifesciences BMEYE.

AUTHOR CONTRIBUTIONS


REFERENCES