Blood pressure analysis on time scales from seconds to days
Westerhof, B.E.

Citation for published version (APA):
Westerhof, B. E. (2005). Blood pressure analysis on time scales from seconds to days
Chapter 9

Non-invasive blood pressure measurement in relation to a variety of basic and clinical applications

In the past years while the studies described in this Dissertation were in progress, I contributed to a series of other investigations in which my role was to develop methods or apply techniques for a variety of research projects. These were mostly based on clinical questions, a few of which could be answered by application of the theories and techniques developed in this thesis, others by different methods not mentioned in the preceding Chapters. The present Chapter gives an overview of these studies, providing additional demonstrations of usefulness of non-invasive blood pressure measurements.

Pressure transfer analyses

*Physical basis of pressure transfer from periphery to aorta (1)*

We proposed a new method to derive aortic pressure from peripheral pressure and velocity by using a time domain approach. Peripheral pressure was separated into its forward and backward components by waveform analysis, and these components were then shifted with a delay time, which was the ratio of distance and wave speed, and added again to reconstruct aortic pressure. We tested the method on a distributed model of the human systemic arterial tree. From carotid and brachial artery pressure and velocity, aortic systolic and diastolic pressure could be predicted within 0.3 and 0.1 mmHg and 0.4 and 1.0 mmHg, respectively. The central aortic pressure wave shape was also predicted accurately from carotid and brachial pressure and velocity (root mean
square error: 1.07 and 1.56 mmHg, respectively). The pressure transfer function depends on the reflection coefficient at the site of peripheral measurement and the delay time. A 50% decrease in arterial compliance had a considerable effect on reconstructed pressure when the control transfer function was used. A 70% decrease in arm resistance did not affect the reconstructed pressure. The transfer function thus depends on wave speed but has little dependence on vasoactive state. We conclude that central aortic pressure and the transfer function can be derived from peripheral pressure and velocity. The findings of this study gave the impetus for the research described in Chapters 2 & 3.

**Finger pressure measurements with the possibility to reconstruct brachial pressure (2)**

In this study, the objective was to evaluate three methods developed for the reconstruction of brachial pressure from non-invasive finger arterial. Finger arterial pressure (FinAP) may differ from intra-brachial pressure (BAP). First, pulse shape differences can be removed by applying a generalized waveform filter. Next, pressure level differences can be corrected by a generalized level correction equation using filtered systolic and diastolic levels. Finally, a level calibration, which uses an additional return-to-flow (RTF) systolic pressure measurement on the ipsilateral upper arm, can be used for an individual calibration of the reconstructed brachial pressure. These methods were validated in 37 subjects, aged 41 to 83 years after a cardiac catheterization procedure. Intra-brachial and FinAP pressures were recorded simultaneously. FinAP pressures were compared after application of waveform filtering and level correction (flcAP), and after an additional RTF calibration (reBAP). FinAP systolic, diastolic and mean pressures for the group differed from BAP by $-9.7 \pm 13.0$, $-11.6 \pm 8.0$ and $-16.3 \pm 7.9$ mmHg (mean ± SD) respectively. After waveform filtering and level correction, flcAP differed by $-1.1 \pm 10.7$, $-0.2 \pm 6.8$ and $-1.5 \pm 6.6$ mmHg. After individual calibration, reBAP differed by $3.1 \pm 7.6$, $4.0 \pm 5.6$ and $2.7 \pm 4.7$ mmHg. We conclude that reconstruction of BAP from FinAP with waveform filtering and level correction reduces the pressure differences, with an individual RTF calibration to well within AAMI requirements.

**Changes in finger-aortic pressure transfer function with incremental bicycle exercise (3)**

Non-invasive finger blood pressure recording has become a surrogate for central blood pressure under widely varying circumstances. We calculated finger-aorta transfer functions using the AutoRegressive-eXogenous (ARX) model method in 7 cardiac patients during rest, incremental bicycle exercise and post-exercise. Finger pressure was
measured non-invasively using Finapres and aortic pressure using a catheter-tip manometer. When using the individual transfer functions, developed during rest, for reconstruction of aortic pressure (rAortic) during all workloads, systolic pressure was increasingly underestimated, with a large variation between subjects: +4.0 to −18.1 mmHg. In most subjects diastolic pressure (DBP) was overestimated: −3.9 to +5.5 mmHg. In all cases wave distortion was present. Post-exercise, the error in systolic rAortic only slowly declined and diastolic pressure was overestimated in all subjects. During rest, the transfer function gain had a minimum between 3.65 and 4.85 Hz (F_{min}). During exercise this minimum shifted to frequencies between 4.95 and 7.15 Hz at the maximum workload, with no change in gain. Post-exercise, gain in most subjects shifted to values closer to unity, while F_{min} did not return to resting values. Within each subject aorta-Finapres delay was linearly related to mean pressure (MAP). During exercise, both delay and heart rate (HR) were linearly related to F_{min}. During rest and exercise, F_{min} could be predicted by the linear model: 
$$F_{min} = 0.07*(MAP-DBP)+0.019*HR-0.013*delay+2.71$$ with $R^2 = 0.89$.

We conclude that during exercise a general transfer function gives an unreliable reconstruction of aortic pressure. Prediction of transfer functions parameters may be possible, which could improve both reconstructed systolic and diastolic pressure as well as wave shape.

**Hemodynamic analyses**

*Total arterial inertance as the fourth element of the Windkessel model (4)*

In earlier studies it was found that the three-element Windkessel, although an almost perfect load for isolated heart studies, does not lead to accurate estimates of total arterial compliance. To overcome this problem, we introduce an inertial term in parallel with the characteristic impedance. In seven dogs we found that ascending aortic pressure could be predicted better from aortic flow by using the four-element Windkessel than by using the three-element Windkessel: the root-mean-square errors and the Akaike information criterion and Schwarz criterion were smaller for the four-element Windkessel. The three-element Windkessel overestimated total arterial compliance compared with the values derived from the area method and the pulse pressure method ($P = 0.0047$, paired t-test), whereas the four-element Windkessel compliance estimates were not different ($P = 0.81$). The characteristic impedance was underestimated using the three-element Windkessel, whereas the four-element Windkessel estimation differed marginally from
the averaged impedance modulus at high frequencies ($P = 0.0017$ and $0.031$, respectively). When applied to the human, the four-element Windkessel also was more accurate in these same aspects. Using a distributed model of the systemic arterial tree, we found that the inertial term results from the proper summation of all local inertial terms, and we call it total arterial inertance. We conclude that the four-element Windkessel, with all its elements having a hemodynamic meaning, is superior to the three-element Windkessel as a lumped-parameter model of the entire systemic tree or as a model for parameter estimation of vascular properties.

Left ventricular wall stress normalization in chronic pressure-overloaded heart (5)
It is generally accepted that the left ventricle (LV) hypertrophies (LVH) to normalize systolic wall stress ($\sigma_s$) in chronic pressure overload. However, LV filling pressure ($P_v$) may be elevated as well, supporting the alternative hypothesis of end-diastolic wall stress ($\sigma_d$) normalization in LVH. We used an LV time-varying elastance model coupled to an arterial four-element lumped-parameter model to study ventricular-arterial interaction in hypertension-induced LVH. We assessed model parameters for normotensive controls and applied arterial changes as observed in hypertensive patients with LVH (resistance +40%, compliance –25%) and assumed 1) no cardiac adaptation, 2) normalization of $\sigma_s$ by LVH, and 3) normalization of $\sigma_d$ by LVH and increase in $P_v$, such that $\sigma_d$ is normalized as well. In patients, systolic and diastolic blood pressures increase by ~40%, cardiac output (CO) is constant, and wall thickness increases by 30–55%. In scenarios 1 and 2, blood pressure increased by only 10% while CO dropped by 20%. In scenario 2, LV wall thickness increased by only 10%. The predictions of scenario 3 were in qualitative and quantitative agreement with in vivo human data. LVH thus contributes to the elevated blood pressure in hypertension, and cardiac adaptations include an increase in $P_v$, normalization of $\sigma_s$, and preservation of CO in the presence of an impaired diastolic function.
Pulse wave analyses

Beta-blocking therapy in patients with the Marfan syndrome and entire aortic replacement (6)
In non-operated patients with Marfan’s syndrome, use of β-adrenergic blocking therapy has been shown to reduce the rate of aortic dilation and the development of aortic dissection. However, its efficacy after entire aortic replacement is unknown. The aim of this study was to describe the influence of (nearly) entire aortic replacement and β-blocking therapy on blood pressure and wave reflections in Marfan patients.

Four Marfan patients (mean age 316 ± 3 years) and 8 age matched control subjects were studied. Blood pressure and wave reflections (reflection coefficient and augmentation index) were studied by means of magnetic resonance imaging, continuous non-invasive blood pressure measurements and applanation tonometry. Patients were studied with atenolol, labetalol and without β-blocking therapy.

In Marfan patients, aortic systolic pressure (129 ± 13 vs. 114 ± 10 mmHg), pulse pressure (58 ± 13 vs. 40 ± 5 mmHg), wave speed (11 ± 3 vs. 4 ± 0.4 m s⁻¹) and reflection coefficient (65 ± 22 vs. 41 ± 5%) were significantly increased compared to controls. There was no difference in aortic pressure between various medications in Marfan patients (atenolol 129/76 mmHg, labetalol 121/75 mmHg and without β-blocking therapy 129/71 mmHg). Higher reflection coefficients were seen in patients with atenolol compared to discontinued medication (73 ± 18 vs. 65 ± 22%), and also the augmentation index was higher with atenolol compared to labetalol and discontinued medication (24 ± 22 vs. 17 ± 17 vs. 22 ± 22%, respectively).

Our results describe increased pulse pressure, systolic pressure, wave speed and wave reflections in four Marfan patients after entire aortic replacement. The use of atenolol or labetalol did not decrease aortic pressure and with atenolol increased wave reflections were observed. Therefore, the beneficial effect of atenolol in these patients is doubtful.

Aortic pressure-area relation in Marfan patients with and without β blocking agents (7)
Our objective was to investigate the heterogeneous response to β blockade in patients with Marfan syndrome by non-invasive assessment of the aortic pressure–area curve. Twenty-five patients with the Marfan syndrome who used β-blocking agents (aged 29 ± 10 years; 20 men, five women), seven without β blockade (34 ± 14 years; five men, two women), and 10 controls (29 ± 5 years; seven men, three women) underwent magnetic
resonance imaging and non-invasive continuous blood pressure measurement. Pressure–area curves were constructed at the level of the descending thoracic aorta. A transition point was defined as the pressure at which the pressure–area relation deviated from its elastic (linear) to the collagen (exponential) course.

In six patients (five with and one without β blockade), a transition point in the pressure–area curve was observed, indicating that the load bearing component was not only elastin but also collagen. In the remaining 26 Marfan patients and in the control subjects a linear pressure–area relation was observed.

This new non-invasive method to derive aortic pressure–area curves showed that most patients with Marfan syndrome have a similar pressure–area curve to controls with similar blood pressures. Five patients on β blockade showed a transition point in the pressure–area curve which could play a crucial role in the heterogeneous response to β blocker treatment in Marfan patients. Patients with a transition point at low blood pressures may not benefit from β blocking agents.

*The mean pressure is not calculated adequately by adding 1/3 of the pulse pressure to the diastolic pressure (8)*

The mean arterial pressure at the upper arm is traditionally calculated by adding 1/3 of the pulse pressure to the diastolic pressure. We tested the validity of this formula in previously recorded intra-brachial pressure and Riva-Rocci / Korotkoff blood pressure measurements in 57 subjects (study A) and 24-hour intra-arterial recordings in 22 subjects (study B). In study A the intra-arterially measured mean pressure was found at 39.5 ± 2.5 % of the pulse-pressure above the diastolic pressure. Mean pressure was higher than at the expected 33.3 % of the pulse-pressure in all individuals. Mean pressure calculated with the traditional 1/3 rule underestimated the actual mean pressure by 4.9 ± 5.3 mmHg (P < 0.01). The error was similar for calculations based on Riva-Rocci-Korotkoff-measurements. In study B we showed activity related variations in the relative level of the mean pressure; this level increased by 1.8 ± 1.4 % (P < 0.01) during sleep, and decreased by 0.5 ± 0.9 % during walking (P < 0.05) and by 0.8 ± 1.3 % during cycling (P < 0.01). Results were not related to age, blood pressure, pulse-pressure or heart rate. We propose an improved formula to calculate the mean pressure at the upper arm. Adding 0.4 times the pulse-pressure to the diastolic pressure reduces the error in calculating the mean pressure from −4.9 ± 5.3 mmHg (P < 0.01) to 0.4 ± 5.1 mmHg (n.s.).
In conclusion, the mean pressure at the upper arm is underestimated when calculated with the traditional formula of adding \( \frac{1}{3} \) of the pulse pressure to the diastolic pressure. This underestimation can be overcome by adding 0.4 times the pulse pressure to the diastolic pressure.

**Baroreflex sensitivity analysis**

Sublingual nitroglycerin used in routine tilt testing provokes a cardiac output-mediated vasovagal response (9)

We set out to determine the effect of sublingual nitroglycerin (NTG), as used during routine tilt testing in patients with unexplained syncope, on hemodynamic characteristics and baroreflex control of heart rate (HR) and systemic vascular resistance (SVR). Nitroglycerin is used in tilt testing to elicit a vasovagal response. It is known to induce venous dilation and enhance pooling. Also, NTG is lipophilic and readily passes cell membranes, and animal studies suggest a sympatho-inhibitory effect of NTG on circulatory control.

Routine tilt testing was conducted in 39 patients with suspected vasovagal syncope (age 36 ± 16 years, 18 females). Patients were otherwise healthy and free of medication. Before a loss of consciousness set in, oncoming syncope was cut short by tilt-back or counter-maneuvers. Finger arterial pressure was monitored continuously (Finapres). Left ventricular stroke volume (SV) was computed from the pressure pulsations using a model. Spontaneous baroreflex control of HR was estimated in the time and frequency domains.

During tilt testing, 22 patients developed presyncope. After NTG administration but before presyncope, SV and cardiac output (CO) decreased \( (P < 0.001) \), whereas SVR and HR increased \( (P < 0.001) \) in all patients. Arterial pressure was initially maintained. Baroreflex sensitivity decreased after NTG. On Cox regression analysis, the occurrence of a vasovagal response was related to a drop in SV after NTG (hazard ratio 0.86, \( P = 0.005 \)).

The cardiovascular response to NTG is similar in vasovagal and non-vasovagal patients, but more pronounced in those with tilt-positive results. The NTG-facilitated presyncope appears to be CO-mediated, and there is no evidence of NTG-induced sympathetic inhibition.


8. Bos WJW, Vincent HH, Westerhof BE, van Montfrans GA. The mean pressure is not calculated adequately by adding 1/3 of the pulse pressure to the diastolic pressure. *Submitted*.