Blood pressure analysis on time scales from seconds to days
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“primum non nocere”

Chapter 1

Introduction

The maxim “First, do no harm” \(^1\) is chosen as a motto for this thesis, as all exploration in this work is directed towards methods that allow diagnosis based on non-invasive measurements of blood pressure.

Blood pressure

Blood pressure is the result of the heart pumping against the arterial load. Pressure should be maintained while different tissues tap flow according to their needs for oxygen and nutrients. Particularly the brain and the heart muscle itself are very dependent on a sufficient supply of oxygen at all time. Several activities influence blood pressure, for instance tensing of the leg muscles returns venous blood to the heart which then will be pumped out and increase pressure. Other processes may tend to decrease pressure by requiring more flow, or in other words, by lowering the resistance. The autonomic nervous system has several options to stabilize blood pressure. Changing venous compliance greatly enhances filling of the heart; modulating the vascular resistance is also very effective. Varying heart rate is less effective, but more noticeable. With fever, the higher body temperature and thus metabolic rate requires more oxygen to be delivered, often resulting in high heart rates and palpitations.

\(^1\) “First, do no harm” is widely believed to be part of the Hippocratic oath, which, however, it is not. Hippocrates did articulate a similar conviction in his *Epidemics, Book I, Section XI*: “(...) to help, or at least to do no harm”. The Greek physician Galen may have first used the phrase in Latin as cited above while working in Rome.
Continually interacting processes result in continually varying blood pressure and heart rate. Simple daily activities such as talking or even breathing have an effect on blood pressure. Blood pressure can double with anxiety, heart rate can triple with physical activity, while cardiac output, the product of the volume pumped out by the heart per beat (stroke volume) times heart rate can increase four- to perhaps six-fold in well-trained athletes.

**Clinical importance**

When blood pressure is out of its normal range for longer periods, one speaks of high blood pressure, hypertension, or low blood pressure, hypotension. Hypotension is usually no threat to health in daily life as long as no light-headedness or fainting occurs. It can pose an acute threat due to underperfusion in for instance sepsis patients. Hypertension is an acute risk when extremely high, but even moderate hypertension is considered to be very dangerous on the long run. Hypertension is defined when the highest value of the pressure curve, the systolic blood pressure, exceeds 140 mmHg (systolic hypertension) or when the lowest value, diastolic blood pressure, exceeds 90 mmHg (diastolic hypertension). Up to 30% of the adult population in most countries suffers from hypertension and it is one of the most important preventable causes of death worldwide. Together with other modifiable risk factors including high cholesterol, diet, inactive lifestyle and smoking, hypertension accounts for about 75% of cardiovascular diseases (WHO, Cardiovascular Disease: Prevention and Control. 2003).

**Methods of measurements**

Early and accurate diagnosis may be a key factor in prevention of or therapy for hypertension. The feeling of the pulse is one of the oldest manners of diagnosis, believed to be the invention of Herophilus (335 – 280 B.C.). It was centuries later before Hales performed quantitative measurements in 1733 (1). The level to which the blood of a horse rose in the glass tubing connected to the ‘crural’ artery gave the level of blood pressure in cmH₂O (or cm blood, to be precise). Obviously this method was unfit for use in humans. A breakthrough was made by Riva-Rocci in 1896 (2), the year when he presented an air-inflatable arm cuff connected to a manometer; by deflating the cuff and feeling for the pulse distal of the cuff systolic blood pressure could be determined. In

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2 Often the reference to Hales’ measurement is accompanied by a well-known engraving by Cuzzo. This artist reconstruction was made in 1944 and shows the tube connected to the carotid artery in stead of to a crural artery as described by Hales.
1905 Korotkoff (3) refined the technique further with the auscultatory method. With the introduction of the use of a stethoscope diastolic pressure could be determined as well.

The Riva-Rocci / Korotkoff method remains the standard for blood pressure measurement until today. Nowadays, automated measurements, mostly with oscillometric devices, are becoming more and more accepted. These devices measure the pressure in a cuff, which is first inflated above systolic pressure and then deflated to below diastolic pressure. Oscillation in the cuff pressure is maximal at mean arterial pressure; mathematical algorithms determine systolic and diastolic values from the oscillations. What was lost however, with these cuff methods, was the possibility to observe the shape of the pulse wave.

**Figure 1**

Hales had noted the oscillation of the blood in his glass tube and later (1838) Poiseuille designed an instrument specifically for the quantifying these variations, basically a
mercury filled u-shaped tube with a scale. Ludwig (4) described the kymograph (Figure 1) in 1847 with which blood pressure oscillation could be recorded on a drum. These instruments measured invasively, thus restricting their use. One of the most accurate apparatuses designed for non-invasive wave shape analysis was Marey’s (5) sphygmograph (1860). A lever system amplified the radial pulse (Figure 2), which then was graphed on a smoke-blackened moving strip (Figure 3).

Figure 2

Marey’s Sphygmograph

A technique that combines accuracy with maximal information is the continuous pressure recording with the direct intra-arterial method. First mentions date back to 1914, when Bleichroeder (6) performed a catheterization of his own radial artery. Whether he recorded his blood pressure is not clear, however, it would have been possible at that time. Frank developed a manometer that could accurately measure pulsatile pressure in 1903 (7). High fidelity catheter-tip manometers were introduced by Millar in 1972 (8). Intra-arterial measurements are routinely performed in operation theaters and intensive care settings, in other words, those circumstances in which it is vital to continuously monitor blood pressure, mostly to prevent pressures to become too low. When no such imperative reasons are present it may not be ethical to measure intra-arterial pressure. If nonetheless the pressure wave shape is required, applanation tonometry is a non-invasive alternative. Measurements are performed by placing a

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3 Hoff and Geddes argue (4) that Ludwig may not have been the first to use graphic registration in physiology.
pressure sensor externally on a superficial artery. Usually, the radial or the carotid artery is assessed. However, measurement over a longer period of time or during maneuvers is difficult, and pressure values are relative, not absolute.

**Figure 3**

Blood pressure tracings from Marey’s Sphygmograph

A very important development is the non-invasive measurement of finger arterial pressure (10,11). With this method blood pressure can be continuously measured, even during exercise, and values are calibrated. The method is well validated for various circumstances and is in use in research and clinical investigations (12-42). A great part of the work in this thesis is related to this method.

**Blood pressure measurements in hypertension**

In hypertension, the brachial systolic and diastolic pressures are the pressures on which epidemiological studies are based and on which clinical decisions are made. Although finger arterial pressure is well accepted now and used in studies of blood pressure regulation, for diagnosis in hypertension, brachial pressures are the standard.
Twenty-four hour recordings of blood pressure, or even 48 hours, are becoming more frequent in studies on hypertension and for diagnosis (43). It is generally accepted nowadays that 24-hour recordings of blood pressure are better predictors of cardiovascular morbidity and mortality and to correlate closer to organ damage than “office blood pressure”: the blood pressure determined by the doctor when examining the patient. Here one enters the discussions of the “white coat effect” (44); the finding that blood pressure can be elevated by the stress of the environment. Thus it plays a role by whom and where the measurements are taken: measurement by nurse, doctor, or self, measurement by machine at home or in the office, and combinations of all the above. A special class is defined recently as the masked hypertensives (45): hypertensives who remain undetected because they, for unknown reasons, have pressures below the limits of hypertension when measured in the office, but have elevated blood pressures in daily life. In other words, the time of measurement also plays an important role and this is why an ambulatory method gives superior insight in the blood pressure of a person.

In the field of 24-hour recordings, patients can be classified as dippers, non-dippers, and reverse dippers (46,47,48). Dippers lower their blood pressure by more than 10 mmHg or by more than 10 % during the nighttime hours. Non-dippers decrease less in pressure and reverse dippers increase their blood pressure during the night. All classes have been associated with different levels of risk for cardiac and cerebrovascular incidents.

Ambulatory 24-hour measurements are generally carried out with oscillometric devices on the upper arm, and usually these measurements give sufficient information for diagnostic purposes. However, in research, continuous measurements are obviously much more valuable. For instance, in the investigation of silent ischemia (49), i.e. ischemia not noted by the patient but detectable from the ECG, oscillometric devices do not have the required time-resolution. Another field in which interest is growing is sleep apnea, known to be a risk factor for hypertension (50). The combination of continuous blood pressure with ECG, ventilation and perhaps blood oxygenation gives much more information needed for thorough research.

**Limitations of the methods**

Non-invasive pressure is, necessarily, measured in peripheral vessels, usually the brachial, radial or finger arteries as mentioned. The amplitudes and the wave shapes of these pressures differ from ascending aortic pressure and these differences are not constant but variable, for instance during medication (51). It is central pressure that forms the load on the heart during systole and that determines the perfusion pressure for coronary circulation during diastole, the period in which most of the myocardial
perfusion takes place (52). Wave shape analysis, for instance to obtain a measure of arterial stiffness, should preferably be performed on central pressure as well. Information contained in the wave shape made available by continuous non-invasive methods from peripheral vessels can nevertheless help to reconstruct central pressure. When only systolic and diastolic pressures are available possibilities to reconstruct central pressure are very limited.

Blood pressure not only varies with time within a heartbeat but also from one beat to another and a single measurement is only of limited value. As pointed out, there is a tendency to follow blood pressure over 24 hours or even two days, since not only the absolute values are important, blood pressure variability is an important parameter as well. With automated devices measurements can be taken at most every few minutes; however, even more insight into the processes determining systemic pressure can be obtained when beat-to-beat blood pressure values are available. In this case, heart rate and pressure variability can be analyzed in great detail and baroreflex sensitivity can be calculated from the relation between heart rate and blood pressure. The baroreflex is important to stabilize blood pressure by increasing or decreasing heart rate in reaction to pressure changes. Baroreflex sensitivity is a prognostic factor in cardiology (53,54,55).
This thesis

Overview
This thesis aims to improve the possibilities of retrieving information from blood pressure measurements especially when this pressure is obtained non-invasively from the finger.

First, an effort is made to develop and test transfer functions between central and peripheral blood pressure. For this, continuous information on these pressures is required and the systolic and diastolic pressure values are not sufficient. Transfer function analysis is on a time scale of milliseconds. The main conclusion is that a single generalized transfer function is usually sufficient to reconstruct central pressure from peripheral pressure.

We also developed a new method to determine wave reflection in the aorta, which is a measure of arterial stiffness, also on a time scale of milliseconds. Although this study was performed using high fidelity central measurements of pressure and flow we expect that the method is applicable without flow measurements with uncalibrated pressure recording.

Having established that central pressure can be reconstructed from peripheral pressure (15,20), this pressure signal can then be used to make a reasonable assumption about the cardiac oxygen demand as measure of cardiac work and cardiac oxygen supply. Cardiac oxygen supply and demand should be in balance, or else cardiac ischemia will develop.

A new method for the determination of baroreflex sensitivity is described next. The new method is then used to investigate the dynamics of the baroreflex during orthostatic stress. The processes related to oxygen supply/demand ratio and baroreceptor reflex take place on the time scale of seconds.

A method to correct the pressure drop that may occur between brachial and finger arterial pressure was examined (20,42). We showed that this method can correct the differences between brachial and finger arterial pressure over 24 hours and it facilitates the blood pressure measurement over days.
Below we will discuss the relevance of these studies in some detail.

**Transfer functions**

Non-invasive pressure measurements are typically obtained from peripheral sites as the radial artery by applanation tonometry (56,57) or from the finger with the so-called “volume-clamp”/“physiocal” method (10,11). Applanation of the carotid artery gives an accepted “surrogate” of central arterial pressure. Pressure measurement by applanation tonometry cannot give absolute values, since no objective criteria exist for the operator to know if the pressure is indeed representing the intra-arterial values. Simply fitting the measured curves to brachial diastolic and mean pressure (60) can give a reasonable approximation. However, one can do much better using the concepts from signal analysis directed to describing relationships between causally related signals. So-called transfer functions form a powerful method to do so. Hence, the application of transfer functions allows the calculation of central pressure from peripheral pressure and thereby estimation of the inherent consequences of generated pressure for the heart. Transfer functions are widely used in the literature nowadays and are advocated by many (12,15,19-21,30,31,42,57-64). In contrast, some groups have proposed to distil important parameters pertaining to cardiovascular condition directly form peripheral pressures (65,66), thus circumventing the use of transfer functions.

In a physiological model we set out to investigate which vessel wall- and blood properties have the largest influence on the pressure transfer. The results of this sensitivity analysis are summarized in Chapter 2. The central to peripheral time delay of the upstroke in pressure can be measured and we investigated the potential of this parameter in adjusting the transfer function to improve reconstructed central pressures. The findings of this research are presented in Chapter 3.

**Reflection indices**

The augmentation index (secondary rise in systolic pressure divided by pulse pressure) is a popular construct used in trials and associated with virtually any other index in the field of hemodynamics and hypertension. Originally, the index was devised to get an indication of wave reflection, which in turn should give an indication of arterial stiffness. A fundamentally better estimate of arterial stiffness is obtained by pulse wave velocity measurement. Indeed these measurements are also performed frequently (67). The great advantage of augmentation index measurement is that only one arterial site has to be assessed, usually the carotid artery, whereas for pulse wave velocity measurements two
sites are required. Most customary sites are carotid and femoral artery, to have a relatively large part of the aorta included in the measurement.

As will be discussed in Chapter 4 the calculation of the reflection index requires the pressure wave as well as the flow wave. It has been suggested that the description of the aortic valve flow wave by a triangular shape in systole would be a useful approximation (68). This method simplifies the determination of the reflection index considerably. Moreover, it circumvents a weakness of the augmentation index since this conventional signal analysis cannot detect reflection when the summation of the reflected wave and forward wave result in a waveform without discontinuity in the rising pressure waveform. This new method opens the way to non-invasive measurements allowing large-scale population research.

Cardiac oxygen supply and demand

Morning excess in cardiovascular incidents has always been attributed to an increase in cardiac oxygen demand (69,70), caused by increasing blood pressure and heart rate. In the literature, decreased oxygen supply has always been associated with increased coronary tone, coronary vasospasm, stenosis or atherosclerosis, or heightened platelet aggregability, but never with decreased cardiac oxygen supply potential (71). However, we show that not only cardiac oxygen demand increases in the morning but that cardiac oxygen supply-potential decreases as well. To estimate cardiac oxygen demand we used the Rate-Pressure Product (52,72), an index that is well accepted; to estimate cardiac supply potential we used the Diastolic Time Fraction, which is recently emerging as a good indicator of subendocardial perfusion (73,74). Both indices show a strong correlation with heart rate, oxygen demand increasing with increasing heart rate and oxygen supply potential decreasing. In relation to the heart rate increase after rising it is heartening to note that the hypertensive population in our study has a smaller increase than the normotensives controls: this limits the morning imbalance between supply and demand (Chapter 5).

Baroreflex sensitivity

Baroreflex can be calculated from changes in interbeat-interval following changes in blood pressure. Blood pressure changes can be spontaneous or provoked. The provocation of blood pressure changes can be accomplished by infusion of vasoactive drugs. First, angiotensin was used (75), but this substance was shown to have a central effect on the baroreflex. Later, phenylephrine and nitroprusside were used to increase and decrease blood pressure, respectively (76). Both substances affect the baroreflex as well (77,78) by changing the properties of the vascular wall where the receptors are
located. Another accepted method is neck suction or pressure (79). With a neck-cuff pressure changes can be transferred to the carotid sinus, thus deceiving the system that arterial pressure is too high or too low.

Using the spontaneous variations in interbeat interval and blood pressure allows much more agreeable determination of baroreflex sensitivity. The so-called sequential method (80) searches for sequences in which interbeat interval and blood pressure jointly increase or decrease. When a sequence of three or more normal beats is recognized, the linear regression through interbeat interval values as a function of blood pressure values is calculated and the angle of the regression line is taken as baroreflex sensitivity. Usually the delay between blood pressure and interbeat interval changes is prescribed at zero or one beat.

In a recently proposed method, cross-correlations between pressure and interbeat interval are calculated for time delays from 0 to 5 seconds of interbeat interval (41). The linear regression with the highest coefficient of correlation renders the slope, quantifying the baroreflex sensitivity. The time delay is not prescribed but retrieved from the measurements, giving extra information. We call this the xBRS method for cross-correlation baroreflex sensitivity.

This method was evaluated (Chapter 6) on a set of data of the EUROBAVAR working group, available through the Internet for this purpose. We found that the method gives results comparable to other methods using these data, but with a larger number of estimations per unit of time and with less scatter. The publication was accompanied by an editorial comment, which is included in an Appendix to this thesis.

The tilt table is an excellent method to challenge the baroreflex and we investigated whether we could document that with our new method (Chapter 7). The baroreflex sensitivity changed with the tilt angle, and the rate of change appears to be related to the magnitude of change of the tilt angle. The BRS shows a linear relation to the sine of the tilt angle as well: as vagal activity withdrew, the BRS decreased. This is associated by a shift towards longer delays between blood pressure and interbeat interval changes.

**Level correction**

A transfer function is very useful in relating the waveforms measured at the periphery and central. However, it does not entirely account for the differences in the measurement of mean blood pressure. In Chapter 8 it is shown that finger blood pressure can be reconstructed, with a transfer function and a level correction, to brachial blood pressure, with acceptable errors, thus allowing the comparison to standard brachial values. The level correction method (20) was originally developed for transversal use, i.e. for groups
of patients; we now show its usefulness longitudinally, i.e. over 24 hours (42). Tracking is improved and the nocturnal dip is better described. Probably one calibration of reconstructed pressure per day will suffice (21).

**Conclusion**

In this dissertation several methods are explored to advance the use of non-invasive recording of arterial blood pressure for studies in physiology and diagnostics in cardiovascular disease and hypertension. Ordered by increasing time scale, we will describe a physiological model of pressure transfer, and consecutively propose a method for individualization of a pressure transfer function.

Next a method is proposed to calculate the reflection index using pressure wave features. Wave reflections are of interest since they are a measure of arterial stiffness and used as a marker for cardiovascular morbidity and mortality. Usually the augmentation index is calculated as an approximation of the reflection index. It will be show that the suggested method gives results closer to measured reflection index than the established method of augmentation index calculation.

Further, parameters for cardiac oxygen supply potential and cardiac oxygen demand are studied. An accepted concept relates the elevated numbers of cardiovascular incidents in the morning hours to increased cardiac oxygen demand after rising. However, we will demonstrate that cardiac oxygen supply potential decreases as well.

An prognostic factor in cardiology is baroreflex sensitivity, a measure of autonomic blood pressure control. We put forward a new method to determine baroreflex sensitivity, giving more results per unit of time and additionally a time delay in autonomic reaction. This delay may allow us to discriminate between the fast parasympathetic and the slower sympathetic branch of the autonomic system. This assumption will be considered in a study of the influence of orthostatic stress on baroreflex sensitivity.

Finally, on a time scale of 24 hours, a method to improve the reconstruction of brachial artery pressure from finger arterial pressure measurements is tested. We anticipate showing that the diurnal blood pressure pattern can be more accurately described. Dipping or non-dipping of nocturnal pressure is an issue in the classification of the severity of hypertension and reliably discriminating dippers and non-dippers from non-invasive pressures is a useful asset.
In conclusion, several new methods were investigated to advance diagnostics in cardiovascular disease and hypertension, based on non-invasive blood pressure.
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