Blood pressure analysis on time scales from seconds to days
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Chapter 10

Summary and Conclusions

The binding theme of the preceding chapters can be summarized as a pursuit of better diagnostics and earlier recognition of warning signs in cardiovascular disease. Early recognition demands accurate non-invasive measurements and reliable methods of analysis. As shown in this Dissertation, continuous recording of the full pressure wave shape is indispensable for any detailed analysis going beyond determination of systolic and diastolic pressure. Non-invasive finger arterial pressure has all the required features. Some small steps have been taken, testing techniques and proposing approaches, but still there is a long way to go. Studies in large populations of patients are to prove the clinical value of these models and methods.

The purpose of this summary chapter is to give an overview of studies that contributed to obtaining information from the non-invasive measurement of finger arterial pressure, and emphasize the understanding derived from them.

Pressure transfer analyses
Transfer functions, allowing the derivation of aortic pressures from peripheral pressures, are frequently used to obtain better insight into processes involving the interaction between arterial load and the heart. Generalized transfer functions give useful results, especially in larger study populations. However, more detailed information might be obtained by individualization of the transfer function, i.e. made optimal for an individual.
Sensitivity of pressure transfer to arterial parameters

Applying transfer functions to pressure measurements requires insight into the variability within and between individuals. We therefore investigated the quantitative contribution of all local arterial, blood and distal load properties to the pressure transfer function from aorta to brachial artery (Chapter 2). This theoretical analysis of the pressure transfer started out with anatomical data on vessel dimensions, including relative geometric taper, Young’s modulus, wall viscosity, blood viscosity and blood density. A three-element Windkessel represented the load to the model of the vessel. The sensitivity analysis was performed in terms of frequency and magnitude of the peak in the transfer function and in terms of systolic and diastolic aortic pressure. The percent change of these variables for a 25% alteration of each of the model parameters was calculated. The Root Mean Square Error (RMSE) described the inaccuracy in wave shape. Sensitivity was less than 3% for systolic and diastolic pressure and RMSE less than 1.8mmHg. Vessel length and diameter had the greatest influence. From these data we concluded that the intra-individual variability was small.

To investigate to which extent the tapering of the vessel influences the transfer function, a single uniform tube was modeled. This simplification introduced only small errors in systolic and diastolic pressures (1% and 0%). Wave shape was less well described (RMSE 2.06 mmHg). When the reflection coefficient $\Gamma$ was changed to zero or to unity still reasonable results were obtained, showing that vasodilation and vasoconstriction have little effect on the transfer function.

We conclude that vessel length and diameter are the most important parameters determining pressure transfer. Because of this we may conclude that delay time is the main determinant. Vasodilation and constriction have little effect. Thus, a simple uniform tube with known delay time, possibly measured, and an estimate of the distal reflection coefficient are sufficient to obtain an accurate description of pressure transfer.

Parameter adaptation to individualize pressure reconstruction

Based on the parameter analysis presented above, we hypothesized that the transfer function could be individualized by a representative time delay. Chapter 3 describes a study in a group of 50 patients: measured ascending aortic pressure was 119 ± 20 / 70 ± 9 mmHg, (mean ± SD, systolic / diastolic) and intra-arterially measured brachial pressure was 131 ± 18 / 67 ± 9 mmHg. The Root Mean Square Error, RMSE, as measure of difference in wave shape was 7.5 ± 2.1 mmHg. When individual transfer functions were used with optimized delay, reconstructed pressure was 121 ± 19 / 69 ± 9 mmHg and RMSE reduced to 4.1 ± 2.0 mmHg. Using a generalized transfer function with a
population-averaged delay, reconstructed pressure was $122 \pm 19 / 69 \pm 9$ mmHg and RMSE was $4.4 \pm 2.0$ mmHg. Details of the wave shape that were reproduced by the individualized transfer function were lost with the generalized transfer function. Thus, with the extra information of time delay, we were able to obtain a transfer function that was optimal for the individual, giving better results than a generalized transfer function.

**Hemodynamic analyses**

Hemodynamic analysis is a broad denominator. In this thesis we investigated two phenomena, both related to central blood pressure and both determinants of cardiac performance. The first is the reflection index in Chapter 4, the second is the cardiac oxygen supply and demand ratio in Chapter 5.

*Quantification of wave reflection in the human aorta from pressure alone*

Wave reflections are apparent from the proximal aortic pressure signal when a secondary systolic rise in pressure is found. Since reflection may increase systolic pressure it is an important factor to consider when studying systolic hypertension.

A frequently used measure of wave reflection is the Augmentation Index (AI), the ratio of the secondary rise in pressure and pulse pressure. However, this index has the weakness that it only can discern a reflection when the secondary rise in pressure is detectable. The timing of the reflected wave may be such that the secondary rise in pressure is not quantifiable.

A more accurate measure is the reflection index (RI), obtainable after separation of pressure in its forward and reflected components, so-called waveform analysis. However, this requires measurement of aortic flow, often not readily available. We therefore explored the possibility of replacing the unknown flow by an artificial triangular wave. Flow duration was set to ejection time; peak flow at the inflection point of pressure, $F_{IP}$, and, for a second analysis, at 30% of ejection time, $F_{30}$. Wave separation then gave forward, $P_f$, and backward, $P_b$, pressure waves. RI was defined as:

$$RI = \frac{|P_b|}{(|P_f| + |P_b|)}.$$

Twelve healthy subjects, including interventions such as exercise and Valsalva maneuvers, and 5 patients with ischemic heart disease were analyzed. RIs using $F_{IP}$ and $F_{30}$ were compared with $RI_{mf}$ using measured flow, $F_m$, recorded with a Millar catheter with high fidelity pressure and velocity sensors at the tip. $RI_{mf} = 0.41 \pm 0.05$, (mean ±
Variations in cardiac oxygen supply and demand in hypertensive subjects after rising

The increase in heart rate and blood pressure soon after awakening increases cardiac oxygen demand, which has been associated with morning excess of acute myocardial infarction. Oxygen demand is elevated in hypertensive subjects and we tested the hypothesis that in hypertensive subjects this early morning increase in heart rate and blood pressure also affects the oxygen supply potential. Since it is the ratio between supply and demand that determines whether subendocardial ischemia may occur, we considered this an important question.

Aortic pressure was reconstructed from 24-hour intra-brachial and finger pressure recordings in 14 hypertensive patients and in 8 normotensive subjects as reference. Supply was assessed by Diastolic Time Fraction (DTF), demand by Rate-Pressure Product (RPP) and supply/demand ratio by $A_{\text{dia}}/A_{\text{sys}}$ with $A_{\text{dia}}$ and $A_{\text{sys}}$ diastolic and systolic area under the aortic pressure curve. In the morning, blood pressure and heart rate (HR) increased in both groups. HR increased 33% in hypertensives and 55% in normotensives to become similar in the morning. DTF and $A_{\text{dia}}/A_{\text{sys}}$ ratio decreased in both groups ($P < 0.001$), while demand increased in both groups ($P < 0.001$). Parameters correlated closely with HR ($R^2 \sim 0.9$). Compared to normotensives, hypertensive subjects had lower supply as well as lower supply/demand ratio, and a higher demand ($P < 0.001$) during the night that persisted ($P < 0.001$) during the morning.

The data suggest that in hypertensive vs. normotensive subjects the cardiac oxygen demand around awakening becomes elevated. The morning imbalance in supply and demand is related not only to increased demand but to decreased supply as well. The deterioration of the balance between supply and demand appears limited by a smaller morning rise in HR in hypertensives.
Baroreflex sensitivity analyses

Baroreflex sensitivity analysis is widely used to obtain insight in the functioning of the autonomic system in health and disease. A method rapidly giving reliable information on baroreflex sensitivity is a sought after tool.

Time-domain cross-correlation baroreflex sensitivity: Performance on the EUROBAVAR data set

To test a new method (xBRS) for time domain baroreflex sensitivity (BRS) computation on spontaneous blood pressure and heart interval variability we used the EUROBAVAR data set which is available from the internet1. This set is especially compiled for evaluation and comparison of methods determining baroreflex sensitivity (see Appendix).

In Chapter 6, the xBRS method was put to use on the 42 records in the EUROBAVAR data set, obtained on 21 patients in lying and standing position. One patient had a recent heart transplant and one was diabetic with evident cardiac autonomic neuropathy. xBRS computes correlation between beat to beat pressure and interval, resampled at 1 Hz, in a sliding 10 s window, with delays of 0 to 5 s for interval. The delay with the highest positive correlation is selected and, when significant at \( P = 0.01 \), slope (ms/mmHg) and delay (s) are recorded as one xBRS value. Each second of the recording is the start of a new computation. Non-parametric tests are used.

Lying, xBRS yields 12.4 versus EUROBAVAR sequential 16.2 ms/mmHg, standing 6.2 versus 6.7 ms/mmHg, lying to stand ratio 1.96 versus 2.10. xBRS gave results on all files, 20 values per minute on average at a lower within patient variance. Best xBRS delays were 0, 1, and 2 s, and delay increased 100 ms in stand position. xBRS gave results on the diabetic and the heart transplant patient, while other methods were unable to do so.

The xBRS method should be considered for experimental and clinical use since xBRS yields values strongly correlated with and close to EUROBAVAR averages, yields more values per minute, has lower within patient variance, and measures baroreflex delay.

1 http://www.cbi.dongnocchi.it/glossary/eurobavar.html
Dynamics of baroreflex sensitivity during postural stress

Postural stress requires immediate autonomic nervous action to maintain blood pressure. This can be explored by determining continuous time domain baroreflex sensitivity (BRS) during stepwise changes in angles of body axis (α). Our hypothesis was that with increasing postural stress, BRS becomes reduced by a reduction in its vagal component (Chapter 7).

In 10 healthy young volunteers α included 20 degrees head-down tilt (–20º), supine (0º), 30 and 70 degrees head-up tilt (30º, 70º) and free standing (90º). Non-invasive blood pressure recordings were analyzed over 6 min periods before and after each change in α. BRS was determined by frequency-domain analysis and with xBRS, a high-resolution time-domain method additionally providing the time delay τ between systolic blood pressure and interbeat interval variations.

On average, between 28 (–20º) to 45 (90º) xBRS estimates per minute became available for analysis. Following a change in α, xBRS altered in the first minute in 78% of the cases and in 93% within 6 minutes. With increasing tilt angle, decrease in BRS was described as

\[ \text{BRS} = -10.1 \cdot \sin(\alpha) + 18.7; \ R^2 = 0.99, \]

with good correlation between xBRS and cross-spectral gain (R² = 0.98 for the low-frequency band and R² = 0.97 for the high-frequency band. The time delay τ shifted towards higher values and correspondingly the phase in the spectral analysis tended to become more negative.

In conclusion, with progressive orthostatic stress, time- and frequency-domain baroreflex sensitivity declined linearly with the sine of α. The increase in delay τ at higher levels of orthostatic stress appears to correspond with decreased vagal and increased sympathetic cardiac tone.

Diurnal blood pressure analyses

The circadian blood pressure pattern and the day-night differences in blood pressure give more accurate prognostic values than office blood pressure measurements and better insight in blood pressure regulation.
Variable day/night bias in 24-hour non-invasive finger pressure against intra-brachial artery pressure is removed by waveform filtering and level correction

The nocturnal blood pressure dip is overestimated by finger blood pressure, since it shows a negative bias against intra-brachial artery pressure and the bias is greater during the night. We have available a methodology to reconstruct brachial from finger artery blood pressure by waveform filtering (transfer function) and generalized level (bias) correction that reduces the bias for short term blood pressure records. We wanted to investigate (Chapter 8) if this methodology also decreases the extra bias during the night thereby yielding a better estimate of the nocturnal dip.

Twenty-four-hour finger (FinAP) and intra-brachial (BAP) blood pressure recordings were simultaneously obtained in 8 healthy normotensive volunteers and 14 hypertensive patients (aged 19 to 60 y), during standardized scheduled activities. The data were analyzed off-line, applying the brachial reconstruction technique (reBAP) consisting of a waveform filter and level correction. Simultaneous beats yielded systolic, diastolic and mean pressures, which were averaged per half hour, per day, per night, per activity, over the 24-hour period, and for volunteers and patients, separately.

Over the full 24 hours FinAP systolic, diastolic and mean pressures for the total group differed +1 ± 10, –8 ± 7, and –10 ± 8 mmHg (mean ± SD), respectively, from BAP. Similarly, reBAP differed +1 ± 11, –2 ± 7, and –2 ± 7 mmHg. BAP dipped 20 ± 8, 13 ± 6, and 15 ± 6 mmHg during the night. These dips were overestimated +8, +4, and +4 mmHg by FinAP but not by reBAP: –1, +1, and +1 mmHg. The volunteer and the patient groups showed slight differences in results, which were not statistically significant.

The generalized reconstruction technique to obtain near-brachial pressure from noninvasive finger pressure almost completely removes bias over the full 24-hour day-night period and allows accurate tracking of diurnal changes for systolic, diastolic and mean pressures.
Concluding remarks

Starting on a time scale of milliseconds, we investigated a physiological model of pressure transfer, concluding that the time delay between proximal and distal pressure is an important measurable parameter for individualization of a pressure transfer function. Next, we tested this finding on a set of measurements, demonstrating that a simple transfer function could be improved by incorporating the time delay, thus facilitating more accurate assessment of central pressures, the pressure that matters to the heart and hence important for diagnostics. Also on a small time scale, we proposed a method to calculate the reflection index from pressure alone, improving on the established method of augmentation index calculation. Augmentation index is widely used as a simple measure of arterial stiffness, which is in its turn an important marker for cardiovascular morbidity and mortality.

Moving to a time scale of seconds, we analyzed parameters for cardiac oxygen supply potential and cardiac oxygen demand. Not only oxygen demand increases after rising, which is an accepted concept, but supply potential decreases, providing new insight in the balance between supply and demand, perhaps giving an indication for use of medication. A new method to calculate baroreflex sensitivity was established to give values comparable to findings with other methods, but at a higher rate, allowing assessment of baroreflex sensitivity in a shorter time span. The higher time resolution also facilitates detailed analysis of changes in baroreflex sensitivity. We consecutively analyzed the baroreflex sensitivity during orthostatic stress, discovering a tight relation between baroreflex sensitivity and the tilt angle. We also showed that the new method gives an indication of the sympatho-vagal balance. Finally, on a time scale of 24 hours, we demonstrated a method to improve brachial artery pressure tracking by finger arterial pressure measurements, so that dipper and non-dippers can be reliably distinguished from non-invasive pressures.

We demonstrated in these studies that the non-invasive assessment of blood pressure can be performed reliably and that it can help in increasing our understanding of blood pressure control as well as in early detection of disease and effect of treatment.