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

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Chapter 3

Parameter adaptation to individualize pressure reconstruction

Berend E Westerhof¹, Ilja Guelen¹, Wim J Stok², Karel H Wesseling¹, Nico Westerhof³, Willem Jan W Bos⁴, Nikos Stergiopulos⁵, Jos AE Spaan⁶

The use of transfer functions (TFs) to reconstruct central pressure from, preferably, non-invasively obtained peripheral pressure, has received a great deal of attention in the literature (see below). TFs allow the acquisition of aortic pressure and thereby give more accurate information about the load on the heart and therefore should have better prognostic value in the field of cardiovascular disease. Generalized functions, averaged over groups of subjects, have been shown to provide sufficient improvement to determine mean and diastolic aortic pressure within limits of accuracy as set by the AAMI (1). Systolic pressure, being the most variable value, is somewhat more difficult to derive correctly. Systolic and diastolic pressures are evidently of importance, but the knowledge of the wave shape of aortic pressure allows for waveform analysis, i.e. the calculation of the augmentation index (15), reflection index (19,20,28), and indexes of cardiac oxygen supply and demand (30).

¹ BMEYE, Amsterdam, The Netherlands
² Dept of Physiology, Academic Medical Center, University of Amsterdam, The Netherlands
³ Lab for Physiology, ICaR-VU, VU University medical center, Amsterdam, The Netherlands
⁴ Dept of Internal Medicine, St Antonius Ziekenhuis, Nieuwegein, The Netherlands
⁵ Biomedical Engineering Laboratory, Swiss Federal Institute of Technology, Lausanne, Switzerland
⁶ Dept of Medical Physics, Academic Medical Center, University of Amsterdam, The Netherlands
Several approaches have been taken to acquire usable transfer functions, starting as early as 1970 (3,5,7,9,13,14,16,21-25,27) including methods for calibration (2,3,10-12,29). Recently, an extensive review of the literature was published (8). Compared to a generalized TF, more exact results may be expected when a TF is individualized, i.e. optimized for a particular subject. For instance, a TF can be made more accurate by accounting for age (9) or sex (13). If extra measurements are performed details of an individual TF might be obtained (14,25,26).

Earlier we found that the time delay between central and peripheral pressure is an important parameter in the description of pressure transfer (25,26,31). As this time delay can be non-invasively obtained, we set out to investigate whether this parameter could be used to individualize the TF. We tested a simple mathematical TF in which time delay is incorporated. We used a set of invasively determined brachial and aortic pressures to explore the usefulness of the approach. We calculated remaining errors for the case in which the parameters of the TF are optimized for each individual and for the case in which the parameters are averaged values.

**Methods**

**Measurements**

Patients and methods have been described in the report by Lasance et al. (16). Pull-back pressure recordings were made with a fluid filled catheter in ascending aorta, aortic arch, descending aorta, brachiocephalic, subclavian, axillary and brachial artery. The data were sampled at 100 Hz. For our main study we use ascending aortic pressure and brachial pressure. Aortic and brachial pressure beats were selected so that mean pressure and heart period were optimally matched. If no pair could be attained with a mean pressure difference smaller than 9 mmHg and with a difference in heart period less than 90 ms, the beats were not used. With these restrictions, 50 pairs of beats remained of the 74 patients.
Pressure transformation analysis

Transfer function
The simple mathematical TF (25) that we use to test our hypothesis, based on a single uniform tube, is:

\[ \frac{P_{\text{distal}}}{P_{\text{proximal}}} = \frac{(1 + \Gamma) \cdot e^{-j \omega D t}}{1 + \Gamma \cdot e^{-2j \omega D t}} \]

with \( \Gamma \) the reflection coefficient at the distal site, taken to be real (24), \( \Delta t \) the time delay between the distal and proximal site, \( j \) the imaginary unit and \( \omega \) angular frequency. The Fourier transformation of the brachial pressure wave divided by the TF gave the “reconstructed pressure”. After inverse Fourier transformation the reconstructed pressure was compared to the measured aortic pressure.

Calculations
First, systolic and diastolic pressures were determined of the aortic and brachial beats. The Root Mean Square Error (RMSE), calculated with the measured aortic and measured brachial beat shifted in time with respect to each other so that minimal errors were obtained, described the difference in wave shape. Next, for each pair of pressures, the optimal TF (equation 1) was found by iterative procedures. Optimal in this respect is defined as giving minimal RMSE between aortic and reconstructed pressure. For each pair of beats, optimal \( \Gamma \) and \( \Delta t \) were recorded together with the errors in systolic and diastolic pressures and the RMSE. Subsequently four models were defined. In model 1, optimal \( \Delta t \) and \( \Gamma \) for each individual were used. A simplified model requiring only individualization of \( \Delta t \) while \( \Gamma \) was set at the group average was called model 2. Model 3 was a generalized TF with both \( \Gamma \) and \( \Delta t \) set at the group average. Finally, in model 4, we set \( \Delta t \) to the average value and \( \Gamma \) to 1, representing total reflection. Augmentation Index, AI, (15) was calculated from the results of the individualized TF (model 1) and for the generalized TF (model 3) and compared to the AIs of the ascending aortic pressure waves as another indication of the truthfulness of the reconstructed wave shape.

Statistics
The RMSE and systolic, diastolic and pulse pressure after reconstruction with each of the TFs were compared to measured aortic pressure, using a paired t-test. Differences were assumed to be significant for \( P < 0.05 \).
### Aortic-, Brachial- and Reconstructed pressures

<table>
<thead>
<tr>
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<th>Measured</th>
<th>Reconstructed</th>
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<tbody>
<tr>
<td></td>
<td>Asc</td>
<td>Brac</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Sys</td>
<td>119 ± 20</td>
<td>131 ± 18</td>
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<td></td>
<td>&lt; 0.001</td>
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<tr>
<td>Dia</td>
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<td>67 ± 9</td>
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<tr>
<td></td>
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<tr>
<td>PP</td>
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<td>64 ± 13</td>
</tr>
<tr>
<td></td>
<td>&lt; 0.001</td>
<td></td>
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<tr>
<td>RMSE</td>
<td>7.5 ± 2.1</td>
<td>4.0 ± 2.0</td>
</tr>
</tbody>
</table>

Asc is ascending aortic pressure, brac is brachial pressure. In the further columns, the values of the reconstructed pressures after application of the TF models are listed with the parameters given in the heading.
Results

For the 50 selected beat pairs the difference in mean pressure between brachial artery and ascending aortic pressure measurements was $-0.4 \pm 3.4$ mmHg (range $-9$ to $9$ mmHg). Difference in interbeat interval (IBI) for these beats was $-3.4 \pm 27$ ms (range $-80$ to $50$ ms). In Figure 1 the averaged TF calculated from these beats is shown. For each pair of beats the TF was determined using Fourier analysis, harmonics of each TF were interpolated and resampled at 1 Hz before averaging. In Table 1, measured ascending aortic pressure and brachial pressure are listed together with reconstructed pressure using the four different TF models. Brachial pressure and each of the reconstructed pressures are tested against aortic pressure. Best results are obtained using the TF with both $\Delta t$ and $\Gamma$ individualized. Each step of generalization involves an increase in RMSE, which is small, but statistically significant. Figure 2 shows the mathematical TFs for the generalized case with and the $\Delta t = 0.048$ and $\Gamma = 0.6$ and 1, respectively.

Figure 1

Transfer Function of ascending aorta to brachial artery, obtained in 50 patients. Top panel: amplitude of the gain, bottom panel: phase in radians. Errors are SEM.
Because RMSE data only give global information of the fits but no details on the wave shape of the reconstructed aortic pressure wave, four examples are given in Figure 3. In each case the generalized TF gives distinctly less accurate results compared to the individualized TF. In the top panel, reconstructed pressure using the generalized TF has no secondary rise in pressure, called pressure augmentation, while the pressure from the individualized TF has. The second panel from the top, both reconstructed pressure show an augmentation but the pressure reconstructed with the individualized TF has a closer fit. In the third panel, the generalized TF does not damp but augments the oscillations found in the brachial artery pressure. In the bottom panel, the pressure augmentation is exaggerated by the generalized TF.

**Figure 2**

![Mathematical Transfer Functions.](image)

Top panel: amplitude of the gain, bottom panel: phase in radians. On the horizontal axis: frequency in Hz. The fully drawn line represents the Transfer Function with optimal parameters for the group (\(t = 0.048\) s, \(G = 0.6\)). The dashed line is a Transfer Function with complete reflection (\(t = 0.048\) s, \(\Gamma = 1\)). Phase of this Transfer Function is undetermined (“standing wave”).

For the AI we found average values of \(AI_{asc} = 27 \pm 15\) for ascending aortic pressure; \(AI_{RecInd} = 30 \pm 14\) (NS) for the individualized model 1; \(AI_{RecGen} = 25 \pm 12\) (\(P < 0.05\)) for the generalized model 3. In the ascending aortic pressures, no AI was found in 2 cases; using the individualized model no AI was found in 4 cases, while with the generalized model this number was 7. Linear regression analysis gave the following descriptions:
\[ AI_{\text{Recl}} = 0.88 \cdot AI_{\text{asc}} + 5.4, R^2 = 0.77 \]
\[ AI_{\text{RecGen}} = 0.72 \cdot AI_{\text{asc}} + 4.5, R^2 = 0.52. \]

Figure 3

Four examples in which the individualized Transfer Functions gives better results than the generalized Transfer Function. Left, brachial pressures, middle, ascending aortic pressure (drawn) with reconstructed pressure (dashed) using the generalized Transfer Function. Right, again ascending aortic pressure (drawn) with reconstructed pressure (dotted) using the individualized Transfer Functions.
Discussion

We investigated whether individualization of a simple mathematical TF would result in better estimation of central pressure values and in a better-predicted wave shape. We found that the wave shape with the individualized TF is better than with the generalized one; this improvement is significant, but limited. The parameters of the simple TF, $\Delta t$ and $\Gamma$, travel time of the pressure wave and reflection coefficient at the end of the transmission line, respectively, can be measured. Travel time could be measured performing simultaneous pressure measurements at the sites between which the TF is defined, and $\Gamma$ by measuring pressure and flow at the peripheral site. In the present study we did not perform these extra measurements but analyzed a set of aortic and brachial pressures to investigate if the approach would be fruitful. Therefore, we calculated individual $\Delta t$ and $\Gamma$ from the actual measurements. We then analyzed the results from each of four different TFs. As expected, the smallest RMSE was found when individual TFs were used, i.e. with individual $\Delta t$ and $\Gamma$. When $\Gamma$ was fixed to an average value, RMSE showed a statistically significant increase. Also fixing $\Delta t$ to an average value again resulted in a larger RMSE. We found travel time to be the most important parameter; $\Gamma$ was less influential on the results. Comparing the generalized TF with $\Delta t = 0.048$ and $\Gamma = 0.6$ (Figure 2) to the measured data of Figure 1, it can be seen that the first 4 harmonics are closely approximated by the TF generated by procedure which minimizes RMSE, at the cost of higher frequencies. The harmonic at 5 Hz is amply overestimated by the mathematical TF. Thus, the first four harmonics are the most important for accurate pressure reconstruction. This explains why the TF with $\Gamma = 1$ gives acceptable results; Figure 2 demonstrates that for the first four harmonics the difference between both mathematical TFs is negligible.

The AI of the reconstructed pressure using the individualized TF was not significantly different from the AI of measured ascending aortic pressure, while the AI of the generalized pressure was. The coefficient of determination was higher in the individualized model. This is corroborates the findings in RMSE reported above.
Figure 4 gives a further underpinning of the importance of delay as a model parameter. As our set of measurements included brachiocephalic, subclavian, axillary artery, we calculated TFs between those sites and brachial artery as well. From the Figure it is apparent that with shorter length of the intermediate arteries, the peak in the TF moves to higher frequencies. When the mathematical TF was fitted to the first four harmonics, delays of 0.043s, 0.037s and 0.025s were found, respectively.

**Figure 4**

Transfer functions from brachiocephalic, subclavian and axillary artery to brachial artery. With shortening of travel time, the peak moves to a higher frequency. Mathematical Transfer Functions (no error bars) were fitted to the first 4 harmonics.
Sugimachi et al. (26) took our earlier work (25) as a basis for further research as well. They used the distal Windkessel load of their model to determine flow and use wave separation and the shift theorem (25) with individualized time delay to reconstruct central pressure. They also concluded this delay is the key parameter to individualize the TF and that Windkessel parameters are of limited importance. However, they were not able to improve reconstruction with individualization, which was probably due to the rather small study group and the relative uniformity of the subjects.

Obviously, for the method to be useful in practice, the extra measurements should be non-invasive and convenient. As $\Gamma$ was found to be of less importance than $\Delta t$, the latter should preferably be measured. One option is to simultaneous measurement of brachial and axillary artery pressure by applanation tonometry and determining the delay. Echocardiography could also be considered for the required central information. Another possibility is to use the delay between the R-top in the ECG and the upstroke in peripheral pressure, although the preejection period remains an uncertain factor. Sugimachi et al. (26) further suggest the use of carotid and radial pulse recordings or the use of the second heart sound and the dicrotic notch of the distal pulse.

The finding that a generalized TF can be used to accurately reconstruct central pressures corresponds to findings in literature (5,8,14), which, however, have been questioned as well (13,17). One could summarize that in individual cases a generalized TF might not be adequate, for group averages however the results can be very good. Thus, inter-individual differences may be a problem, but intra-individual differences have been shown to be smaller (5). This could imply that one individualization procedure may be sufficient, allowing following a subject over a longer period of time (11,29).

It has also been noticed that the peripheral pressure (4) or photoplethysmographic wave shape (6,18) changes little during local infusion of vasoactive drugs, thus confirming the conclusion that the TF is quite insensitive to changes in $\Gamma$ (31). On the other hand, systemic infusion of these vasoactive substances has much greater effect on difference between central and peripheral wave shape (4,6,18). This may result from to the change in mean systemic pressure: for instance, an increase in mean pressure will decrease arterial compliance and thus increase wave speed. This will decrease $\Delta t$ and thus modify one of the most sensitive parameters describing the TF. Therefore, although individualization of TF may have only a minor effect in the present study, the method may prove useful in protocols involving systemic infusion of vasoactive drugs.
For higher frequencies, our generalized TF in Figure 1 differs somewhat from the original TF as given by Lasance et al. (16). One reason is that, in the original study, pairs of 2 successive aortic as well as 2 successive brachial beats were selected for analysis, while we used single beats, so that a meaningful RMSE could be calculated. Another obvious reason is that the study populations differ in size. We discarded pairs of beats with too large differences in mean pressure and heart period. Mean pressure will fall due to resistance in the arteries. However, resistance of the larger arteries like the brachial artery is usually quite small and a pressure drop of 10 mmHg in mean pressure not likely to occur. Since the measurements were not recorded simultaneously, we wanted to exclude beats in which mean pressure did not remain stable between measurements. A similar reasoning holds for IBI. Nonetheless, the first few harmonics of both TFs are remarkably close.

**Limitations**

In this study we determined the optimal time delay from the actual measurements of ascending aortic and brachial pressure. In a practical application, the time delay should be determined from other measurements as the central pressure will not be available. However, here we wanted to investigate the feasibility of the procedure before further effort was put into developing a method to establish a time delay.

Another limitation of the study is that the generalized TF is based on the measurements of central and distal pressure, in other words, the learning population and the study population are the same. Therefore the results are optimal for this group and the same TF would perform less well in a random population.
Future developments

A time delay might be conveniently obtained from a time difference between ECG and distal pressure. A formula would have to be developed to predict travel time from this delay by correcting for the time between R-top and ejection. Whether this method would give delays of sufficient accuracy remains to be determined.

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References


