Individualization of transfer function in estimation of central aortic pressure from the peripheral pulse is not required in patients at rest

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Westerhof BE, Guelen I, Stok WJ, Lasance HA, Ascoop CA, Wesseling KH, Westerhof N, Bos WJ, Stergiopulos N, Spaan JA. Individualization of transfer function in estimation of central aortic pressure from the peripheral pulse is not required in patients at rest. J Appl Physiol 105: 1858–1863, 2008. First published October 9, 2008; doi:10.1152/japplphysiol.91052.2008.—Central aortic pressure gives better insight into ventriculo-arterial coupling and better prognosis of cardiovascular complications than peripheral pressures. Therefore transfer functions (TF), reconstructing aortic pressure from peripheral pressures, are of great interest. Generalized TFs (GTF) give useful results, especially in larger study populations, but detailed information on aortic pressure might be improved by individualization of the TF. We found earlier that the time delay, representing the travel time of the pressure wave between measurement site and aorta is the main determinant of the TF. Therefore, we hypothesized that the TF might be individualized (ITF) using this time delay. In a group of 50 patients at rest, aged 28–66 yr (43 men), undergoing diagnostic angiography, ascending aortic pressure was 119 ± 20/70 ± 9 mmHg (systolic/diastolic). Brachial pressure, almost simultaneously measured using catheter pullback, was 131 ± 18/67 ± 9 mmHg. We obtained brachial-to-aorta ITFs using time delays optimized for the individual and a GTF using averaged delay. With the use of ITFs, reconstructed aortic pressure was 121 ± 19/69 ± 9 mmHg and the root mean square error (RMSE), as measure of difference in wave shape, was 4.1 ± 2.0 mmHg. With the use of the GTF, reconstructed pressure was 122 ± 19/69 ± 9 mmHg and RMSE 4.4 ± 2.0 mmHg. The augmentation index (AI) of the measured aortic pressure was 26 ± 13%, and with ITF and GTF the AIs were 28 ± 12% and 30 ± 11%, respectively. Details of the wave shape were reproduced slightly better with ITF but not significantly, thus individualization of pressure transfer is not effective in resting patients.

peripheral pressure, has received a great deal of attention, and has generated lively debate (12, 24). Generalized transfer functions, i.e., averaged over groups of subjects, have been shown to provide mean and diastolic aortic pressure values within limits of accuracy as set by the AAMI (1). However, systolic pressure, being the most variable, is more difficult to derive correctly. Additionally, waveform analysis, such as the calculation of the reflection index (21, 22, 37), augmentation index (16), and estimation of cardiac output (33) rely on detailed information on aortic systolic pressure waveform and magnitude.

Several approaches have been taken to acquire transfer functions, starting as early as 1970 (5, 7, 11, 15, 23, 24). Calibration (4, 8, 10, 30, 35) has become an issue in itself (32). Usually, a generalized transfer function (GTF) is used; however, more exact results may be expected when a TF is individualized (ITF), i.e., optimized for a particular subject. For instance, an ITF can account for age or sex (13); with extra measurements an ITF might be improved even more (14, 27, 29).

Earlier we showed that the time delay between central and peripheral pressure is the most important parameter determining the pressure transfer function (27, 36). As this time delay can be noninvasively obtained, we set out to investigate if this parameter could be used to individualize the TF and if the use of an individual TF predicts aortic pressure better than a generalized TF. We used a set of invasively, almost simultaneously measured brachial and aortic pressures to test this.

METHODS

Measurements. Blood pressure recordings were taken from an earlier study by Lasance et al. (18). In short, pressure recordings were made in 74 subjects in whom elective coronary arteriography was performed. A fluid-filled catheter, inserted with the Sones technique, was placed in the ascending aorta and pulled back to the brachial artery. The frequency response of the fluid-filled system was regularly checked during the measurements. The resonance frequency was always higher than 50 Hz, thus the fluid-filled system did not distort the pressure signal. The data were sampled at 100 Hz. Since measurements were not performed simultaneously, aortic and brachial pressure beats were selected such that heart period differed <90 ms
and mean pressures differed <9 mmHg, since in these patients a larger mean pressure difference must result from instability of the cardiovascular system. For each patient, a single aortic and brachial pressure beat was used since the catheter was kept at each site for only a few seconds. Recordings of Lasance et al. (18) were made during a few seconds. Recordings of Lasance et al. (18) were made during a few seconds. Recordings of Lasance et al. (18) were made during a few seconds. Recordings of Lasance et al. (18) were made during a few seconds. Recordings of Lasance et al. (18) were made during a few seconds. Recordings of Lasance et al. (18) were made during a few seconds.

Transfer function. A simple mathematical function, describing pressure transfer over a single uniform tube (27, 36) forms the basis of our models. It has two parameters:

$$P_{\text{dist}}/P_{\text{proximal}} = (1 + \Gamma) \cdot e^{-j2\pi f\Delta t}/(1 + \Gamma \cdot e^{-j2\pi f\Delta t}) \quad (1)$$

with $\Gamma$ the reflection coefficient at the distal site, taken to be real, $\Delta t$ the time delay between the distal and proximal site (brachial artery and aorta), j the imaginary unit, and $\omega$ the angular frequency, i.e., $2\pi f$ with $f$ heart frequency. This function was shown to give a good description of pressure transfer (27, 36). The Fourier transformation of the brachial pressure wave divided by the TF gave the “reconstructed aortic pressure.” After inverse Fourier transformation, the reconstructed aortic pressure as a function of time was calculated and compared with measured aortic pressure.

Calculations. First, systolic, and diastolic pressures were determined of the aortic and brachial pressure curves. The root mean square error (RMSE) was calculated with the measured aortic and measured brachial pressure shifted in time with respect to each other so that minimal errors were obtained. In this way, the remaining errors are a measure of the difference in wave shape and not artificially large due to differences in timing.

For each patient, only a single aortic and brachial pressure beat was used, since the catheter was kept at each site for only a few seconds. Next, for the pair of pressures of each patient, the optimal $\Gamma$ and $\Delta t$ of the TF (eq. 1) were found by searching for the $\Gamma$ and $\Delta t$ that minimize the RMSE between reconstructed and measured aortic pressure. This was done with a brute force approach. Aortic pressure was reconstructed with TFs with $\Gamma$ varying between 0.3 and 0.9 with steps of 0.05 and $2\pi \Delta t$ varying between 0.2 s and 0.4 s with steps of 0.05 s (thus $\Delta t$ varied between 0.0318 s and 0.0637 s with steps of 0.00796 s). Then $\Gamma$ and $\Delta t$ giving the smallest RMSE were selected. Subsequently, four transfer models were defined. In model 1, optimal $\Gamma$ and $\Delta t$ for each individual were used. In model 2 optimal $\Delta t$ was used while $\Gamma$ was set at the group average. Model 3 was a GTF 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, to assess the importance of the parameter $\Gamma$. Systolic, diastolic, and pulse pressure and RMSE of the reconstructed aortic pressure using the four TF models were compared with measured aortic pressure.

Augmentation index (AI; 16) was calculated from the results of all models and compared with the AI of the ascending aortic pressure waves as another indication of the correctness of the reconstructed wave. Calculations were implemented as described by Segers et al. (25).

Statistics. Results of the four TF models were compared with measured aortic pressure using Dunnett’s method for multiple comparisons vs. control. Differences between consecutive models were evaluated with paired t-tests. Differences were assumed to be significant for $P < 0.05$.

RESULTS

Ascending aortic and brachial pressure waves within the limits given in the Methods were obtained in 50 patients (43 men and 7 women) aged 51 ± 9 yr (range 28–66). The

![Figure 1. Transfer functions (TF) of ascending aorta to brachial artery. Top, amplitude of the gain; bottom, phase in radians. The TF with error bars (SE) is obtained in 50 patients. Solid line represents the TF with averaged parameters for the group (model 3; $\Delta t = 0.048$ s, $\Gamma = 0.6$). Dashed line is a TF with complete reflection (model 4; $\Delta t = 0.048$ s, $\Gamma = 1$). Phase of this TF is undetermined (“standing wave”).](image-url)

### Table 1. Aortic, brachial, and reconstructed pressures

<table>
<thead>
<tr>
<th></th>
<th>Measured</th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
<th>Model 4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Asc</td>
<td>Brac</td>
<td>Test</td>
<td>Asc</td>
<td>Brac</td>
</tr>
<tr>
<td></td>
<td>$\Delta t =$ ind; $\Gamma =$ ind</td>
<td>$\Delta t =$ ind; $\Gamma =$ 0.6</td>
<td>$\Delta t =$ 0.048; $\Gamma =$ 0.6</td>
<td>$\Delta t =$ 0.048; $\Gamma =$ 1</td>
<td></td>
</tr>
<tr>
<td>Sys</td>
<td>119 ± 20</td>
<td>131 ± 18</td>
<td>*</td>
<td>121 ± 18</td>
<td>121 ± 19</td>
</tr>
<tr>
<td>Dia</td>
<td>70 ± 9</td>
<td>67 ± 9</td>
<td>*</td>
<td>69 ± 9</td>
<td>69 ± 9</td>
</tr>
<tr>
<td>PP</td>
<td>50 ± 15</td>
<td>64 ± 13</td>
<td>*</td>
<td>52 ± 13</td>
<td>52 ± 13</td>
</tr>
<tr>
<td>AI</td>
<td>26 ± 13</td>
<td>29 ± 14</td>
<td>*</td>
<td>28 ± 12</td>
<td>28 ± 12</td>
</tr>
<tr>
<td>RMSE</td>
<td>7.5 ± 2.1</td>
<td>4.0 ± 2.0</td>
<td>4.1 ± 2.0</td>
<td>4.4 ± 2.0</td>
<td>4.9 ± 1.9</td>
</tr>
</tbody>
</table>

Asc, ascending aortic pressure; Brac, brachial pressure; $\Gamma$, reflection coefficient at the distal site; $\Delta t$, time delay between the brachial artery and ascending aorta. In the “Model” columns, the values of the reconstructed pressures (Recon) are listed with the model parameters. Sys, Dia and PP, systolic, diastolic, and pulse pressure, respectively; AI, augmentation index; RMSE, root mean square error. *Significant difference by multiple comparisons vs. Asc as control (Dunnett’s method). Superscript numbers, significant difference when sequentially testing a next model with the previous ($^1$, $^2$, and $^3$ indicate a difference from model 1, model 2, and model 3, respectively, by t-test).
difference in mean pressure between brachial artery and ascending aortic pressure was $-0.4 \pm 3.4$ mmHg. Difference in interbeat interval (IBI) for these beats was $-3.4 \pm 27$ ms. For $\Delta t$ we found $0.048 \pm 0.010$ s and for and $\Gamma$ was $0.6 \pm 0.13$. Figure 1 shows the TF calculated from these measured pressure pairs and also the TFs according to eq. 1 for the generalized cases with the averaged $\Delta t$ and averaged $\Gamma$ (model 3) and for averaged $\Delta t$ with $\Gamma = 1$ (model 4).

Table 1 lists measured ascending aortic pressure and brachial pressure values together with reconstructed pressure values using the four different TF models. Brachial pressure and each of the reconstructed pressures are all tested against measured aortic pressure (Dunnett) and only brachial systolic and pulse pressure are different. Between the models, best results are obtained with models 1 and 2 (with both $\Delta t$ and $\Gamma$ individualized and with only $\Delta t$ individualized and with $\Gamma$ at group average). Between models 2 and 3 slight differences start to arise, which are significant by $t$-test. Between models 3 and 4, results again deteriorate somewhat. The AIs of the models are not different from ascending aortic AI except for model 4 with $\Gamma = 1$. Similarly, the differences in the AIs between the models ($t$-test) are significant only for model 4 vs. model 3. Table 2

![Fig. 2. Bland-Altman representations of the model 1 (individualized TFs, left) and model 3 (generalized TF with $\Delta t = 0.048$ s and $\Gamma = 0.6$, right). The models give indistinguishable results.](image-url)
lists the linear regression coefficients of the model AIs on ascending aortic AI. Finally, in Table 1, each step of generalization involves an increase in RMSE, which is small, but statistically significant (t-test) between the models.

In Fig. 2 the Bland-Altman plots of systolic, diastolic, PP, and AI are shown of model 1 and model 3. The improvement by individualization is negligible.

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 Fig. 3. In these cases GTF gives distinctly less accurate results compared with the individualized TF. In Fig. 3, top (patient a), reconstructed pressure using the GTF has no obvious secondary rise in pressure, or pressure augmentation, while the pressure from the individualized TF has. In Fig. 3, second panel (patient b), both reconstructed pressures show an augmentation but the pressure reconstructed with the individualized TF has a closer fit. In Fig. 3, third panel (patient c), the GTF does not dampen but augments the oscillations found in the brachial artery pressure. In Fig. 4, bottom panel (patient d), the pressure augmentation is exaggerated by the GTF.

Thus, although the use of an ITF has on average little advantage, in some cases (patient c in Fig. 2) individualization (model 1), or even an individualized Δt and Γ = 0.6 (model 2, not shown), improves the reconstructed aortic pressure wave shape.

DISCUSSION

We found that the aortic wave shape reconstruction with the individualized TF is not significantly better than with the generalized one. Thus, in this group of resting patients, a generalized TF can be used without loss of accuracy of reconstruction. If an individualized TF is preferred, the one based on measured Δt and Γ = 0.6 (model 2) is the simplest to obtain and gives very accurate results.

We used a simple mathematical description of arterial pressure transfer, which requires only two parameters: Δt and Γ, the travel time of the pressure wave from aorta to measurement site and reflection coefficient at the site of pressure measurement. We hoped that by determining these parameters for an individual patient, a more accurate reconstruction of ascending aortic pressure could be obtained. However, all models gave similar results, except the one with Γ set to 1 (model 4), which overestimated pulse pressure. With stringent testing minor differences could be determined between consecutive models, which are statistically significant but not clinically relevant (Table 1).

Obviously, for an individualization method to be useful in practice, the measurements to obtain Δt and Γ should be noninvasive and convenient. Γ could be determined by measuring pressure and flow at the peripheral site (27). This is cumbersome and since using the individualized Γ gives the same results as an average Γ (Table 1, model 2 vs. 1), this

Table 2. Regression of model on aortic augmentation index

<table>
<thead>
<tr>
<th>Model</th>
<th>a</th>
<th>b</th>
<th>R²</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.87</td>
<td>0.06</td>
<td>0.73</td>
</tr>
<tr>
<td>2</td>
<td>0.73</td>
<td>0.09</td>
<td>0.69</td>
</tr>
<tr>
<td>3</td>
<td>0.69</td>
<td>0.12</td>
<td>0.65</td>
</tr>
<tr>
<td>4</td>
<td>0.05</td>
<td>0.40</td>
<td>0.00</td>
</tr>
</tbody>
</table>

AI_{model} = a AI_{asc} + b.
averaged $\Gamma$ can be used. Of note, the Sones technique of
catheter insertion involves ligation and heparization of the
distal artery. Nonetheless, the $\Gamma$ that was found was not
extremely high, i.e., close to unity. Figure 1 demonstrates that
the first four harmonics of the models are virtually independent
of $\Gamma$. This supports the findings in Table 1.

We found travel time $\Delta t$ to be the more important parameter.
The $\Delta t$ determines the location of the maxima of the TF (Fig.
1). This also came forward from a model study (36). It can be
seen in Fig. 1 that the first four harmonics are closely approxi-
imated by the TF generated by our procedure, which minimizes
RMSE. So the first four harmonics are the most important for
accurate pressure reconstruction (5).

To obtain $\Delta t$, one option is to simultaneously measure
brachial and axillary artery pressure by applanation tonometry,
as accessible points most relevant to the trajectory, and deter-
mining the foot-foot time delay. Echo- or impedance cardiog-
raphy could also be considered for the required central infor-
information. Another possibility is to use the delay between the
R-top in the ECG and the upstroke in peripheral pressure,
although the pre-ejection period remains an uncertain factor
(31). In the present study we did not perform these extra
measurements but analyzed a set of aortic and brachial pres-
sures and calculated for each individual which $\Delta t$ and $\Gamma$ was
best.

Sugimachi et al. (29) also took the work of Stergiopulos
et al. (27) as a basis for further research on the TF between
radial artery and aorta. They used the distal Windkessel load of
their model to determine flow and use wave separation and the
“shift theorem” (27) with individualized time delay to recon-
struct central pressure. They also concluded this delay is the
key parameter to individualize the TF and that Windkessel
parameters, and thus reflection coefficient, are of limited im-
portance. Similarly, they were not able to improve reconstruc-
tion with individualization.

The AIs of the reconstructed pressures were not significantly
different from the AI of measured ascending aortic pressure,
except in model 4. The coefficients of determination in Table 2
show a decrease with generalization, from model 1 to model 4,
consistent with the findings in Table 1. While generalization
tends to have some effect on AI, the results of methods using
time-integrated values of the central pressure, such as pulse
contour cardiac output methods (34) and cardiac oxygen sup-
ply/demand indexes (9, 38), are probably even less influenced
by the TF.

The finding that a GTF can be used to reconstruct central
pressures corresponds with findings in the literature (5), al-
though the use of GTFs has been questioned (13, 19). In the
study of Chen et al. (5) the prediction of aortic pressure from
radial applanation tonometry showed good results even during
changes in left ventricular filling. These authors concluded that
the transfer function of arm vessels appears rather unaffected
by body morphology, age, sex, and blood pressure. During the
Valsalva maneuver in some patients, with similar decrease in
arterial pressure, substantial variability in the transfer function
was occasionally observed by these authors and the GTF
predicted aortic pressure inaccurately. Thus, in certain cases,
individualization could be effective (see our Fig. 3), although
on average the improvement is small (Fig. 2). From the present
findings it emerges that retrieval of detailed information on
pressure wave shape, as described by the RMSE, may be
somewhat improved by using an ITF while features as systolic
and diastolic pressure levels are well represented using a GTF
(Table 1). A similar suggestion comes forward from Table 2,
showing tighter regressions of the individualized AIs.

It has been reported that the peripheral pressure (3) or
photoplethysmographic wave shape (6, 20) changes little dur-
ding local infusion of vasoactive drugs, confirming the conclu-
sion that the TF is quite insensitive to changes in $\Gamma$ On the
other hand, systemic infusion of vasoactive substances has
much greater effect on difference between central and periph-
eral wave shape (3, 6, 20). Therefore, although individualiza-
tion 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 (3, 39).

In exercise it was found that a generalized transfer function
can give acceptable results on average at lower exercise load
(26) and after calibration with a measured central pressure;
however, it was also shown that the interindividual variability
may be substantial, especially at higher heart rates (28). With
increasing heart rate, harmonics are shifted to higher frequen-
cies, so that the first few harmonics, in which most information
is contained, are more influenced by the peak of the TF. In
these cases, individualization may help in a more accurate
prediction of aortic pressure. Time delay might be obtained
from a time difference between ECG and noninvasively mea-
sured finger arterial pressure (28), since these methods are
reliable during exercise. Whether this method would give
delays of sufficient accuracy remains to be determined.

It is a limitation of our study that we included only patients
who presented with cardiac problems, most of whom were
diagnosed with CAD. This limitation is difficult to circumvent,
since central catheterization is rarely performed in healthy
subjects. In the present study, ITFs showed only slightly better
results than the GTF. Whether the improvement would be
greater in a healthy population we cannot predict.

TFs are most useful for estimating central pressure from
noninvasively measured peripheral pressures. For this explor-
atory study we used invasively obtained data. We determined
the optimal time delay from the actual measurements of as-
cending 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. Given the limited
improvements, if any, by using this time delay, it seems hardly
useful to individualize the TF. We conclude that in the resting
patient it is sufficient to use a generalized transfer function.

DISCLOSURES

B. E. Westerhof owns shares of and works for BMeye. No conflict of
interest. I. Guelen owns shares of and works for BMeye. No conflict of
interest.

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