Non-invasive wave reflection quantification in patients with reduced ejection fraction

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Non-invasive wave reflection quantification in patients with reduced ejection fraction

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Abstract

The non-invasive quantification of arterial wave reflection is an increasingly important concept in cardiovascular research. It is commonly based on pulse wave analysis (PWA) of aortic pressure. Alternatively, wave separation analysis (WSA) considering both aortic pressure and flow waveforms can be applied. Necessary estimates of aortic flow can be measured by Doppler ultrasound or provided by mathematical models. However, this approach has not been investigated intensively up to now in subjects developing systolic heart failure characterized by highly reduced ejection fraction (EF). We used non-invasively generated aortic pressure waveforms and Doppler flow measurements to derive wave reflection parameters in 61 patients with highly reduced and 122 patients with normal EF. Additionally we compared these readings with estimates from three different flow models known from literature (triangular, averaged, Windkessel). After correction for confounding factors, all parameters of wave reflection (PWA and WSA) were comparable for patients with reduced and normal EF. Wave separations assessed with the Windkessel based model were similar to those derived from Doppler flow in both groups. The averaged waveform performed poorer in reduced than in normal EF, whereas triangular flow represented a better approximation for reduced EF. Overall, the non-invasive assessment of WSA parameters based on mathematical models compared to ultrasound seems feasible in patients with reduced EF.
1. Introduction

The quantification of aortic blood pressure and wave reflection has become an increasingly important concept in cardiovascular research. Parameters gained from pulse wave analysis (PWA) provided insight into the mechanisms of arterial stiffness and cardiovascular pathophysiology (Nichols et al 2011). In contrast to general outcomes, similar relations could not be found in that clarity in cohorts developing systolic heart failure (SHF). These cohorts are mainly characterized by modified left ventricular outflow patterns with a reduced ejection fraction (EF) as well as increased heart rate (HR) and reduced ejection duration (ED). Compared to subjects from control groups, pulse pressure and augmentation index (AIx) are lower (Tartiere et al 2006, Denardo et al 2010) and it has been argued that general implications for risk stratification may need adaption for such cases (Weber et al 2007, Regnault et al 2014). Although a paradox at the first glance, recent data suggest that low pulse pressure in conjunction with increased left ventricular work may be explained by wave dynamics and certain patterns of wave reflections (Pahlevan and Gharib 2011). A widely accepted way to quantify wave reflection is the use of wave separation analysis (WSA) introduced by Westerhof et al (1972) considering both arterial pressure and flow waves. Unfortunately, the non-invasive measurement of aortic flow waves is much more challenging than acquiring pressure curves. Therefore, blood flow models have been introduced (Westerhof et al 2006, Kips et al 2009, Hametner et al 2013a). Parameters derived from such model based approaches using the WSA paradigm showed independent and additive prognostic value for cardiovascular risk estimation in general population (Wang et al 2010, Chirinos et al 2012), in subjects with white coat hypertension (Sung et al 2013) as well as in cohorts suffering from arterial stiffness (Weber et al 2012) or heart failure with preserved EF (Weber et al 2013). However, less is known about the behavior of such approaches in patients with SHF, especially due to the fact that aortic root flow patterns in SHF differ in shape and amplitude compared to patterns of controls (Nichols et al 2011). Therefore, the aim of this work is the investigation of wave reflection in patients with SHF by the means of PWA and WSA parameters derived from various blood flow models found in literature and its comparison to WSA parameters derived from flow waveforms acquired by echocardiography.

2. Materials and methods

2.1. Study population

The study population consisted of 183 patients with suspected coronary artery disease of whom 61 were diagnosed with highly reduced EF (EF < 50%). The remaining 122 patients were included as control group with similar characteristics, but normal EF. Exclusion criteria were arrhythmias, valvular heart disease and unstable clinical conditions. All measurements were performed at the university teaching hospital of Wels-Grieskirchen in Wels, Austria, within the scope of ongoing studies, which have been approved by the regional ethics committee, and participants gave written informed consent.
2.2. Data acquisition

The aortic flow waveforms were assessed by pulsed wave Doppler ultrasound measurement (Philips iE33 Ultrasound) of the blood velocity in the left ventricular outflow tract in the apical five chamber view with the sample volume placed in the middle of the outflow tract, and subsequent manual tracing of the spectral density recordings in the digitized echocardiogram based on the recommendations of the American Society of Echocardiography (Quinones et al. 2002). Aortic pressure waveforms and the corresponding PWA parameters were obtained from recordings of the radial pressure curve (Millar SPT 301 tonometer) using the validated SphygmoCor system (AtCor Medical Pty. Ltd, West Ryde, Australia) and its inbuilt generalized transfer function (Karamanoglu et al. 1993). Thereafter, central flow and pressure waveforms were aligned in time in order to perform WSA. More precisely, the flow was scaled such that its width from the beginning of upstroke to the first zero crossing matched the estimated ED provided by the SphygmoCor system. All steps of the data acquisition are schematically depicted in figure 1.

2.3. Blood flow models

To reduce the effort required for flow acquisition, different blood flow models based solely on pressure readings have been presented in literature, whereof three were used in this study: an averaged waveform published by Kips et al. (2009), a triangular approximation introduced by Westerhof et al. (2006) and a modified Windkessel (WK) flow computed with the ARCSolver (Austrian Institute of Technology, Vienna, Austria) algorithms (Hametner et al. 2013a). The averaged waveform was scaled in time for each patient in order to match the actual ED derived from the pressure measurement. The triangular flow was constructed following Westerhof et al. (2006): the ED forms the base of the triangle and the position of the maximum is set to the time when the inflection point in the pressure signal occurs. The ARCSolver method for flow estimation is based on the well-established three-element WK model. Thus, the generated flow waveform is directly affected by the properties of the arterial system considered in the WK model. A detailed mathematical description can be found in Wassertheurer et al. (2008) and Hametner et al. (2013a).
2.4. Wave separation analysis

In addition to the central pressure ($P_m$) and flow ($Q_m$) wave, the characteristic impedance ($Z_c$) is needed for wave separation. Therefore, the complex input impedance $Z_i$ is calculated as the ratio of $P_m$ to $Q_m$ in the frequency domain and the moduli of $Z_i$ for the harmonics 4–10 are averaged, excluding values higher than three times the median, to provide an estimate of $Z_c$ (Swillens and Segers 2008, Hametner et al 2013a, 2013b). $P_m$ is then separated into a forward ($P_f$) and backward ($P_b$) traveling component according to the formulas $P_f = 0.5(P_m + Z_cQ_m)$, $P_b = 0.5(P_m - Z_cQ_m)$ (Westerhof et al 1972, Qasem and Avolio 2008), compare figure 1. $Z_c$, $P_f$, $P_b$ as well as the amplitudes $|P_f|$ and $|P_b|$ were calculated separately for each flow waveform normalized to 100 arbitrary units (AU) since the absolute values of flow do not affect the pressure wave separation (Qasem and Avolio 2008). To assess the accuracy of the shapes of $P_f$ and $P_b$ when using a flow estimate, the backward and forward pressure waves obtained with the Doppler flow were taken as reference ($P_{b\text{ ref}}$, $P_{f\text{ ref}}$) and the root mean squared error (RMSE) between the waveforms was calculated. All computations were carried out in Matlab (The MathWorks, Inc., Natick, United States).

2.5. Statistics

Statistical analyses were performed using MedCalc 12.7.5 (MedCalc Software, Ostend, Belgium) and, unless stated otherwise, all results are presented as mean ± SD (standard deviation). Correlations were determined with Pearson’s correlation coefficient and Bland–Altman plots were used for method comparison. Between-group differences were statistically evaluated with Student’s or Welch’s $t$-test (normally and log-normally distributed data with equal or unequal variances respectively) or the Mann–Whitney-test (non-normally distributed data), as appropriate. Normality was assessed with the Shapiro–Wilk test. Analysis of covariance (ANCOVA) was used to adjust for confounding factors. A two-tailed $P < 0.05$ was considered significant.

3. Results

Patients with highly reduced EF were aged between 27 and 87 with a median age of 58; those with normal EF were ranging from 33 to 80 with a median age of 59. Table 1 summarizes...
Table 2. Between-group comparison of hemodynamic and wave reflection parameters: raw data (first three rows), data adjusted for HR (rows 4–6), for ED (rows 7–9) and for HR and ED (rows 10–12).

<table>
<thead>
<tr>
<th></th>
<th>pPP (mmHg)</th>
<th>cPP (mmHg)</th>
<th>AP (mmHg)</th>
<th>P1 (mmHg)</th>
<th>P_fref (mmHg)</th>
<th>P_bref (mmHg)</th>
<th>PP amp (%)</th>
<th>AIx (%)</th>
<th>RM (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>rEF</td>
<td>46.2 ± 14.5</td>
<td>33.1 ± 12.8</td>
<td>6.9 ± 6.6</td>
<td>26.9 ± 7.8</td>
<td>24.6 ± 8.0</td>
<td>13.9 ± 5.8</td>
<td>144 ± 17</td>
<td>18.1 ± 10.0</td>
<td>56.3 ± 11.7</td>
</tr>
<tr>
<td>nEF</td>
<td>47.5 ± 11.4</td>
<td>36.4 ± 9.7</td>
<td>9.4 ± 4.9</td>
<td>27.0 ± 6.8</td>
<td>24.7 ± 6.5</td>
<td>15.2 ± 4.2</td>
<td>132 ± 15</td>
<td>24.8 ± 10.3</td>
<td>62.1 ± 9.6</td>
</tr>
<tr>
<td>P</td>
<td>0.30</td>
<td>0.02*</td>
<td>&lt;0.001*</td>
<td>0.66</td>
<td>0.68</td>
<td>0.02*</td>
<td>&lt;0.001*</td>
<td>&lt;0.001*</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>HR</td>
<td>rEF</td>
<td>47.3</td>
<td>35.0</td>
<td>8.0</td>
<td>27.5</td>
<td>25.4</td>
<td>14.9</td>
<td>138.8</td>
<td>20.3</td>
</tr>
<tr>
<td></td>
<td>nEF</td>
<td>47.0</td>
<td>35.5</td>
<td>8.9</td>
<td>26.8</td>
<td>24.3</td>
<td>14.7</td>
<td>134.6</td>
<td>23.7</td>
</tr>
<tr>
<td></td>
<td>P</td>
<td>0.88</td>
<td>0.79</td>
<td>0.30</td>
<td>0.55</td>
<td>0.37</td>
<td>0.82</td>
<td>0.047*</td>
<td>0.15</td>
</tr>
<tr>
<td>ED</td>
<td>rEF</td>
<td>48.9</td>
<td>37.2</td>
<td>9.3</td>
<td>28.2</td>
<td>26.3</td>
<td>15.7</td>
<td>135.3</td>
<td>22.2</td>
</tr>
<tr>
<td></td>
<td>nEF</td>
<td>46.2</td>
<td>34.4</td>
<td>8.3</td>
<td>26.4</td>
<td>23.8</td>
<td>14.3</td>
<td>136.4</td>
<td>22.8</td>
</tr>
<tr>
<td></td>
<td>P</td>
<td>0.25</td>
<td>0.14</td>
<td>0.30</td>
<td>0.18</td>
<td>0.06</td>
<td>0.11</td>
<td>0.64</td>
<td>0.71</td>
</tr>
<tr>
<td>HR, ED</td>
<td>rEF</td>
<td>48.9</td>
<td>37.1</td>
<td>9.2</td>
<td>28.2</td>
<td>26.3</td>
<td>15.6</td>
<td>135.8</td>
<td>21.9</td>
</tr>
<tr>
<td></td>
<td>nEF</td>
<td>46.2</td>
<td>34.4</td>
<td>8.3</td>
<td>26.4</td>
<td>23.8</td>
<td>14.4</td>
<td>136.1</td>
<td>22.9</td>
</tr>
<tr>
<td></td>
<td>P</td>
<td>0.25</td>
<td>0.16</td>
<td>0.34</td>
<td>0.19</td>
<td>0.06</td>
<td>0.14</td>
<td>0.90</td>
<td>0.57</td>
</tr>
</tbody>
</table>

rEF, highly reduced EF; nEF, normal EF; PP, pulse pressure; p, peripheral; c, central; AP, augmentation pressure; P1, unaugmented pressure; P_fref, amplitude of the forward/backward traveling pressure wave derived from the Doppler flow; PP amp, PP amplification; AIx, augmentation index; RM, reflection magnitude derived from the Doppler flow.

Values are presented as mean ± SD (raw data) or estimated mean (adjusted data).

P-values for adjusted data indicate statistical significance of EF status in the ANCOVA analysis. *P < 0.05.
the basic characteristics of both groups, whereby significant differences in HR and ED could be observed. Parameters describing the pulsatile hemodynamics obtained by PWA and WSA using the Doppler derived flow, as well as the results of ANCOVA analyses to examine the influence of HR and ED on these parameters are given in Table 2 and Figure 2. Please note that four patients with reduced EF had to be partly excluded from the analysis because their AIx could not be determined.

The WSA parameters showed for all flow models that the calculated amplitudes of $P_f$ and $P_b$ were highly correlated ($r > 0.8$) with those obtained with the ultrasound derived flow in both groups. Mean values of $|P_f|$ and $|P_b|$ in the group with highly reduced EF were $24.6 \pm 8.0$ mmHg and $13.9 \pm 5.8$ mmHg respectively for the Doppler flow, $27.0 \pm 9.5$ mmHg and $13.8 \pm 6.2$ mmHg using the triangular flow, $21.9 \pm 7.8$ mmHg and $16.1 \pm 6.3$ mmHg when applying the averaged waveform and finally $23.4 \pm 8.0$ mmHg and $12.9 \pm 5.6$ mmHg for the modified WK flow. All results are given in detail in Table 3. Differences in $|P_f|$ and $|P_b|$ between modified WK and Doppler flow are also presented in a Bland–Altman plot in Figure 3.

Regarding the wave shapes, the RMSE between $P_f$ and $P_f^{ref}$ was lowest for the modified WK flow in both patient groups: $0.92 \pm 0.61$ mmHg for highly reduced and $0.76 \pm 0.49$ mmHg for normal EF. The averaged waveform resulted in a lower RMSE than the triangular flow for patients with normal EF ($0.92 \pm 0.47$ mmHg compared to $2.09 \pm 1.33$ mmHg), whereas for patients with highly reduced EF, the RMSE was very similar for the two flow estimates, see Table 3. Several Doppler flow waveforms and the corresponding flow estimates are also shown in Figure 4.

Comparison of the reference values $|P_b^{ref}|$ and $|P_f^{ref}|$ with respect to whether EF was normal or reduced revealed a significant difference in the amplitudes of the backward ($P = 0.02$), but not the forward traveling waves ($P = 0.68$). The same held for the modified WK flow, but neither for the averaged waveform, where $|P_f|$ but not $|P_b|$ was significantly different according to EF, nor for the triangular flow, where differences in $|P_f|$ and $|P_b|$ were both significant.
### Table 3. Comparison of blood flow models and Doppler flow.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Doppler flow</th>
<th>Triangular flow</th>
<th>Averaged flow</th>
<th>Modified WK flow</th>
</tr>
</thead>
<tbody>
<tr>
<td>RMSE flow (AU)</td>
<td>—</td>
<td>6.71 ± 2.21</td>
<td>9.12 ± 2.09*</td>
<td>5.68 ± 2.24*</td>
</tr>
<tr>
<td>$t_{\text{max/ED}}$ (%)</td>
<td>36.9 ± 7.4*</td>
<td>41.3 ± 7.5*</td>
<td>26.6 ± 1.0</td>
<td>33.0 ± 3.8*</td>
</tr>
<tr>
<td>RMSE $P_f$ (mmHg)</td>
<td>—</td>
<td>1.08 ± 0.83*</td>
<td>1.14 ± 0.62*</td>
<td>0.92 ± 0.61</td>
</tr>
<tr>
<td>$</td>
<td>P_f</td>
<td>$ (mmHg)</td>
<td>24.6 ± 8.0</td>
<td>27.0 ± 9.5*</td>
</tr>
<tr>
<td></td>
<td>[22.6,26.7]</td>
<td>[19.9,23.9]</td>
<td></td>
<td>[21.4,25.5]</td>
</tr>
<tr>
<td>$r(P_f^{ref} \text{versus }</td>
<td>P_f</td>
<td>$)</td>
<td>—</td>
<td>0.94 [0.90,0.96]</td>
</tr>
<tr>
<td>$</td>
<td>P_f</td>
<td>-</td>
<td>P_f^{ref}</td>
<td>$ (mmHg)</td>
</tr>
<tr>
<td>$P_{\delta}$ (mmHg)</td>
<td>13.9 ± 5.8*</td>
<td>13.8 ± 6.2*</td>
<td>16.1 ± 6.3</td>
<td>12.9 ± 5.6*</td>
</tr>
<tr>
<td></td>
<td>[12.4,15.4]</td>
<td>[12.2,15.4]</td>
<td>[14.5,17.8]</td>
<td>[11.4,14.3]</td>
</tr>
<tr>
<td>$r(P_{\delta} \text{versus } P_{\delta}^{ref})$</td>
<td>—</td>
<td>0.93 [0.89,0.96]</td>
<td>0.98 [0.96,0.99]</td>
<td>0.98 [0.97,0.99]</td>
</tr>
<tr>
<td>$</td>
<td>P_f</td>
<td>-</td>
<td>P_f^{ref}</td>
<td>$ (mmHg)</td>
</tr>
<tr>
<td>RM (%)</td>
<td>56.3 ± 11.7* [53.3,59.3]</td>
<td>50.4 ± 9.0* [48.1,52.7]</td>
<td>73.4 ± 6.9 [71.6,75.1]</td>
<td>54.0 ± 9.3* [51.6,56.4]</td>
</tr>
<tr>
<td>RMSE flow (AU)</td>
<td>—</td>
<td>6.54 ± 2.51</td>
<td>8.08 ± 1.26*</td>
<td>4.46 ± 1.94*</td>
</tr>
<tr>
<td>$t_{\text{max/ED}}$ (%)</td>
<td>27.4 ± 3.5*</td>
<td>34.6 ± 5.8*</td>
<td>26.4 ± 1.4</td>
<td>28.3 ± 2.4*</td>
</tr>
<tr>
<td>RMSE $P_f$ (mmHg)</td>
<td>—</td>
<td>2.09 ± 1.33*</td>
<td>0.92 ± 0.47*</td>
<td>0.76 ± 0.49</td>
</tr>
<tr>
<td>$</td>
<td>P_f</td>
<td>$ (mmHg)</td>
<td>24.7 ± 6.5</td>
<td>30.4 ± 8.7*</td>
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<tr>
<td></td>
<td>[23.5,25.8]</td>
<td>[28.8,32.0]</td>
<td>[22.9,25.2]</td>
<td>[23.4,25.6]</td>
</tr>
<tr>
<td>$r(P_f^{ref} \text{versus }</td>
<td>P_f</td>
<td>$)</td>
<td>—</td>
<td>0.89 [0.85,0.92]</td>
</tr>
<tr>
<td>$</td>
<td>P_f</td>
<td>-</td>
<td>P_f^{ref}</td>
<td>$ (mmHg)</td>
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<td>$P_{\delta}$ (mmHg)</td>
<td>15.2 ± 4.2*</td>
<td>16.7 ± 5.6*</td>
<td>17.3 ± 4.5</td>
<td>14.4 ± 4.2*</td>
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<td></td>
<td>[14.5,16.0]</td>
<td>[15.7,17.7]</td>
<td>[16.5,18.2]</td>
<td>[13.6,15.2]</td>
</tr>
<tr>
<td>$r(P_{\delta} \text{versus } P_{\delta}^{ref})$</td>
<td>—</td>
<td>0.83 [0.77,0.88]</td>
<td>0.96 [0.94,0.97]</td>
<td>0.96 [0.95,0.98]</td>
</tr>
<tr>
<td>$</td>
<td>P_f</td>
<td>-</td>
<td>P_f^{ref}</td>
<td>$ (mmHg)</td>
</tr>
<tr>
<td>RM (%)</td>
<td>62.1 ± 9.6* [60.4,63.8]</td>
<td>55.0 ± 9.1* [53.4,56.6]</td>
<td>72.4 ± 6.5 [71.2,73.6]</td>
<td>58.7 ± 9.1* [57.0,60.3]</td>
</tr>
</tbody>
</table>

$|P_f,b|$, amplitude of the forward/backward traveling pressure wave; ref, reference values obtained with the Doppler derived flow; $r$, Pearson’s correlation coefficient; RMSE, root mean squared error; $t_{\text{max}}$, time of maximum flow; RM, reflection magnitude.

Values are given as mean ± SD and listed intervals represent the 95% confidence intervals of the mean or the correlation coefficient.

* $P<0.05$ highly reduced versus normal EF.
Figure 3. Bland–Altman plots of $|P_f|$ (a, b) and $|P_b|$ (c, d) for patients with highly reduced (a, c) and normal EF (b, d) respectively.

Figure 4. Left: Comparison of the averaged Doppler flow waveform for patients with rEF (dashed line) and nEF (solid line) when scaled to an ED corresponding to the respective group mean. Right: Doppler flow curves (solid) and the corresponding triangular (dashed), averaged (dotted) and modified WK (dashed–dotted) estimates. The flow curve examples for patients with reduced EF are arranged such that their maximum is reached later from left to right and thus the averaged waveform deviates more and more, while the triangular as well as the WK flow adapt in shape. For patients with normal EF, the shapes of the Doppler flow curves resemble each other.
4. Discussion

In this study we examined parameters quantifying wave reflection obtained with WSA and PWA as well as the applicability of blood flow models in WSA in patients with impaired systolic function compared to controls.

Even though peripheral blood pressure levels were similar in both patient groups, central pulse pressure cPP was significantly lower in the reduced EF group, which is consistent with findings from Weber et al (2007). Also, augmentation pressure (AP) and Alx, commonly seen as a marker of aortic stiffness and wave reflection defined as the ratio of AP to cPP, were lower for patients with SHF in accordance with previous observations (Tartiere et al 2006, Weber et al 2007, Denardo et al 2010). A possible reason for these disparities can be sought in the increased HR and reduced ED that are characteristic for patients suffering from SHF. Adjustment for HR by ANCOVA indeed diminished the statistical significance of the differences in cPP (35.0 and 35.5 mmHg cPP, \( P = 0.79 \), for subjects with reduced and preserved EF respectively), while differences in the peripheral PP remained non-significant. Since the aortic waveforms and pressure values are derived non-invasively from radial recordings by a general transfer function and no differences in peripheral diastolic blood pressure (DBP) or systolic blood pressure (SBP) were evident between the EF groups, this HR dependence might be induced by arterial properties or the transfer function itself. The lower values of Alx, in contrast, could not be fully explained by HR in the ANCOVA analysis. However, by using ED and HR as covariates, the EF status became a non-significant factor. The same held for the PP amplification, the ratio of peripheral PP to cPP. Although ED is linearly related to HR (Wilkinson et al 2000), recent results show that ED provides additional information and prognostic value not contained in HR (Haiden et al 2014). Moreover, Wilkinson et al (2000) already suggested that the impact of HR on Alx is mainly due to the associated changes in ED, which is consistent with results from Sharman et al (2009) who found that ED was the strongest independent correlate of Alx in patients undergoing dobutamine stressed echocardiography. These considerations corroborate the observed effect of ED on Alx in the present study. Our results therefore indicate that, as proposed before (Westerhof and O’Rourke 1995, Sharman et al 2009), the decrease in Alx in patients with SHF might be caused by the altered interplay of the weakened heart and the vascular system and the resulting reduction in ED. Further investigation is certainly needed to clarify these relations.

The WSA parameter \( P_{\text{ref}} \), the amplitude of the forward traveling pressure wave obtained with the Doppler flow, was very similar for both patient groups. One reason for this might lie in the way \( P_t \) is derived: By considering flow in the computation, the left ventricular function is, to some degree, implicitly already accounted for. The amplitudes of the backward traveling wave \( |P_{b}\| \) as well as the reflection magnitude (RM) defined as the ratio of \(|P_b|\) to \(|P_f|\), on the contrary, were significantly lower for patients with reduced EF compared to controls. However, when adjusted for HR, these differences evened out. Considering that the generated central pressure pulse is affected by HR as well, this seems to imply that the magnitude of wave reflection assessed by WSA might actually be comparable for patients with impaired systolic function and controls, as already suggested by previous results obtained from invasive measurements (Laskey and Kussmaul 1987).

When comparing the two approaches PWA and WSA, a similar behavior of the PWA parameters \( P_1 \) and AP and the WSA parameters \(|P_f|\) and \(|P_b|\) could be observed. However, the corresponding relative measures of wave reflection, Alx and RM, showed qualitative differences regarding the influence of HR and ED. Nevertheless, after adjusting for HR and ED, all parameters of wave reflection were similar for both the two paradigms and the two groups of patients, as shown in figure 2.
The three blood flow models as well as the derived WSA parameters have been investigated earlier by Hametner et al (2013a) in a cohort with preserved EF. They reported a good agreement between modified WK and Doppler flow and found the WSA parameters derived with the WK flow to be comparable to those using the averaged waveform, both being favorable to the triangular approximation. We found the same relations in our control group. With reference to the values characterizing the shapes of the flow curves given in table 3, the position of the maximum therefore seems to be an important indicator for the performance of the blood flow models in WSA as shown in figure 4. For patients with reduced EF, the modified WK flow still provided acceptable results and the triangular estimate outperformed the averaged waveform. The latter might have been expected, considering that Kips et al (2009) used measured flow patterns of middle-aged, healthy subjects to generate the averaged flow wave, whereas patients developing SHF often show modified ejection patterns with a concave form and a late maximum (Nichols et al 2011). Nevertheless, the corresponding amplitudes of the forward and backward travelling waves were still highly correlated with the reference values. The delayed maximum might also be the reason why the triangular curve provides a better approximation for patients with impaired systolic function than for healthy subjects. The maxima of Doppler and triangular flow were closer aligned for the lower EF group than for controls, thus indicating that the time of the inflection point in the pressure signal might coincide better with the moment of maximum flow for patients with SHF. Comparison of the results obtained in both patient groups suggests that a flow model with the capability to change in shape might be preferable for the use in a general population.

Overall, the WK flow was the only blood flow estimate that resulted in the same qualitative and quantitative behavior as the Doppler flow independent of the EF status, including a remarkable similarity in the variances of $|P_f|$ and $|P_b|$. Moreover, no obvious relation between the differences and the magnitude of $|P_f|$ or $|P_b|$ derived with the modified WK flow with respect to the reference method was evident in the Bland–Altman plots, and the limits of agreement in $|P_b|$ were very similar for both patient groups, see figure 3. A reason for the wider scatter seen in $|P_f|$ for patients with SHF might again be the shape of the flow pattern, since $|P_f|$ is strongly dependent on the timing of maximal flow. Nevertheless, neither $|P_f|$ itself nor the RMSE differed significantly from controls. For the triangular flow, the predictive power of $|P_b|$ for the occurrence of cardiovascular events has already been demonstrated in patients with preserved and reduced EF in a cohort suffering from acute heart failure syndrome (Sung et al 2012). Our results suggest that the use of a flow approximation based on mathematical models might improve the wave separation compared to the triangle and thereby, hopefully, also the impact of the derived parameters for both, patients with impaired and normal systolic function. Yet these results have to be confirmed in larger cohorts, ideally with invasive data as reference.

4.1. Limitations

The exclusive use of non-invasive data in our study has to be stated as one of the main limitations. Moreover, the arterial pressure waveforms were generated from peripheral pressure readings via a general transfer function and, as addressed earlier, the Doppler ultrasound velocity profiles were digitized manually to obtain the flow waveforms. These are both possible sources of errors and should be kept in mind when interpreting the results. Another limitation is the low proportion of women included in this study and that gender differences could therefore neither be investigated nor accounted for.
4.2. Conclusion

In conclusion, our results indicate that the non-invasive assessment of WSA parameters either from pressure and flow measurements or from pressure alone by means of blood flow models is feasible in patients with reduced EF. Replacing flow measurements with estimates derived from the pressure wave would greatly reduce the costs and complexity involved and could therefore facilitate the quantification of wave reflections by central WSA in large population studies. Further studies need to show the clinical impact.

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