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Pressure difference estimation in nonstenotic carotid bifurcation phantoms using vector flow imaging.

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Abstract

Local pressure differences estimated using vector flow imaging (VFI) and direct catheterization in seven carotid bifurcation phantoms were compared with simulated pressure fields. VFI correlated strongly with simulated peak pressure differences ($r=0.99$, $p<0.00001$) with an average overestimation of 12.3 Pa (28.6%). The range between the lowest and highest pressure difference of VFI underestimated simulations by 4.6 Pa (8.06%) ($r=0.99$, $p<0.0001$). The catheter method showed no correlation ($r=-0.09$, $p=0.85$). Ten repeated measurements on one phantom showed a small standard deviation (SD) for VFI (SD 8.4%; mean estimated SD 11.5%), but not for the catheter method (SD 785.6%). An in vivo peak systolic pressure difference of 97.9 Pa (estimated SD 30%) was measured using VFI in one healthy individual. This study demonstrated that VFI pressure difference estimation was feasible in phantoms and in vivo and realistic estimate of the SD could be attained from the data.

Keywords

Pressure difference estimation, ultrasound, vector flow imaging, fluid-filled pressure catheter, computational fluid dynamics, fluid-structure interaction, carotid bifurcation
Introduction

The heart and blood vessels make up the circulatory system and facilitate the distribution of nutrients to the cells in the body. The blood vessels branch out into complex shapes with varying diameters, and the high arterial blood flow velocities can cause the flow fields to become complex (Secomb 2016). Complex blood flow may also be associated with local vessel pathology (Markl et al. 2011), and advanced evaluation of the hemodynamics may be helpful for identifying vascular diseases. Pressure differences are routinely estimated noninvasively using ultrasound when assessing the severity of cardiovascular diseases (Baumgartner et al. 2017; Warnes et al. 2008), but the current clinical reference standard for evaluating intravascular hemodynamics is using fluid-filled pressure catheters (Baumgartner et al. 2017; Feltes et al. 2011; Nishimura and Carabello 2012). However, endovascular catheterization is an invasive and time-consuming procedure associated with various complications, and ionizing radiation is required for guidance of the catheter (Mermel 2000; Omran et al. 2003). Additionally, the catheter itself interferes with the flow field, which may impact the measurements (de Vecchi et al. 2014). As a result, noninvasive and nonionizing alternatives are preferred. Spectral Doppler ultrasound can be used to estimate intravascular pressure differences noninvasively from peak flow velocities by using the simplified Bernoulli equation (Yoganathan et al. 1988). However, the accuracy of this method is limited, as it ignores the full complexity of hemodynamics (Donati et al. 2017; Garcia et al. 2000). Furthermore, velocity estimation with spectral Doppler ultrasound is susceptible to error due to inaccurate beam-to-flow angle adjustments (Hatle et al. 1980; Lui et al. 2005).

An alternative to the conventional spectral Doppler ultrasound method could be vector flow imaging (VFI). It is an angle-independent blood flow estimation method for ultrasound, which enables real-time visualization of the 2-D velocity vector field (Anderson 1998; Jensen and Munk 1998), thereby allowing more advanced evaluation of flow to be performed compared with conventional ultrasound. With this method, pressure difference estimation can be performed along an arbitrarily defined line by using the
unsteady Bernoulli equation (Nguyen et al. 2019; Olesen et al. 2014; Olesen et al. 2018), rather than a single velocity measurement. The pressure difference was obtained along the defined line in space at every time frame over multiple flow cycles.

We aimed to evaluate the accuracy and repeatability of the VFI approach for estimating intravascular pressure differences in the carotid bifurcation. For this purpose, seven carotid bifurcation phantoms were scanned with VFI and catheterized. The results were compared with computer simulated flow data from the same phantoms, and the simulated pressure differences were used as the reference standard for both VFI and the catheter measurements. Furthermore, a peak systolic pressure difference (systolic $\Delta P$) was obtained with VFI in one healthy volunteer to evaluate if the technique was transferable to in vivo use. We hypothesized VFI to be more accurate and more precise than the conventional and invasive catheter approach.

Materials and Methods

Volunteers

Magnetic resonance imaging (MRI) data of seven carotid bifurcations obtained by Holbek et al. (2017) were used to manufacture seven carotid bifurcation phantom models. The study was approved by the Danish National Committee on Biomedical Research Ethics (ethics: journal nr. H-1-2014-FSP-072), and informed and written consent were obtained from all volunteers. The volunteer data consisted of one female and six males with an average age of 32.9 years. Additionally, one healthy volunteer (male, 46) was scanned with VFI for this study as an in vivo example (ethics: journal nr. H-19035605). MRI was not performed on the healthy volunteer.
**Phantoms**

The manufacturing process of the seven phantoms is described in previous papers (Lai et al. 2013; Olesen et al. 2018). Briefly, the lumen of the carotid artery segmented from MRI data originated from the seven healthy volunteers. Each segmented lumen was redesigned with appropriate extensions using computer aided design (CAD) in SolidWorks (Dessault Systemes, Vélizy-Villacoublay, France) and fixed in an in-house designed container suitable for mounting in the experimental setup for VFI data acquisition. After mounting the core in the container, it was casted in polyvinyl alcohol (PVA) cryogel to mimic the mechanical behavior of human tissue. After the casting procedure had ended, the lumen was removed, and the result was a wall-less phantom model replica of the carotid bifurcation geometry (Fig. 1). The final dimensions of the surrounding PVA cryogel block were in all cases 160 x 90 x 65 mm. The diameter of the common carotid artery varied for all seven models, as these were obtained from seven different volunteers. Each of the seven phantoms was connected to a flow system (CompuFlow 1000, Shelley Medical Imaging Technologies, Toronto, Canada) that induced a time-varying waveform to the blood-mimicking fluid (BMF-US, Shelley Medical Imaging Technologies, Toronto, Canada) (Ramnarine et al. 1998). The flow was set to simulate an in vivo carotid waveform with a peak volume flow of 25 mL/s for all seven phantoms (Fig. 2).

**Catheterization**

A 4-French fluid-filled catheter (Mariner, AngioDynamics Netherlands BV, BR Amsterdam, Netherlands) was connected to a pressure monitor (IntelliVue X2, Philips Medizin Systeme, Boeblingen, Germany) before it was introduced to the phantom through an arterial sheath. The catheter-tip was navigated to the common carotid artery under B-mode ultrasound guidance. The pressure transducer was zeroed in accordance with local guidelines for intravascular pressure measurements. The three-way stopcock near the catheter was closed to isolate the pressure transducer from the phantom flow environment. A three-way stopcock near the pressure transducer was opened to the air to equalize the pressure to atmospheric
pressure. The pressure transducer was placed in level with the phantom and zeroing was initiated by selecting the “Zeroing”-option in the menu on the monitor. The three-way stopcock remained open to atmospheric pressure during the procedure. After zeroing, a flat horizontal pressure curve was displayed on the pressure monitor, and both three-way stopcocks were opened to the phantom flow. The first pressure measurement was performed in the common carotid artery of the phantom. The monitor updated the diastolic and peak systolic pressure readings every one or two flow cycles, and a diastolic and peak systolic pressure was noted when it had stabilized. Pressures were measured in mmHg. Subsequently, the catheter was navigated to the carotid bulb, where a second measurement was noted without prior re-zeroing. To assess repeatability, 10 peak systolic pressures were alternately measured in the common carotid artery and the carotid bulb in carotid phantom #2 with re-zeroing being performed between each data set.

Vector flow imaging

VFI data were acquired on a modified commercial ultrasound scanner (bk5000, BK Medical Aps, Herlev, Denmark) using a linear transducer (8L2, BK Medical Aps, Herlev, Denmark). The handheld transducer was positioned to fit the carotid bifurcation inside the VFI color box with the carotid bulb in the center. Aliasing was visually identified on the scanner display, and the pulse repetition frequency (PRF) was set to the lowest setting without aliasing for each individual phantom to ensure the best possible estimation of the velocities (PRF range: 1.3 – 3.0 kHz). A VFI sequence of 13 seconds was obtained at a framerate of 30 frames per second for each phantom and stored on the scanner. Additionally, 10 consecutive acquisitions were obtained in carotid phantom #2 to assess repeatability.

The VFI data were processed and analyzed using an in-house built program in MATLAB (MathWorks, Natick, MA, USA) on an offline workstation (Moshavegh et al. 2016). A line was drawn between the common carotid artery and carotid bulb (Fig. 3), where the start and end of the line approximated the positions of the catheter measurements, which were obtained just prior to the VFI acquisition. Between the
start and end points, two to four “guiding points” were inserted to bend the line, allowing it to follow the flow vectors. In principle, the line could be drawn arbitrarily, because VFI data were available everywhere inside the VFI color box. The unsteady Bernoulli equation was used to estimate the pressure difference along the line (Olesen et al. 2018),

\[
\Delta P(t) = -\rho \left[ \frac{v_s^2(t) - v_{s1}^2(t)}{2} + \int_{l_1}^{l_2} \frac{\partial v_s(t)}{\partial t} ds \right],
\]

where \(\Delta P(t)\) (Pa) is the summed pressure difference along the line between the start- and endpoint, \(l_1\) and \(l_2\) in an isolated frame of velocity vectors at time \(t\), \(\rho\) (kg/m\(^3\)) is the fluid density, and \(v_s(t)\) (m/s) is the magnitude of the velocity along the line. The VFI setup acquired velocity vectors in two dimensions, and the third out-of-plane velocity vector was assumed to be negligible. Quantitative estimations of \(\Delta P\) were processed from the data, and a pressure difference graph was produced with a legend box listing the median pressure difference at peak systole. Incomplete flow cycles, such as at the beginning and end of an acquisition or “fragmented” flow cycles due to movement of the transducer, were automatically discarded from the pressure difference analysis. For each analysis, a standard deviation (SD) of the systolic \(\Delta P\) and diastolic pressure difference (diastolic \(\Delta P\)) was reported as an “estimated SD”. The estimated SD was calculated based on the variations of the measured pump or heart cycles. The pressure curves for the cycles were aligned and the median pressure curve was found. A mean estimated SD across the different measurements was calculated from the estimated SDs. For the ten repeated measurements, an SD of the median systolic \(\Delta P\) results was calculated as well. Additionally, the range between the lowest median diastolic \(\Delta P\) and the median systolic \(\Delta P\) was defined as the “cyclic range” (systolic \(\Delta P\) – diastolic \(\Delta P\)). For the catheter, the range between the pressure difference during diastole and pressure difference during systole was used to calculate the cyclic range. VFI estimations were performed blinded from the catheter estimations and computer simulations.
In vivo experiment

The carotid bifurcation of one healthy volunteer (KLH) was scanned with VFI on a modified commercial ultrasound scanner (bk5000, BK Medical Aps, Herlev, Denmark). The linear transducer (8L2, BK Medical Aps, Herlev, Denmark) was positioned to fit the carotid bifurcation inside the VFI color box. Data were acquired for 12 seconds at a frame rate of 30 frames per second and PRF 4.2 kHz. The data were processed and analyzed in the same program and workstation as the VFI data of the phantoms. A line was drawn between the common carotid artery and carotid bulb (Fig. 4) to measure the pressure difference between the two locations using equation (1).

Computational fluid dynamics simulations

The arterial lumen in the flow simulation models was the same as the one used for the fabrication of the corresponding experimental phantom. Additionally, a block of solid material surrounding the lumen, mimicking the PVA cryogel material in the experimental models, was added to each of the seven simulation models. No flow simulation was performed for the healthy volunteer since MRI was not obtained.

The fluid flow in the computational simulation model of the flow is governed by the Navier-Stokes equation,

\[ \rho_f \left( \frac{\partial \vec{v}(l, t)}{\partial t} + \vec{v}(l, t) \cdot \nabla \vec{v}(l, t) \right) = -\nabla p(l, t) + \eta \nabla^2 \vec{v}(l, t) + \rho_f \vec{g}, \]

where \( \vec{l}(x, y, z) \) is the spatial position in the model, \( \vec{v}(l, t) \) is the computed velocity field, \( p(l, t) \) is pressure, and \( \vec{g} \) is gravity. The physical quantities for mass density and viscosity of the blood-mimicking fluid (Ramnarine et al. 1998) are given in Table 1. The surrounding tissue mimicking material was modelled as a
Neo-Hookean hyper-elastic material with the shear modulus derived from Youngs modulus, $E$ (Chee et al. 2016), and Poisson’s ratio $\nu$ (Holzapfel 2000). The material properties are provided in Table 1.

The inlet to the fluid domain was modelled using the measured spatial mean velocity across the vessel diameter. This was obtained for 10 flow cycles, and the velocity profile is based on the mean across these after alignment of the 10 flow cycles. The profile was used to reconstruct a smooth and continuous velocity field. The velocity field is a function of time and space based on the Womersley-Evans model (Evans 1982; Womersley 1955),

$$v(r, t) = 2v_0\left(1 - \frac{r^2}{R^2}\right) + \sum_{m=1}^{\infty} |V_m| |\psi_m| \cos(\omega m t - \phi_m + \chi_m),$$  \hspace{1cm} (3)

where the first term is steady flow with a parabolic profile and $v_0$ is the spatial mean velocity. The last term is the superpositioning of the hamonics, $V_m$, of the spatial mean velocity multiplied by the function $\psi_m$, describing how the velocity changes with time and position over one period for each harmonic (Evans 1982). $\psi_m$ depends on the radial position, $r$, in the artery, the angular frequency, $\omega = 2\pi f$, and the properties of the blood-mimicking fluid. The outlet conditions were set to a pressure of 0 Pa, hence the impedance from the downstream tubing was omitted for simplification. The interacting fluid-structure boundary between the lumen and PVA cryogel allows the artery to pulsate according to the applied physiological flow profile. The boundary movement is fully coupled and handled by an Arbitrary Lagrange-Eulerian (ALE) implementation in the numerical solver (COMSOL Multiphysics Reference Manual, Version: COMSOL 5.4, © 1998-2018 COMSOL). For the solid part, the outer surfaces of the block of PVA cryogel were fixed.

All computational flow simulations were carried out using COMSOL Multiphysics (Comsol AB, Stockholm, Sweden). The numerical solutions were obtained using the built-in solvers MUMPS (Multifrontal Massively Parallel Sparse Direct Solver) for the solid mechanics, and PARDISO (Partial Direct Sparse Solver).
for the fluid dynamics. The fluid-structure interaction was handled by GMRES (Generalized Minimum Residual method). The models were meshed according to standard meshing algorithms defined in COMSOL Multiphysics which were optimized to the applied physics. The seven individual finite element models consisted of 150,886 to 221,274 elements. Each model was solved using the central DTU High Performance Computing Cluster (Lenovo ThinkSystem SD530 with 2x Intel Xeon Gold 6126 CPUs per node).

Statistical analysis

Data were analyzed with descriptive statistics. The linear relationship between the three methods was assessed with a Pearson's product-moment correlation coefficient in the statistical programming software, R (R Foundation for Statistical Computing, Vienna, Austria), and a $p$-value $< 0.05$ was considered as being statistically significant.

Results

Phantom experiment

Diastolic $\Delta P$, systolic $\Delta P$, and cyclic ranges measured using the catheter, VFI, and computational fluid dynamics simulations are listed in Table 2. For VFI, an average of 12.7 flow cycles (range: 11 – 14) were analyzed within the 13 seconds of recorded data. Simulated flow and VFI measured pressure increases in all phantoms, while the fluid-filled pressure catheter measured no pressure difference in two, a pressure increase in three, and a pressure drop in two of the phantoms.

On average, the catheter method underestimated the simulated systolic $\Delta P$ by 4.9 Pa (-11.4%), but showed no significant linear correlation ($r = -0.09$, $p = 0.85$). The VFI method overestimated the simulated systolic $\Delta P$ by 12.3 Pa (28.6%) and showed a strong correlation ($r = 0.99$, $p < 0.00001$). However, four of the
seven catheter systolic $\Delta P$ were measured to be either zero or below. When the root mean square was calculated, the catheter method overestimated the simulated systolic $\Delta P$ by 194.3 Pa (269.7%), whereas VFI overestimated the simulated systolic $\Delta P$ by 9.8 Pa (18.6%). Similarly, the root mean square of the discrepancies between the methods was 248.5 Pa for the catheter and 12.9 Pa for VFI. Using all flow cycles, the mean estimated SD across the seven phantoms was 16.1% (8.9 Pa) for VFI and 3.0% (1.3 Pa) for simulated flow. A similar estimate could not be calculated for the catheter measurements.

Graphs for the median pressure difference across the flow cycles obtained with VFI and simulated flow are shown in Fig. 5. Scatter plots and Bland-Altman plots of the systolic $\Delta P$ using the catheter and VFI are plotted against simulated flow in Fig. 6. Quantitatively, all pressure difference curves obtained using VFI measured higher pressure differences compared with the simulated flow models. Qualitatively, they followed the same overall trend throughout the flow cycles. Prominent second peaks were observed in four phantoms with VFI and five with the simulated flow. Phantoms without a second peak presented a slow and gradual decline from the first peak. There was a rapid decrease in pressure difference immediately before the peak systole in all flow simulations, whereas only a small decrease was observed in two VFI graphs.

For the cyclic ranges, VFI underestimated the simulation by 4.6 Pa on average and showed a strong linear correlation ($r = 0.99$, $p < 0.0001$). This corresponds to an accuracy of 8.06% relative to the simulated flow and is within the estimated SD of 8.9 Pa found across the seven phantoms. The catheter method correlated strongly with the simulated flow ($r = -0.78$, $p = 0.04$), but had a wide 95% confidence interval for the correlation coefficient ([−0.97; −0.06]). The average overestimation of the cyclic range was 152.4 Pa, which corresponds to an accuracy of 266.9% relative to the simulated flow. Scatter plots and Bland-Altman plots of the cyclic ranges are illustrated in Fig. 7.

The results for 10 repeated catheter and VFI measurements in Carotid 2 are listed in Table 3. On average, the pressure catheter measured a pressure decrease of -133.3 Pa between the common carotid artery and the carotid bulb with an SD of 785.6%. VFI measured a small average pressure increase of 31.7 Pa
with an SD of 8.4%. The mean estimated SD for VFI was 11.5% (3.7 Pa), thereby showing good agreement with the measured SD in this experiment (8.4%) and the estimated SD from the single measurements (16.1%).

In vivo experiment

The in vivo pressure difference graph obtained on a healthy volunteer with VFI is illustrated in Fig. 8. The systolic $\Delta P$ of 97.9 Pa (estimated SD 30%) was within the range of the phantoms and slightly above the highest systolic $\Delta P$ among the simulations, Carotid 5 (97.2 Pa). The diastolic $\Delta P$ was -8.3 Pa, resulting in a cyclic range of 106.2 Pa which was slightly above the simulated range in Carotid 5 (106.0 Pa). The pressure difference curve for the first peak resembled the patterns observed in the phantoms, but the second peak was barely noticeable. Also, the decrease in pressure difference after the first peak was less gradual compared with the phantoms.

Discussion

The noninvasive VFI method measured a pressure difference in all phantoms with the same order of magnitude as the computer simulated flows. VFI had high repeatability and accuracy with strong correlations, albeit with an average overestimation of 12.3 Pa of the systolic $\Delta P$ compared with the simulations (Table 2 and Fig. 6A and B). The pressure difference curves obtained with VFI in combination with the unsteady Bernoulli equation followed the same trends as those obtained in simulations (Fig. 5). When the cyclic ranges were compared, VFI underestimated the simulations by 4.6 Pa with a relative accuracy of 8.06%. The VFI method had a mean estimated SD of 11.5% for repeated measurements in a single phantom. This was in the same order of magnitude as the measured SD of 8.4% across the seven phantoms, indicating that the estimated SD was a reliable measure of the variance. The in vivo VFI scan was
also in line with the phantoms, thereby confirming the feasibility of in vivo pressure difference estimation with this method. These results contribute to the findings of earlier studies (Nguyen et al. 2019; Olesen et al. 2014; Olesen et al. 2018) by demonstrating that the method can estimate small pressure differences in nonstenotic carotid bifurcations with various different geometries. The catheter method was less reliable and measured systolic $\Delta P$ drops in two phantoms, despite no negative systolic $\Delta P$ being simulated in any of the phantoms. This method showed no correlation with the simulations and there was a large discrepancy in most of the individual phantoms (Table 2). Also, the ten repeated measurements in a single phantom produced pressure differences with a large SD. The cyclic range of the catheter measurements overestimated the simulated flow by 152.4 Pa, which equals to about 1.1 mmHg. This may have been caused by the low sensitivity of the pressure catheter setup used in this study. A more sensitive catheter method usable in the relevant pressure range should be used for future validation studies. Nevertheless, these results were unexpected and experimental flaws cannot be dismissed.

Endovascular catheterization is referred to as the clinical reference method for measuring pressure differences (Baumgartner et al. 2017; Feltes et al. 2011; Nishimura and Carabello 2012) and associated with a low morbidity and mortality rate (Al-Hijji et al. 2019; Arif et al. 2016). However, the invasive nature makes it an undesired procedure unless noninvasive data acquisition is inadequate (Nishimura et al. 2014). Additional flow information obtained with VFI could potentially reduce the number of patients needing to undergo diagnostic catheterization.

The pressure difference graph provided by VFI includes a time curve for the entire flow cycle and a standard deviation for the measurement. The location of measurement is clearly seen with VFI, whereas the exact location of the catheter-tip may be more challenging to determine and document during fluoroscopy. As a noninvasive ultrasound approach, VFI is safer, less time consuming, and uses no ionizing radiation. Blood flow velocity and volume flow are estimated with high precision (Bechsgaard et al. 2017; Brandt et al. 2016), and the acquired data can be revisited for further analysis if needed.
One limitation of the VFI method used in the current study is the need for a continuous flow line through the 2-D vector field. Therefore, it cannot measure correctly in aliased flow, where vectors are reversed and the flow line discontinued. Another limitation is its feasibility in complex flow where the out-of-plane component may be significant, but is omitted by the algorithm (1), thus decreasing accuracy as discussed by Olesen et al. (2018). As such, pressure difference estimation with VFI may be challenging in tortuous vessels or vascular pathologies, where flow complexity may be increased (Markl et al. 2011; Olesen et al. 2018).

The simplified Bernoulli equation estimates an intravascular systolic $\Delta P$ based on a single peak velocity estimate (Donati et al. 2017; Yoganathan et al. 1988). However, this method comes with various limitations. Firstly, the prestenotic velocity is assumed to be negligible compared with the distal velocity and is omitted from the calculation (Yoganathan et al. 1988). This situation may occur in stenotic vascular diseases, but one study reported poor correlation between the systolic $\Delta P$ measured using the Doppler method and direct catheterization in patients with carotid stenosis (Illig et al. 1996). Velocities acquired with spectral Doppler ultrasound are susceptible to being incorrect due to erroneous assumptions of the peak velocity direction (Hatle et al. 1980; Lui et al. 2005). An angle error of 5 degrees at a 60 degree Doppler angle can result in an approximately 18% velocity estimation error (Holland et al. 1998). The VFI method bypasses this issue by being angle independent. Additionally, the VFI method used in the current study did not use the simplified Bernoulli equation, but the unsteady Bernoulli equation (1). This allowed pressure differences throughout the entire flow cycle to be estimated and averaged across more than 10 consecutive cycles. Here, the pressure difference is obtained along any arbitrary drawn line for each frame, as VFI provides flow data for everywhere inside the VFI box. This enabled pressure difference estimation to be performed between two precisely known locations and in an environment with small velocity differences, such as in nonstenotic carotid bifurcations (Blackshear et al. 1980; Kochanowicz et al. 2009). Also, data can be analyzed retrospectively, and the estimated SD can be found indicating the precision of the attained estimate.
The catheter method used in the current study was unable to correctly measure the small pressure differences in the carotid bifurcation phantoms. Large discrepancies were observed in the repeated tests, making the catheter appear as an unreliable method in this setup. Invasive catheterization changes the original flow conditions and narrows the available lumen, and fluid-filled catheters have been reported to measure inaccurately compared with thinner pressure wires and microcatheters (de Vecchi et al. 2014; Imbesi and Kerber 1999). Furthermore, one study omitted catheterization completely and reported agreement between pressure differences measured through perpendicularly located pressure valves and numerically simulated values in stenotic phantoms (Bertolotti et al. 2006). Phase-contrast MRI is often regarded as the “gold standard” for in vivo flow estimation (Andersson et al. 2016; Dyverfeldt et al. 2015; Sohns et al. 2015), and future studies could use MRI as a reference for pressure difference measurement instead of a catheter.

When comparing the obtained pressure difference waveforms of VFI and simulated flow, the simulation model produced negative pressure differences during the flow cycles (Fig. 5). In all cases, a negative pressure difference value was observed just prior to the systole. This may be explained by the simulation model not having downstream impedance applied to the outlets, which influenced the pressure waveforms. Additionally, the material properties used for the PVA cryogel material in the simulations were adapted from literature (Chee et al. 2016). Discrepancies in the material properties used in the simulations and the elastic recoil of the experimental phantoms would also result in different waveforms.

Limitations

This study has several limitations. The pressure monitor system was designed to measure pressure differences in human individuals and could only measure in increments of +/- 1 mmHg (133.3 Pa), which was above the scale of the pressure differences estimated in the phantoms with the computer simulations. A more sensitive monitor system and an experimental setup similar to Bertolotti et al (2006) could have
resulted in better agreement with simulated flow, but would also no longer be as representative of catheterized pressure measurements. Still, the catheter measurements in our study were unreliable and experimental flaws such as suboptimal catheterization technique or faulty equipment cannot be dismissed. Dampening of the pressure wave going through the catheter may play a significant role at this scale of pressure difference. The sample size was small and future studies should include more volunteers and phantoms. The start and end points of the lines in both simulated flow and VFI were not co-registered with the catheter-tip, but positioned individually by free-hand guided by vessel geometry and the flow vectors visualized using VFI. Hence, deviations between the drawn lines, when comparing pressure differences obtained using simulations and VFI, may partly explain the discrepancies in pressure differences and pressure difference curves. Furthermore, since the line was drawn by an operator and not fully automatic, redrawing the line on the same VFI acquisition could result in a slightly different selection, which could influence the estimated pressure difference and estimated SD. The significant oscillation of the pressure difference curve in the simulated results compared with VFI can be due to the simplification of the outlet condition in the simulation models. The simplification corresponds to neglecting the peripheral resistance present in the cardiovascular system. Meanwhile, this resistance was present in the experimental setup with the phantoms. To reduce these oscillations in the simulations, a Windkessel model can be implemented as the outlet condition for providing the outlet flow resistance. The inlet boundary conditions of the computer simulations were based on velocities obtained using VFI. Therefore, results obtained with VFI and simulated flows were not completely independent. Another limitation was that VFI data were acquired handheld, which likely increased the variation of the repeated measurements, but at the same time represents the performance to be expected in the clinic. Finally, we compared a noninvasive 2-D method and direct catheterization with simulated fluid flow in full 3-D, and discrepancies were to be expected between the three methods.
Conclusion

VFI offers a noninvasive approach for a quick and safe estimation of intravascular pressure differences. It produces similarly trending pressure difference graphs when compared with computer simulations. Any line can be selected retrospectively from the data, and the method also indicates the attainable standard deviation. This study showed the feasibility of \textit{in vivo} VFI measurement of small pressure differences in nonstenotic carotid bifurcations. Future studies could include investigation of carotid flow in individuals with essential hypertension, and further development could potentially allow pressure difference measurement in other vascular geometries.

Conflicts of interest

Jacob Bjerring Olesen and Ramin Moshavegh are employed at BK Medical Aps. Jørgen Arendt Jensen developed and patented the vector flow imaging technique.
Reference list


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Figure caption list

Fig. 1: B-mode ultrasound of carotid phantom #6 fabricated using geometries based on MRI data of one healthy individual. The common carotid artery (left) branches into the internal (top right) and external carotid artery (bottom right). The carotid bulb is centered in the image.

Fig. 2: The programmed volume flow waveform delivered by the flow system. The volume flow at peak systole was 25 mL/s and the length of the cycle was 0.83 seconds.

Fig. 3: VFI of carotid phantom #6 at PRF 2.1 kHz at peak systole. The colors indicate the direction of flow according to the color wheel in the bottom right corner, and arrows have been superimposed onto the image to ease interpretation. The velocity value above the color wheel indicates the highest measureable velocity for the selected PRF. A pressure difference is measured along a line drawn between the common carotid artery (start point, L1) and carotid bulb (end point, L2).

Fig. 4: VFI of the carotid bifurcation at peak systole in one healthy volunteer. Blood is flowing from the common carotid artery (right side) and branches into the internal carotid artery (top left) and external carotid artery (bottom left). The colors indicate the direction of flow according to the color wheel in the bottom right corner, and arrows have been superimposed onto the image to ease interpretation. The velocity value above the color wheel indicates the highest measureable velocity for the selected PRF. A vortex is formed in the carotid bulb located at the entrance to the internal carotid artery. A pressure difference was measured along a yellow line drawn in the arterial lumen.
Fig. 5: Comparison of the estimated median VFI (yellow) and simulated (blue) pressure difference variation over the flow cycle for the seven carotid bifurcation phantoms (Carotid 1-7). The pressure differences were estimated along an arbitrary line as seen in Fig. 3. The greyed area is the standard deviation for VFI throughout the cycles. “Plus”-symbols mark the highest and lowest median pressure difference for VFI (red) and simulated flow (blue). The legend boxes list the median pressure differences at peak systole for VFI.

Fig. 6: Scatter plots and Bland-Altman plots of systolic and diastolic $\Delta P$ for VFI (A through D) and the catheter method (E through H) plotted against simulated flow. The error bars in Fig 6A and 6C indicate the estimated standard deviation of each of the VFI measurements. A line of equality is inserted as a dotted line in each of the scatter plots. In the Bland-Altman plots, the dotted line represents the mean bias and the two dashed lines represent the upper and lower limits of agreement.

Fig. 7: Scatter plots and Bland-Altman plots of the cyclic ranges for VFI (A and B) and the catheter method (C and D) plotted against simulated flow. A line of equality is inserted as a dotted line in each of the scatter plots. In the Bland-Altman plots, the dotted line represents the mean bias, the two dashed lines represent the upper and lower limits of agreement, and the fully drawn line represents a mean bias of zero.

Fig. 8 Median pressure difference (yellow line) and standard deviation (greyed area) across 11 cardiac cycles between the common carotid artery and carotid bulb in one healthy individual as represented in Fig. 4.
Table 1. Material parameters for blood mimicking fluid and Poly Vinyl Alcohol cryogel applied in the computational simulation models.

<table>
<thead>
<tr>
<th>Parameter description</th>
<th>Symbol</th>
<th>Unit</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mass density of blood-mimicking fluid</td>
<td>( \rho_f )</td>
<td>kg/m(^3)</td>
<td>1,030</td>
</tr>
<tr>
<td>Viscosity of blood mimicking fluid</td>
<td>( \eta )</td>
<td>Pa(\cdot)s</td>
<td>0.004</td>
</tr>
<tr>
<td>Youngs modulus of PVA cryogel</td>
<td>( E )</td>
<td>Pa</td>
<td>106.1(\cdot)10(^3)</td>
</tr>
<tr>
<td>Poisson’s ratio of PVA cryogel</td>
<td>( \nu )</td>
<td>-</td>
<td>0.49</td>
</tr>
</tbody>
</table>
Table 2. Diastolic $\Delta P$, systolic $\Delta P$, and cyclic ranges between the common carotid artery and carotid bulb measured using a catheter, VFI, and simulated flow (Sim). Estimated standard deviations (eSD) are listed for VFI and Sim. Catheter measurements were measured peak-to-peak, while diastolic and systolic $\Delta P$ for VFI and Sim are the median $\Delta P$ at diastole and systole across a given number of flow cycles.

<table>
<thead>
<tr>
<th></th>
<th>Diastolic $\Delta P$ [Pa]</th>
<th>Systolic $\Delta P$ [Pa]</th>
<th>Cyclic range [Pa]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Catheter</td>
<td>VFI (eSD)</td>
<td>Sim (eSD)</td>
</tr>
<tr>
<td>Carotid 1</td>
<td>-400</td>
<td>3.0 (107%)</td>
<td>-12.4 (4.0%)</td>
</tr>
<tr>
<td>Carotid 2</td>
<td>-133.3</td>
<td>4.7 (17%)</td>
<td>-10.9 (1.8%)</td>
</tr>
<tr>
<td>Carotid 3</td>
<td>0</td>
<td>1.3 (131%)</td>
<td>-17.3 (1.2%)</td>
</tr>
<tr>
<td>Carotid 4</td>
<td>0</td>
<td>5.8 (31%)</td>
<td>-15.8 (9.5%)</td>
</tr>
<tr>
<td>Carotid 5</td>
<td>133.3</td>
<td>1.5 (193%)</td>
<td>-13.2 (5.3%)</td>
</tr>
<tr>
<td>Carotid 6</td>
<td>0</td>
<td>7.9 (48%)</td>
<td>-11.4 (0.9%)</td>
</tr>
<tr>
<td>Carotid 7</td>
<td>-800</td>
<td>-4.5 (78%)</td>
<td>-17.8 (2.2%)</td>
</tr>
<tr>
<td>Average</td>
<td>-171.4</td>
<td>2.8</td>
<td>-14.1</td>
</tr>
</tbody>
</table>
Table 3. Ten repeated measurements of the systolic $\Delta P$ between the common carotid artery and carotid bulb using the catheter and VFI method in one phantom (Carotid 2). Estimated standard deviations (eSD) are listed for VFI.

<table>
<thead>
<tr>
<th></th>
<th>Catheter [Pa]</th>
<th>VFI [Pa] (eSD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
<td>35.6 (7%)</td>
</tr>
<tr>
<td>2</td>
<td>2000</td>
<td>34.4 (15%)</td>
</tr>
<tr>
<td>3</td>
<td>0</td>
<td>31.1 (8%)</td>
</tr>
<tr>
<td>4</td>
<td>0</td>
<td>29.2 (10%)</td>
</tr>
<tr>
<td>5</td>
<td>0</td>
<td>28.7 (16%)</td>
</tr>
<tr>
<td>6</td>
<td>133</td>
<td>29.3 (13%)</td>
</tr>
<tr>
<td>7</td>
<td>0</td>
<td>31.3 (8%)</td>
</tr>
<tr>
<td>8</td>
<td>0</td>
<td>34.6 (14%)</td>
</tr>
<tr>
<td>9</td>
<td>-1600</td>
<td>33.9 (12%)</td>
</tr>
<tr>
<td>10</td>
<td>-1867</td>
<td>29.1 (7%)</td>
</tr>
<tr>
<td>Average</td>
<td>-133.3</td>
<td>31.7 (11.5%)</td>
</tr>
<tr>
<td>SD</td>
<td>785.6%</td>
<td>8.4%</td>
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</tbody>
</table>