Ultrasound in Med. & Biol., Vol. ■■, No. ■■, pp. ■■–■■, 2018

0301-5629/$ - see front matter

https://doi.org/10.1016/j.ultrasmedbio.2018.02.013

● *Original Contribution*

MEASUREMENT OF WALL SHEAR STRESS EXERTED BY FLOWING BLOOD IN THE HUMAN CAROTID ARTERY: ULTRASOUND DOPPLER VELOCIMETRY AND ECHO PARTICLE IMAGE VELOCIMETRY

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(*Received* 29 *June* 2017; *revised* 22 *January* 2018; *in final form* 26 *February* 2018)

Abstract—Vascular endothelial cells lining the arteries are sensitive to wall shear stress (WSS) exerted by flowing blood. An important component of the pathophysiology of vascular diseases, WSS is commonly estimated by centerline ultrasound Doppler velocimetry (UDV). However, the accuracy of this method is uncertain. We have previously validated the use of a novel, ultrasound-based, particle image velocimetry technique (echo PIV) to compute 2-D velocity vector fields, which can easily be converted into WSS data. We compared WSS data derived from UDV and echo PIV in the common carotid artery of 27 healthy participants. Compared with echo PIV, time-averaged WSS was lower using UDV (28 ± 35%). Echo PIV revealed that this was due to considerable spatiotemporal variation in the flow velocity profile, contrary to the assumption that flow is steady and the velocity profile is parabolic throughout the cardiac cycle. The largest WSS underestimation by UDV was found during peak systole (118 ± 16%) and the smallest during mid-diastole (4.3± 46%). The UDV method underestimated WSS for the accelerating and decelerating systolic measurements (68 ± 30% and 24 ± 51%), whereas WSS was overestimated for end-diastolic measurements (–44 ± 55%). Our data indicate that UDV estimates of WSS provided limited and largely inaccurate information about WSS and that the complex spatiotemporal flow patterns do not fit well with traditional assumptions about blood flow in arteries. Echo PIV-derived WSS provides detailed information about this important but poorly understood stimulus that influences vascular endothelial pathophysiology. (E-mail: Robin.Shandas@UCDenver.edu)

Key Words: **Ultrasound, Echo particle image velocimetry, Ultrasound imaging velocimetry, Blood flow, Hemodynamics, Vascular.**

INTRODUCTION

Hemodynamic wall shear stress (WSS) plays an important role in the development and progression of vascular endothelial dysfunction and atherosclerosis (Caro 2009; Gimbrone 1999; Ku et al. 1985; Markl et al. 2013; Reneman et al. 2006). Endothelial cells lining the arterial walls are sensitive to the mechanical forces exerted by flowing blood and respond to the different types of WSS transduced (Barakat and Lieu 2003). For example, the low and oscillatory type of WSS is known to be atherogenic (Caro 2009; Reneman et al. 2006). However, it is difficult to accurately quantitate *in vivo* WSS in humans, and this has limited our mechanistic understanding of the significance of low and/or oscillatory flow in endothelial dysfunction, atherogenesis and plaque rupture (Barakat and Lieu 2003; Li et al. 2009; Nagel et al. 1999; Peiffer et al. 2013; White et al. 2001). In particular, it is difficult to measure flow with the spatial and temporal resolution sufficient to determine accurate estimates of WSS. High spatiotemporal resolution means flow patterns can be measured near the vessel walls throughout the cardiac cycle to determine any time-varying characteristics in WSS that might be physiologically and clinically important. This is relevant because spatial gradients in shear enhance

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Conflicts of Interest: R.S. is founder and director of Illumasonix LLC, which has held a license to commercialize echo PIV technology. Illumasonix LLC provided a research grant to the University of Colorado to fund part of this work.

activation of endothelial transcription factors (Nagel et al. 1999), and temporal gradients that are caused by high flow pulsatility are known to stimulate endothelial cell proliferation and inflammatory gene expression (Li et al. 2009; White et al. 2001).

Current methods to estimate *in vivo* WSS are based primarily on two imaging modalities: phase-contrast magnetic resonance imaging (PC-MRI) and ultrasound imaging. PC-MRI provides volumetric flow visualization, but is relatively expensive, is time consuming and has limited spatial and temporal resolution (Markl et al. 2011; Wu et al. 2004; Zhang et al. 2011). Because of this, ultrasound Doppler velocimetry (UDV) has become a popular method to estimate WSS in studies of the natural history of atherosclerotic plaque (*e.g.,* carotid artery plaque) and endothelial function (*e.g.,* flow-mediated dilation (Reneman et al. 2006)). This method is inexpensive and readily available, but it uses a 1-D velocity component rather than measuring the whole velocity vector field. Thus, it is not possible to measure the spatial gradient of the velocity profile near the vessel wall, which is required to calculate WSS. Instead, UDV measures the centerline peak velocity (V_{max}), which is then extrapolated over a theoretical parabola from near to far wall, in accordance with the assumptions of the Hagen–Poiseuille Law and/or Womersley's oscillatory flow theory. However, problems arise if pulsatile arterial flow does not exhibit a parabolic velocity profile, because any discrepancy between the actual and the assumed velocity profiles introduces error into the WSS measurement (Mynard and Steinman 2013a; Mynard et al. 2013b; Reneman et al. 2006).

With the convenience of ultrasound imaging, a method that uses a 2-D ultrasound image of the arterial segment to measure the local flow velocity distribution could provide additional information about blood flow and WSS. We have developed an ultrasound-based method called echo particle image velocimetry (echo PIV) that produces a 2-D velocity vector field within an arterial segment, from which spatial and temporal local WSS measurements are obtained. Our *in vitro* and *in vivo* validation studies have indicated that echo PIV can accurately measure WSS with high spatial and temporal resolution (Gurung et al. 2017; Kim et al. 2004a, 2004b; Liu et al. 2008; Zhang et al. 2011; Zheng et al. 2006). The purpose of this study was to compare common carotid artery (CCA) WSS measurements obtained from UDV with those obtained from echo PIV.

METHODS

Ethical approval

This study conformed to the Declaration of Helsinki and was approved by the U.K. National Research Ethics Service Southwest (09/H0202/49). All participants gave written informed consent.

Participant screening and baseline characteristics

Participants were apparently healthy men and women recruited at the National Institute for Health Research (NIHR) Exeter Clinical Research Facility in the United Kingdom. Participants were asked to refrain from food or drink (except water) at least 2 h before the visit, and to avoid smoking; drinking tea, coffee or alcohol; and strenuous exercise on the study day. Medical history, electrocardiogram (ECG), height, body mass, waist circumference and blood pressure were obtained. Twelve-hour-fasting blood samples were collected in accordance with the U.K. National Quality Assessment Scheme. Doppler ultrasound measurements were collected before contrast agent injection (SonoVue, Bracco, Italy) and echo PIV imaging. Twelve participants were involved in the initial experimentation to determine optimal microbubble concentration as guided by our prior work (Liu et al. 2008; Zheng et al. 2006). Exclusion criteria included history of uncontrolled hypertension, pulmonary hypertension, renal disease, hepatic disease, claudication and hypersensitivity to the contrast agent and age outside the range 20 to 80 y. Inclusion criteria for analysis of subject data files were clear delineation of the lumen boundary on the B-mode image and comparable peak velocity measurements for UDV and echo PIV. Data files were excluded if contrast agent density was inadequate to obtain accurate PIV results.

UDV-based WSS measurement

Pulsed wave Doppler imaging (Ultrasonix 500 RP, Analogic BK Ultrasound, Richmond, BC, Canada) was used to measure maximum blood flow velocity (V_{max}) from the right CCA with the sample volume placed in the center of the vessel at a recorded location upstream of the carotid bifurcation. The pulse repetition frequency was set at 5 kHz with the transducer (L14-5/38) parallel to the centerline axis of the artery and the Doppler angle set at 60° (Bushberg et al. 2002). WSS was calculated from the centerline V_{max} using the standard Hagen–Poiseuille equation (Ford et al. 2008; Mynard and Steinman 2013a)

$$WSS_{V_{max}} = \mu \frac{4V_{max}}{D} \quad (1)$$

where D is carotid artery inner diameter, and μ is dynamic viscosity assumed constant at 0.032 Poise (Fig. 1). Equation (1) uses the Poiseuillean assumptions that flow is steady, is fully developed (*i.e.,* shape of the flow velocity profile does not change and the mean velocity is half the maximum flow velocity) and has a parabolic velocity profile. The UDV-derived WSS measurement (WSS_{Vmax}) provides an estimate of the mean flow WSS within the Poiseuillean flow assumptions.