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Forward-viewing estimation of 3D blood flow velocity fields by intravascular ultrasound: Influence of the catheter on velocity estimation in stenoses

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Abstract

Coronary artery disease is the most common type of cardiovascular disease, affecting > 18 million adults, and is responsible for >365k deaths per year in the U.S. alone. Wall shear stress (WSS) is an emerging indicator of likelihood of plaque rupture in coronary artery disease, however, non-invasive estimation of 3-D blood flow velocity and WSS is challenging due to the requirement for high spatial resolution at deep penetration depths in the presence of significant cardiac motion. Thus we propose minimally-invasive imaging with a catheter-based, 3-D intravascular forward-viewing ultrasound (FV US) transducer and present experiments to quantify the effect of the catheter on flow disturbance in stenotic vessel phantoms with realistic velocities and luminal diameters for both peripheral (6.33 mm) and coronary (4.74 mm) arteries. An external linear array ultrasound transducer was used to quantify 2-D velocity fields in vessel phantoms under various conditions of catheter geometry, luminal diameter, and position of the catheter relative to the stenosis at a frame rate of 5000 frames per second via a particle imaging velocimetry (PIV) approach. While a solid catheter introduced an underestimation of velocity measurement by >20% relative to the case without a catheter, the hollow catheter introduced <10% velocity overestimation, indicating that a hollow catheter design allowing internal blood flow reduces hemodynamic disturbance. In addition, for both peripheral and coronary arteries, the hollow catheter introduced <3% deviation in flow velocity at the minimum luminal area compared to the control case. Finally, an initial comparison was made between velocity measurements acquired using a low frequency, catheter-based, 3-D intravascular FV US transducer and external linear array measurements, with relative error <12% throughout the region of interest for a flow rate of 150 mL/min. While further system development is required, results suggest intravascular

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Conflict of interest

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Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.
ultrasound characterization of blood flow velocity fields in stenotic vessels could be feasible with appropriate catheter design.

**Keywords**

Intravascular ultrasound; blood flow velocity estimation; particle imaging velocimetry; forward viewing

1 Introduction

Stable coronary artery disease (CAD) is one of the leading causes of mortality in the United States, with > 1 million coronary events expected annually in the U.S. [1]. The most common cause of CAD is atherosclerosis, which is characterized by plaque accumulation and reduced blood flow in coronary arteries. While several imaging technologies are used to assess plaque morphology and arterial anatomy in CAD—including angiography, intravascular ultrasound, and intravascular optical coherence tomography—currently fractional flow reserve (FFR) is the only available technology used clinically to provide a direct measurement of coronary artery function by measuring the pressure difference across a stenosis [2-4]. Patients with FFR ≤ 0.8 (indicating a decrease in pressure across the stenosis >20%) are recommended for medical therapy and either coronary artery bypass graft (CABG) or percutaneous coronary intervention (PCI), while those with FFR > 0.8 are typically not prescribed for intervention according to current guidelines [2, 3, 5]. However, approximately 10% of patients with FFR > 0.8 still experience major adverse cardiac events [6]. Thus development of new techniques for risk stratification in coronary artery disease based on direct measurement of local physiology could lead to reduction in rates of major adverse cardiac events such as myocardial infarction (MI).

Recent studies indicate that plaque rupture and plaque erosion are the primary plaque morphologies responsible for the development of atherosclerosis and subsequent myocardial ischemia [7]. In addition to plaque morphology, other factors contributing to likelihood of plaque rupture include mechanical stress and strain [8, 9]. High wall shear stress (WSS), which is the tangential frictional force of blood on the vessel wall, is hypothesized to trigger a change in behavior of endothelial cells and stimulate progression of the atherosclerotic lipid core towards plaque vulnerability [10-12]. A recent study using computational fluid dynamics (CFD) in a clinical population with stable CAD demonstrated that characterization of hemodynamics by computational fluid dynamics (CFD) based on anatomical imaging adds incremental clinical value beyond FFR for predicting future MI [11].

Specifically, CFD techniques based on a 3-D reconstruction of the vessel geometry have been used to estimate the local WSS distribution in coronary arteries [13, 14]. However, obtaining a reliable and reproducible wall shear stress map using CFD is computationally intensive, with the accuracy of results depending on patient-specific boundary conditions, which typically requires invasive measurements such as those made in the cardiac catheterization lab [15]. Thus, other researchers have presented methods for direct estimation of WSS in vivo. Digital subtraction X-ray angiography with contrast injection has been used to estimate blood flow velocity and derive WSS by tracking contrast
agent propagation using either concentration time curves or concentration distance curves from the projection images, although this method uses ionizing radiation [16]. Another method for the direct measurement of velocity and corresponding estimation of WSS in vivo is using phase contrast MRI, however, limited spatial resolution can restrict these techniques to large blood vessels [17-21]. Other groups have used ultrasound approaches to estimate WSS from direct velocity measurements. Based on the similarity of speckle patterns in two subsequent images in time, echo particle imaging velocimetry (PIV) was developed to measure flow velocity vectors [22, 23]. WSS can then be estimated based on the PIV measurements [24-29]. Alternatively, the transverse oscillation technique has been proposed for estimation of 2-D [30-32] and 3-D velocity vectors [33, 34]. Recent developments include combining plane wave transmit with transverse oscillation techniques to achieve 2-D ultrafast vector velocity imaging [35-39] and new methods to increase the maximum detectable velocity [40-42]. More recently, another ultrasound-based approach, ultrafast plane-wave multi-angle Doppler velocimetry, has been developed and validated for vector velocity imaging in vivo [43-46]. In addition, an integrated flow-mediated dilatation response system that utilizes a multi-gate Doppler technique has been developed to simultaneously estimate wall shear rate—the blood velocity gradient at the wall from which WSS is estimated—and its response [47, 48]. Alternatively, Correia et al. have presented a technique for 4-D ultrafast ultrasound flow imaging to map angle-independent 3-D blood flow velocity in carotid arteries [49]. While the carotid arteries represent an accessible target for validation of the technique, these arteries are relatively large and superficial [49].

Although these non-invasive methods have been successfully applied to large arteries at shallow depths, they lack sufficient spatial resolution at depth for coronary artery imaging [49, 50]. For this reason, several authors have proposed minimally-invasive intravascular blood flow velocity measurement techniques, including a dual-mode device with a side-viewing transducer for acquiring B-mode images of the arterial structure and a forward-viewing transducer utilizing pulse wave Doppler for measuring flow velocity along the beam [51], however, this device is limited to measuring a 1-D flow velocity in a fixed spatial location. In addition, several other innovations in catheter-based ultrasound have recently been demonstrated, including high-accuracy catheter localization in the presence of flow [52-54]. In order to estimate real-time 3-D velocity fields inside arteries, our group recently proposed estimation of real-time 3-D blood flow velocity fields using a catheter-based, forward-viewing matrix array transducer in peripheral arteries [55, 56].

When using an intravascular device to measure blood flow dynamics, it is important to consider the effect of the device on the flow dynamics. For example, the Navvus microcatheter system, an intravascular device with a pressure sensor for assessing FFR, was reported to overestimate the stenosis severity compared to the pressure wire measurement and can thus lead to erroneous indication for revascularization due to flow obstruction resulting from its large diameter [57, 58]. Alternatively, Wentzel et al. previously investigated the disturbance of 3-D velocity profiles with the insertion of a catheter-based IVUS transducer using CFD simulations in a straight tube, reporting that velocity profiles are more greatly affected by the location of the catheter in the artery rather than by the dimensions of the catheter, while shear stress measurements are affected by both the size and position of the catheter [59]. However, these studies did not consider the velocity
components in the presence of a stenosis, i.e. the feature of clinical interest, nor did they investigate the catheter structure.

In this work, the effects of a forward-viewing imaging catheter on hemodynamics in front of the catheter are experimentally assessed in phantoms with realistic velocities and luminal diameters for both peripheral and coronary arteries. The effect of the catheter in the presence of a stenosis is investigated in order to determine the conditions under which velocity fields can be accurately estimated using a forward-viewing, catheter-based US transducer. In this work, the primary focus is intermediate, focal stenosis because this is one type of stenosis that presents challenges for risk stratification using FFR. Future work will investigate diffuse disease and tortuous artery shapes. These studies utilize a PIV approach in controlled laboratory experiments in order to provide high resolution, angle-independent 2-D velocity maps under the described varying conditions of artery diameter, catheter geometry, and position (i.e. distance from the catheter to the minimum luminal area). Finally, we also present initial proof-of-concept for comparison between PIV measurements with a linear array and 3-D vector velocity measurements using a 5 MHz catheter-based, intravascular FV US device. The goal of these studies is to drive the design of the next generation forward-viewing imaging catheter by testing the effect of the catheter on hemodynamics in simpler cases such as focal stenosis. This is an early stage study in the development of a forward-viewing imaging catheter for peripheral and coronary arteries; a smaller device needs to be developed for clinical use based on results of this study.

2 Materials and Methods

2.1 Vessel-mimicking Phantom

Custom tissue-mimicking phantoms having vessels of two diameters (4.74 mm corresponding to healthy human adult left main coronary arteries [60, 61], and 6.33 mm corresponding to the common hepatic artery [62]) were synthesized to perform flow experiments (Fig. 1) [63]. For the 6.33 mm diameter vessel, the stenotic throat, the narrowest region in the stenosis, has a diameter of 3.6 mm resulting in a 43% diameter stenosis (%DS). This value of %DS is within the range for an intermediate stenosis in peripheral arteries [64]. For the 4.74 mm diameter vessel, the stenotic throat has a diameter of 2.2 mm, resulting in a 54 %DS. This %DS represents a value that is just greater than the threshold for significant stenosis in the left main coronary artery (50%) and thus represents a “borderline” stenosis that might be encountered in patients with stable coronary artery disease [65-68]. In addition, to test the effects of the catheter in more severe stenotic cases where FFR would be indicated, both 6.33 mm and 4.74 mm diameter vessels with 71 %DS stenoses were prepared. The minimum luminal area of the vessel was positioned more than 80 mm away from the inlet (shown in Fig. 1) to allow the flow to be fully developed before arriving at the stenosis.

As shown in Fig. 1, the flow phantom is placed inside a tank filled with degassed water. A syringe pump (PHD 2000, Harvard Apparatus, Holliston, MA) was used to generate the flow through the phantom vessel. Lipid-shelled microbubbles were synthesized [69, 70] and used as flow tracer for the particle flow velocimetry analysis. Microbubbles were diluted 2000
times in degassed water and infused into the tank, yielding a concentration of approximately $5 \times 10^6$ microbubbles/mL.

### 2.2 Ultrasound Imaging and Data Analysis

#### 2.2.1 Flow velocity measurements using a linear array transducer

In this study, to investigate the influence of a catheter-based intravascular FV transducer on flow dynamics, a customized catheter mimicking the intravascular FV transducer was inserted from the inlet of the vessel phantom. Because different designs of the catheter will affect the flow differently, we first investigated the effects of different catheter designs on flow dynamics and selected the catheter design that introduced minimal disturbance to the flow. Using an external linear array transducer, we then quantified the disturbance caused by the insertion of the catheter in arteries of two different diameters with varying distance from the catheter to the stenosis.

In the first set of experiments (Table 1, #1), to investigate the effects of catheter design on flow dynamics, two types of catheters were tested: 1) a solid catheter with a diameter of 4.18 mm, and 2) a hollow catheter with an inner diameter of 3.81 mm and an outer diameter of 4.18 mm. This outer diameter is similar to the size of our current FV US transducer, and the wall thickness is larger than the commercially-available catheter thickness of 0.13 mm to reduce the risk of puncture due to friction and to ease manipulation and positioning. These catheters were tested in the previously-described 6.33 mm diameter vessel with a 43% DS stenosis. The tip of the catheter was positioned 8.5 mm from the location with the minimum luminal area. The flow rate of the syringe pump was 363 mL/min, consistent with physiological flow rates for the common hepatic artery [71].

In the next set of experiments, the effect of vessel diameter was investigated using both a 6.33 mm diameter vessel with the previously-described hollow catheter (Table 1, #2) and a 4.74 mm diameter vessel with a hollow catheter having an inner diameter of 1.32 mm and an outer diameter of 1.98 mm (Table 1, #4) to test the effect of the catheter on flow dynamics in smaller vessels such as the coronary artery. This outer diameter value corresponds to a typical 2 mm (6-French) diameter catheter used for quantitative coronary catheterization, and the larger wall thickness has been selected to minimize the risk of damage to the catheter and because the smaller, thin-walled catheter is more likely to torque and twist during manipulation [74, 75]. The flow rates of the syringe pump were set to be 363 mL/min for the 6.33 mm vessel and 200 mL/min for the 4.74 mm vessel. These flow rates and corresponding mean flow velocities vessel were chosen according to the physiological flow rate of the left main coronary and the common hepatic arteries measured in adult humans, respectively [71-73]. To determine the effect of the catheter on flow as a function of distance, velocity measurements were acquired at three different distances from the tip of the catheter to the location with the minimum luminal diameter (6.8 mm, 11.6 mm, and 16 mm for a 6.33 mm diameter vessel and 6.1 mm, 10.1 mm, and 14.1 mm for a 4.7 mm diameter vessel). The experimental cases tested in these studies are summarized in Table 1.

A high frame rate ultrasound imaging system (Verasonics Vantage 256, Kirkland, WA, USA) with a linear array transducer (L11-5, ATL, Bothell, WA) was used to acquire images of flow dynamics. Six sets of data were acquired for each case. The transducer was placed...
on the top surface of the phantom (i.e. outside the vessel lumen) and aligned with the long axis of the vessel in the phantom (Fig. 1). Unfocused plane wave transmit events of 1-cycle, 10 MHz pulses at a frame rate of 5000 frames/s were used. The beamformed in-phase and quadrature (IQ) data were filtered via singular value decomposition (SVD) filtering by discarding the first, largest singular value to remove the stationary phantom background while maintaining fast-moving microbubbles [76]. After clutter filtering, the resulting imaging frames were saved with a display dynamic range of 25 dB. Velocity vectors were estimated from images using a standard PIV algorithm (PIVLab) [77]. Velocity vectors were first spatially smoothed [78, 79] and then temporally averaged across 50 frames (0.01 s).

As shown in Fig. 2, centerline velocity magnitudes were derived from the 2-D velocity maps and were displayed as a means of quantitatively summarizing the effect of the inserted catheter on flow dynamics. Furthermore, previous studies have also shown that for simple flow profiles, centerline velocity magnitudes alone contain enough information to derive the parabolic velocity profiles across the cross-section of the artery and allow estimation of WSS [80].

According to previous studies on the underlying mechanism of occlusions, the region containing the stenotic throat with elevated flow velocity and WSS is most prone to clotting due the rapid accumulation of platelets [81]. Therefore, in the present study, the primary region of interest is in the region around the location with the minimum luminal area of the stenosis. Previous studies of flow dynamics in stenoses commonly separate flow into three regions: upstream from the stenosis (proximal), the stenotic throat, and downstream from the stenosis (distal), as hemodynamics differ in each region [10, 11, 82, 83]. Thus in these studies, the location with the minimum luminal area was identified as the center of the stenotic throat, then the lesion was divided into three consecutive 3 mm segments: the upstream region (i), stenotic throat (ii), and downstream region (iii) as shown in Fig. 3. In each segment, the absolute velocity difference between the case with the catheter and without the catheter was calculated for six acquisitions for each case. Non-parametric testing was used in all the analyses via the Kruskal-Wallis test for paired samples, e.g. with and without the catheter. A p-value of 0.05 was considered statistically significant.

### 2.2.2 3-D flow vector measurement using FV US transducer—
Additional experiments were performed as an initial proof-of-concept comparison between PIV measurements with an external linear array transducer and catheter-based 2-D array measurements. A catheter-based FV 2-D array US transducer [55, 56, 84] with 118 elements and a diameter of 4 mm was used to acquire 3-D velocity measurements (Table I #3). It was inserted from the inlet of the 6.33 mm diameter vessel with a 43 %DS stenosis. Three different flow rates (50 mL/min, 100 mL/min, and 150 mL/min) were applied, producing mean inlet velocities of 2.64 cm/s, 5.29 cm/s, and 7.25 cm/s respectively. Only these lower velocities were tested to ensure that high flow velocities and pressures were avoided around the larger, solid catheter transducer. A transmit frequency of 4.8 MHz was used for every transducer element with unfocused transmit events. The acquired data corresponding to one unfocused transmit event was beamformed to produce one volume of 3-D data. The acquisition rate of the 3D data was 4900 volumes/s. Flow velocities were measured using

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both the FV US transducer and the L11-5 linear array transducer that was placed on top of the phantom for comparison.

3-D flow velocity data acquired using the FV US transducer were processed by applying a bandpass filter centered at 1.6 cycles/mm with −6 dB bandwidth of 93% in lateral and elevation directions to introduce transverse oscillation [36, 85, 86]. Fourth-order autocorrelation estimation was used to estimate the lateral and elevation velocity components, and a standard cross-correlation estimator was used to estimate for the axial velocity component [31]. 3-D velocity profiles were shown for three depths each in the upstream region, the stenotic throat, and the downstream region. For comparison, these velocity magnitudes were compared with 2-D flow velocity data acquired using the linear array transducer that were processed in the same way as described in the previous section.

3 Results

3.1 Flow velocity measurements in peripheral-mimicking vessel with an external linear array

B-mode images of the flowing microbubbles in the 6.33 mm and 4.74 mm vessels are shown in Fig. 3 (a) and (b), respectively. With the phantom background signal suppressed significantly by the SVD clutter filter, the stenosis region is successfully identified and manually segmented into 3 regions for investigation. Figure 2 shows how the centerline velocity magnitude is derived from a 2-D velocity color map of a 6.33 mm diameter vessel (peripheral artery) in a phantom with a 43 %DS stenosis. As the centerline velocity magnitude as a function of increasing distance from the tip of the catheter encompasses first order characteristics of flow dynamics and allows rapid comparison between experimental cases, this centerline profile has been used throughout this work to compare the control case and the case when the catheter was inserted.

For the first part of study, the effect of catheter design (i.e. hollow vs. solid) on flow dynamics in a 6.33 mm diameter vessel (peripheral artery) with a 43 %DS in a phantom was investigated (Table 1, #1). It is important to design intravascular devices while considering hemodynamics, as some devices such as pressure sensor-equipped microcatheters have been shown to lead to overestimation of functional stenosis severity because of their large diameter [58]. Therefore, designing the catheter to have minimal impact on the fluid dynamics is critical. We compared two different designs: a hollow catheter that allows internal flow, and a solid catheter design that does not allow internal flow. The results measured by the external linear array are shown in Fig. 4.

In the upstream region (4 mm to 7 mm from the tip of the catheter), the mean centerline velocity magnitude with the hollow catheter averaged across six acquisitions was 7.43 ± 1.45 cm/s greater than the control case, and velocity magnitudes were statistically different from the control case. When the solid catheter was inserted, in the same region, the mean centerline velocity magnitude averaged across six acquisitions was 13.21 ± 2.05 cm/s less than the control case, and velocity magnitudes were also statistically different from the control case. In the stenotic throat region (7 mm to 10 mm from the tip of the catheter), the mean centerline velocity magnitude with the hollow catheter was 5.16 ± 1.37 cm/s
greater than the control case, and in 75% of points in this region, velocity magnitudes were statistically different from the control case. Meanwhile, when the solid catheter was inserted, the mean centerline velocity magnitude with the solid catheter was 26.84 ± 4.32 cm/s less than the control case, and the velocity magnitudes were also statistically different from the control case. At 8.5 mm from the tip of the catheter, where the minimum luminal area was located, the mean centerline velocity magnitude with the hollow catheter was 4.94 cm/s (8%) greater than the control case (control case: 61.73 cm/s ± 1.10 cm/s; with the hollow catheter: 66.66 ± 0.66 cm/s) (p = 0.0039). Meanwhile, when the solid catheter was inserted, the velocity magnitude was 29.88 cm/s (48%) less than the control case (p < 0.05). In the downstream region (10 mm to 13 mm from the tip of the catheter), the mean centerline velocity magnitude with the hollow catheter was 4.28 ± 1.85 cm/s greater than the control case, and in 72% of points in this region, the velocity magnitudes of the case with the catheter were not statistically different from the control case (0.05 < p < 0.0547). However, when the solid catheter was inserted, in the same region, the mean centerline velocity magnitude with the solid catheter was 14.46 ± 3.57 cm/s less than the control case, and the velocity magnitudes were statistically different (p < 0.05). Overall, while introduction of the solid catheter led to velocity underestimation greater than 20% throughout the entire length of the vessel compared to the control case, the hollow catheter introduced less than 10% velocity overestimation.

Then for the second set of experiments, the effects of the catheter on the flow in the 6.33 mm diameter vessel in a phantom with a 43 %DS stenosis was investigated when the catheter was positioned at different distances from the minimum luminal area (Table 1 #2). Table 2 shows the absolute velocity difference between cases with and without the catheter for three segments: the upstream region, stenotic throat, and the downstream region. Figure 5 (a) shows centerline velocity profiles when a hollow catheter with an inner diameter of 3.81 mm and an outer diameter of 4.18 mm was positioned at 6.8 mm from the minimum luminal area. In the upstream region (2.3 mm to 5.3 mm from the tip of the catheter), the velocity magnitudes were statistically different relative to the control case (p < 0.05). In 85% of points in the stenotic throat region (5.3 mm to 8.3 mm from the tip of the catheter), the velocity magnitudes of the case with the catheter was not statistically different from the control case (0.05 < p < 0.4225). The peak velocity magnitude at a distance of 6.8 mm from the tip of the catheter was 1.31 cm/s (2.0%) greater than that of the control case (control case: 64.08 ± 1.34 cm/s; with the catheter: 65.39 ± 0.58 cm/s). However, this difference was not statistically significant (p = 0.1495). In 67% of points in the downstream region (8.3 mm to 11.3 mm from the tip of the catheter), the velocity magnitudes of the case with the catheter were not statistically different relative to the control case without the catheter (0.05 < p < 0.8726). In summary, the flow was not significantly disturbed in the region of stenosis throat but was more affected in the regions upstream and downstream from the stenosis due to the presence of the catheter.

Figure 5 (b) shows centerline velocity magnitudes when the catheter was positioned 11.6 mm from the minimum luminal area. In the upstream region (7.1 mm to 10.1 mm from the tip of the catheter), velocity magnitudes of the case with the catheter were statistically different from the control case (p < 0.03704). In 80% of points in the stenotic throat region (10.1 mm to 13.1 mm from the tip of the catheter), the velocity magnitudes of the case with
the catheter were not statistically different from the control case (0.05 < p < 0.0776). The peak velocity magnitude of the case with the hollow catheter, which is at a distance of 11.6 mm from the tip of the catheter, was 2.09 cm/s (3.26%) less than the control case (control case: 64.08 cm/s ± 1.34 cm/s; with the catheter: 61.99 ± 1.15 cm/s). This difference was again not statistically significant (p = 0.07765). In 50% of points in the downstream region (13.1 mm to 16.1 mm from the tip of the catheter), the velocity magnitudes of the case with the catheter were not statistically different relative to the control case (0.05 < p < 0.52). This suggests the flow dynamics were not significantly affected due to the catheter in the upstream region and in the majority of the stenotic throat but were affected in the region downstream from the stenosis.

Centerline velocity profiles when the catheter was positioned 16 mm from the minimum luminal area are shown in Fig. 5 (c). Throughout all three regions, which are the region upstream from the stenosis (11.5 mm to 14.5 mm from the tip of the catheter), the stenotic throat (14.5 mm to 17.5 mm from the tip of the catheter), and the downstream region (17.5 mm to 20.5 mm from the tip of the catheter), the velocity magnitudes of the case with the catheter were not statistically different from the control case (0.05 < p < 1). The peak velocity magnitude at the stenotic throat for the control case was 1.72 cm/s (2.68%) greater than that of the case with the catheter (control case: 64.08 ± 1.34 cm/s; with the catheter: 65.8 ± 2.82 cm/s). This difference was again not statistically significant (p = 0.1495).

For the third set of experiments, the effects of the catheter on the flow were investigated in a 6.33 diameter vessel in a phantom with a 71 %DS. The catheter was placed 11 mm from the minimum luminal area. The centerline velocity profile is shown in Fig. 6 (a). In the region upstream from the stenosis (7.2 mm to 10.02 mm), the mean centerline velocity magnitude averaged across six acquisitions for the case with the catheter were 2.15 ± 0.81 cm/s greater than the control case, and the difference was not statistically significant (0.05 < p < 0.3865). In the region at the stenotic throat (10.02 mm to 13.08 mm), the mean centerline velocity magnitudes for the control case were 4.3 ± 2.75 cm/s greater than the case with the catheter, and the difference was not statistically significant (0.05 < p < 0.7728). Lastly, in the region downstream from the stenosis (13 mm to 15.81 mm), the mean velocity magnitude difference between the case with the catheter and the control case was 6.31 ± 3.34 cm/s, and 86% of the difference was not statistically significant (0.05 < p < 1).

### 3.2 3-D velocity measurements with FV US transducer

3-D flow velocity results were obtained using the FV US intravascular transducer in the 6.33 mm vessel with a 43 %DS stenosis (Table 1, #3). The 3D flow velocity vectors are shown in Fig. 7. The z-axis in this figure indicates the direction of flow where z=0 is at the tip of the catheter. The catheter was located 9.25 mm away from the minimum luminal area. Each depth (z = 7.2, 9.25, and 11.3 mm) corresponds to three consecutive regions respectively.

As a comparison, the velocity magnitude at the center of the vessel measured using both FV US and the external linear array is shown in Table 3. When the flow rate was 50 mL/min (i.e. mean inlet velocity was 2.65 cm/s), for all the depths tested, the FV US transducer underestimated the velocity magnitude at the center of the vessel relative to that measured by the linear array transducer at the same spatial location (at z = 7.2 mm by 15.76 ± 2.01%:
at $z = 9.25$ mm by $21.67 \pm 3.62\%$; at $z = 11.3$ mm by $3.93 \pm 1.3\%$). When the flow rate was 100 mL/min (i.e. mean inlet velocity was 5.29 cm/s), for all tested distances from the tip of the catheter, the FV US transducer underestimated the velocity magnitudes at the center of the vessel by less than 12% compared to the values measured by the linear array transducer. Similarly, when a flow rate of 150 mL/min (i.e. inlet velocity was 7.94 cm/s) was introduced, for all tested distances from the tip of the catheter, the FV US underestimated the velocity magnitudes at the center of the vessel by less than 10% compared to the values estimated by the linear array transducer.

According to the results from the linear array transducer, when the flow rate was 50 mL/min, the absolute mean velocity magnitude difference between the case with and without the catheter-based FV US transducer was 1.41 cm/s (8.39% of the maximum velocity magnitude in the vessel without the catheter) for all centerline points in the vessel, and for 92% of the points in the entire vessel, this difference was not statistically different ($0.05 < p < 1$). When the flow rate was 100 mL/min, the absolute mean velocity magnitude difference was 2.89 cm/s (7.32% of the maximum velocity magnitude in the vessel without the catheter), and for 85% of the points in the entire vessel, this difference was not statistically different ($0.05 < p < 1$). Finally, when the flow rate was 150 mL/min, the difference was 3.38 cm/s (8.62% of the maximum velocity magnitude in the vessel without the catheter), and for 78% of the points in the entire vessel, this difference was not statistically different ($0.05 < p < 1$). To summarize, when flow rates of 50 and 100 mL/min were introduced, for over 85% of the peripheral artery region, the disturbance to the flow due to the insertion of the FV US transducer was not significant.

### 3.3 Flow velocity measurements in coronary-mimicking vessel with an external linear array

The effect of the catheter on the flow dynamics in the 4.74 mm diameter vessel with a 54 %DS stenosis was investigated when the catheter was positioned at different distances from the minimum luminal area (Table 1 #4). In Table 2, the absolute velocity difference between cases with and without the catheter averaged across six acquisitions are shown in each segment of the vessel.

Figure 8 (a) shows the centerline velocity profile in a 4.74 mm diameter vessel in a phantom with a 54 %DS stenosis when a hollow catheter with an inner diameter of 1.32 mm and an outer diameter of 1.98 mm was positioned 6.1 mm from the location with the minimum luminal area. In 87.5% of the upstream region (1.6 mm to 4.6 mm from the tip of the catheter), the velocity magnitudes were not statistically different from the control case ($0.05 < p < 0.8728$). In 43% of the points in the stenotic throat region (4.6 mm to 7.6 mm from the tip of the catheter), the velocity magnitudes of the case with the catheter were not statistically different from the control case ($0.05 < p < 0.7483$). The peak velocity magnitude of the control case, which occurs at a distance of 6.1 mm from the tip of the transducer, was 6.76 cm/s (6.7%) greater than that with the catheter (control case: 99.94 ± 4.29 cm/s; with the catheter: 93.18 ± 2.43 cm/s), and this difference was statistically different ($p = 0.0247$). In the downstream region (7.6 mm to 10.6 mm from the tip of the catheter), the velocity magnitudes for the case with the catheter were not statistically different from the
control case (0.05 < p < 1). In summary, the disturbance to the flow due to the insertion of the catheter was not significant in the majority of the upstream region and in the region downstream from the stenosis but affected the flow in the stenotic throat. Figure 8 (b) shows that when the catheter was placed 10.1 mm from the minimum luminal area, in 86% of the upstream region (5.6 mm to 8.6 mm from the tip of the catheter), the velocity magnitudes of the case with the catheter were not statistically different from the control case (0.05 < p < 0.8726). While in both the stenotic throat region (8.6 mm to 11.6 mm from the tip of the catheter) and the downstream region (11.6 mm to 14.6 mm from the tip of the catheter), the velocity magnitudes of the case with the catheter were not statistically different from the control case (0.05 < p < 1). The peak velocity magnitude, which occurs at a distance of 10.1 mm from the tip of the catheter for the control case, was 4.83 cm/s (4.8%) greater than that with the catheter, and there was no significant difference between the cases with and without catheter (control case: 99.94 ± 4.29 cm/s; with the catheter: 95.11 ± 5.62 cm/s) (p = 0.1087). This indicates that even with the insertion of the catheter, flow dynamics did not change significantly in the majority of the upstream region and throughout stenotic throat and the downstream regions.

Figure 8 (c) shows the centerline velocity profiles when the catheter was placed 14.1 mm from the minimum luminal area in a 4.74 mm vessel. In 71% of points in the upstream region (9.6 mm to 12.6 mm from the tip of the catheter), the velocity magnitudes of the case with the catheter were not statistically different from the control case (0.05 < p < 0.7483). Similar to the previous case, in both the stenotic throat (12.6 mm to 15.6 mm from the tip of the catheter) and the downstream region (15.6 mm to 18.6 mm from the tip of the catheter), the velocity magnitudes of the case with the catheter were not statistically different from the control case (0.05 < p < 1). The peak velocity magnitude for the control case, which is 14.1 mm from the tip of the catheter, was 2.41 cm/s (2.41%) greater than that with the catheter, and there was no significant difference between the cases with and without catheter (control case: 99.94 ± 4.29 cm/s; with the catheter: 97.53 ± 1.14 cm/s) (p = 0.1087). This indicates that the flow in the vessel did not significantly change even with the catheter in the majority of the upstream region and throughout stenotic throat and the downstream regions.

For the second set of experiments, the effects of the catheter were investigated in a 4.74 mm diameter vessel with a 71 %DS stenosis. The catheter was placed 10.34 mm from the minimum luminal area. The centerline velocity profile is shown in Fig. 6 (b). In the region upstream from the stenosis (5.54 mm to 8.49 mm from the tip of the catheter), the mean velocity magnitudes of the case with the catheter were 3.01 ± 1.04 cm/s greater than the control case, and 87% of points in this region were not statistically different (0.05 < p < 0.8273). In the stenotic throat (8.49 mm to 11.45 mm from the tip of the catheter), the mean velocity magnitudes of the control case were 4.21 ± 2.79 cm/s greater than the case with the catheter, and the mean velocity magnitudes were not statistically different (0.2752 < p < 0.8273). In the region downstream (11.45 mm to 14.4 mm from the tip of the catheter), the mean velocity magnitudes of the control case were 20 ± 6.25 cm/s greater than the case with the catheter, and 68% of the points in this region were not statistically different (0.2752 < p < 1).
4 Discussion

4.1 Flow velocity measurements in peripheral and coronary arteries using an external linear array

First, we investigated the effect of both solid and hollow catheters on the flow dynamics in a 6.33 mm diameter stenotic vessel. In Sec. 3.1, we showed that a solid catheter design causes a 48% underestimation of flow velocity magnitude at the location with minimum luminal area, while the hollow catheter only yielded an overestimation in velocity magnitude of less than 10%. Thus a catheter-based array design with a hollow catheter to allow internal blood flow may allow estimation of blood flow velocities with minimal disturbance to the flow dynamics.

Next, the effect of the location of the hollow catheter (i.e. distance from the tip of the catheter and the location with the minimum luminal area) on flow velocity measurements was investigated in the 6.33 mm diameter vessel with a 43 %DS stenosis as seen in Fig. 5. Across all cases tested (6.8 mm, 11.6 mm, and 16 mm from the tip of the catheter to the minimum luminal area), the velocity difference between the cases with and without a catheter at the location of minimum luminal area remained within 2.09 cm/s, which is 3.26% of the maximum velocity magnitude of the control case. Furthermore, and in more than 80% of the points in the stenotic throat region, velocity magnitudes of the case with the catheter were not statistically different from the control case. Throughout all regions of interest, the absolute velocity difference between the case with the catheter and the control case remained less than 2.5 cm/s, which was less than 4% of the maximum velocity magnitude of the control case. As the catheter was placed further away from the minimum luminal area, the velocity magnitude difference between the case with the catheter and without the catheter became less statistically significant, especially at a distance of 16 mm, the differences were not statistically significant throughout the region of interest (i.e. the 9 mm region around the stenosis). Similar results were observed in a more severe stenosis case, a 6.33 mm vessel with a 71 %DS, where the insertion of the hollow catheter did not yield statistically different velocity magnitudes in the regions upstream and in the stenotic throat compared to the control case. These results indicate that a catheter-based FV US array could potentially be used for measuring the flow velocity across the stenotic throat and estimating WSS when the transducer is deployed upstream from the stenosis.

However, it should also be noted that there was a significant difference in velocity magnitude between the control case and the case with the catheter in the downstream region (i.e. 20 mm from the tip of the catheter in a 43 %DS stenosis in Fig. 5 (c) and 14 mm from the tip of the catheter in a 71 %DS stenosis in Fig. 6) beyond the stenotic throat. It is possible the flow was more disturbed in the downstream region than in the upstream region near the catheter because the downstream region could contain concentrated vortices and turbulence formed due to the expansion of the artery, which may be more sensitive to the change in the upstream region [87]. Because of the rapid increase in diameter from 1.65 mm at the stenotic throat to the original vessel diameter of 6.33 mm in the region downstream from the stenosis in the 6.33 mm vessel with a 71 %DS stenosis, the flow was even more turbulent and therefore more variations in the velocity magnitude were seen after the stenotic...
throat. Also, compared to the case with a 43 %DS, much steeper slopes of the velocity magnitudes with respect to distance were seen at the minimum luminal area (i.e. 11 mm from the tip of the catheter) due to this rapid and significant change in the diameter.

In addition, as shown in Sec. 3.3, for all tested cases in a 4.74 mm vessel with a 54 %DS stenosis, velocity magnitudes between the control and the case with the catheter were statistically different near the tip of the catheter because the flow disturbance happens predominantly in this region. Although peak velocity magnitude at the stenotic throat is significantly greater in the control case than when the catheter was placed 6.1 mm from the stenotic throat, as the catheter is placed further away from the stenotic throat, the difference in peak velocity magnitude at the stenotic throat between the two cases decreased from 6.76 cm/s to 2.41 cm/s and became statistically insignificant. As the distance between the catheter and the stenotic throat increases, the mean velocity differences between the control case and the case with the catheter decreased by 44% for the upstream region, 73% for stenotic throat, and 42% for the downstream region. When the hollow catheter was placed 10.34 mm from the minimum luminal area in a 4.74 mm vessel with a 71 %DS stenosis, most velocity magnitudes in the regions upstream and stenotic throat were not statistically different from the control case. However, in the region downstream from the stenosis, there was more significant flow disturbance when the diameter of the vessel rapidly changed from 1.25 mm to 4.74 mm, which resulted in a greater mean velocity magnitude difference between the case with the catheter and the control case. These results indicate that a FV US array transducer with reduced diameter could potentially be used to estimate the flow velocity and WSS across the stenotic throat in a coronary artery with minimal flow disturbance when the transducer is deployed at a distance of ~10 mm away from the stenosis.

4.2 3-D flow velocity measurements with FV US transducer

We also presented initial proof-of-concept velocity profiles measured from an existing catheter-based FV US device and compared velocity estimates with those acquired using an external linear array transducer. As the flow rate increases, the mean relative error in velocity estimates acquired with the catheter-based FV US transducer compared with the velocity measured using the linear array transducer decreased from 21.67 ± 3.62% to less than 12% for all three regions (Table 3). This means relative error is within the comparative errors shown by Nagel et al., who reported that the mean relative error of MR breath-hold techniques compared with the invasively determined velocity measurements by intravascular ultrasound technique was 15.1 ± 10.7% for all coronary artery segments. Although results from the external linear array transducer show that as the flow rate increases, the absolute velocity magnitude difference between the cases with and without the catheter increases from 1.41 cm/s to 3.38 cm/s, development of a catheter-based ultrasound transducer permitting internal flow—similar to the hollow catheter tested in this study—could allow this value to decrease.

4.3 Limitations

The current study has several limitations. First, the geometries tested in this work do not consider the complex anatomy of human vessels, although a stenosis was built in the vessel to mimic a lesion in arteries. Because atherosclerosis can also be diffuse, for this device to
be translated to a clinical device, it would be important to measure the blood flow velocity in a greater variety of scenarios, including anatomical variants, tortuous vessels, and vessels with diffuse and serial stenoses. For estimation of WSS, measurements of both the velocity profile and vessel diameter are needed, as well as all velocity components near the wall \([88, 89]\). Because movement of the myocardium and changes in blood flow rate affect the vessel diameter, future studies will measure the vessel diameter and its corresponding velocity profile under dynamic pulsatile flow conditions with the catheter inserted. Moreover, limited catheter designs (solid and hollow catheters) are considered in this work. In the future, we plan to design a catheter having openings on the sides of the catheter so that the blood can more easily flow in and out of the catheter. Specific designs that further reduce the disturbance to the hemodynamics due to the insertion of the catheter will be developed, thus allowing more accurate estimation of velocity and WSS. For the catheter to be used in a clinical setting, the diameter of the catheter must be decreased because the forward-viewing catheter tested in this work is limited to larger vessels. The future design will include not only a reduction in outer diameter, but also an optimal inner diameter will need to be determined to reduce the risk of catheter damage and allow manipulation while minimally disturbing the hemodynamics by enabling blood to flow through the catheter inner space. Furthermore, as the position of the catheter with respect to the center of the vessel lumen could affect the velocity profiles and WSS measurements in vessels \([59]\), the effect of positioning to minimize flow disturbance could be investigated in future studies and designs. In addition, in this present study, degassed water was used to mimicking the blood. However, blood is a non-Newtonian fluid, thus viscosity drastically decreases with increasing shear rate. In order to accurately estimate velocity profile and WSS, future work will utilize fluids that more accurately mimic blood mechanical properties.

There are also several imaging tradeoffs that should be discussed. There is a trade-off between detecting high flow velocities and spatial resolution. A high frame rate is usually required to detect the high velocity flow without significant aliasing, which would decrease the number of unfocused transmits during multi-angle compounding and consequently compromise spatial resolution \([90]\). As spatial resolution is more important for detection of the low velocity flow and estimation of WSS near the vessel wall, an increased number of transmit events and a more advanced beamforming strategy may be required depending on flow conditions. In addition, while the flow disturbance due to the catheter decreases with increasing distance from the tip of the transducer, spatial resolution and velocity estimation accuracy deteriorate with increased depth. Finally, although this work used a PIV approach for velocity estimation, future work will compare accuracy of different velocity estimation approaches.

5 Conclusion

Conditions in which the flow velocity in the vessel can be estimated with minimal disturbance using a catheter-based device were experimentally investigated to guide the design of a catheter-based FV US transducer for estimation of WSS in peripheral and coronary arteries. We assessed the effect of the longitudinal position and the structure of the catheter on the flow velocity magnitude profile along the vessel centerline across the stenotic region. For the 6.33 mm diameter vessel with a 43 %DS with a 4.18 mm outer diameter
hollow catheter, the velocity difference between the cases with and without the catheter at the stenotic throat remained within 2.68% of the flow velocity without the catheter across all the catheter locations tested (6.8 mm, 11.6 mm, 16 mm from the stenosis). For the same diameter vessel with a 71% DS, the velocity difference remained within 3.98% of the flow velocity without the catheter when the hollow catheter was inserted 11 mm from the minimum luminal area. For the 4.74 mm diameter vessel with a 54% DS and a 1.98 mm outer diameter hollow catheter, the velocity difference at the stenotic throat between the cases with and without the catheter decreased as the distance between the stenotic throat and the catheter increased, e.g. 14.1 mm, the velocity difference was 2.41% of the flow velocity estimated without a catheter. For the same diameter vessel with a 71% DS, in the regions upstream and stenotic throat, the velocity difference was less than 2.43% of the control case when the hollow catheter was inserted 10.34 mm from the minimum luminal area. In testing straight arteries of two different diameters and with focal stenoses of three different percent diameters, a solid catheter introduced over 20% underestimation of the flow velocity measurement, while a hollow catheter that allows an internal flow minimized the disturbance to the flow dynamics by introducing less than 10% overestimation of the velocity measurement at the stenotic throat. While further testing is needed in different variations in anatomy and types of stenoses in addition to modifications of the catheter design, these results indicate that an intravascular catheter-based FV US transducer that allows internal flow could represent a viable solution for measuring flow velocity and estimating the WSS with minimal flow disturbance. Finally, we also presented initial proof-of-concept velocity profiles measured from the catheter-based FV US device and validated the results with a linear array transducer.

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_Ultrasonics. Author manuscript; available in PMC 2022 December 01._


Highlights

- A catheter-based array transducer was used for 3-D intravascular blood flow velocity measurements
- A hollow catheter reduces hemodynamic disturbance relative to a solid catheter
- The hollow catheter introduced <3% flow velocity difference in stenotic vessels
- Flow measurements using a prototype forward viewing transducer produce error <12%
Fig. 1.
Diagram of the experimental setup. The phantom with a stenosis is placed inside a tank filled with water. An L11-5 linear array transducer is placed on top of the phantom to acquire data along the longitudinal direction of the vessel. Set in refill mode, the water is pulled from the left to the right in a vessel and through the tube to the syringe pump. A catheter is inserted from the inlet.
Fig. 2.
2-D velocity map and corresponding centerline velocity profile in a peripheral artery phantom with a 43%DS when a catheter with an inner diameter of 3.81 mm and an outer diameter of 4.18 mm is placed 16 mm from the minimum luminal area. (a) 2-D velocity color map of the flow in a vessel. Distance indicates the distance from the tip of the catheter. The arrow on the left indicates the location of the vessel centerline. (b) The centerline velocity magnitude profile, which is derived from the 2-D velocity color map, is shown with increasing distance from the tip of the catheter.
Fig. 3.
B-mode images of phantom channels with three 3 mm consecutive regions (upstream, stenotic throat, and downstream) to mimic (a) a common hepatic artery with a 43 %DS stenosis, and (b) a coronary artery with a 54 %DS stenosis.
Fig. 4.
Effect of catheter design on velocity magnitude for a peripheral artery with a 43 %DS stenosis when the tip of the catheter is located 8.5 mm from the minimum luminal area in the vessel. For an inlet velocity of 363 ml/min, the use of a hollow catheter with an inner diameter of 3.81 mm and outer diameter of 4.18 mm results in a velocity magnitude at the center line (green) that is similar to that of the control case without a catheter (purple). For a solid catheter that does not allow internal flow and has the same outer diameter as the hollow catheter, the velocity magnitude deviates significantly from the control case. The shaded area indicates the 95% confidence interval.
Fig. 5.
Centerline velocity profiles in a peripheral artery with a 43 \% DS stenosis for the control case (blue) and when a hollow catheter (purple) with an inner diameter of 3.81 mm and an outer diameter of 4.18 mm is positioned: (a) 6.8 mm (b) 11.6 mm (c) 16 mm from the minimum luminal area. The shaded area indicates the 95\% confidence interval.
Fig. 6.
(a) Centerline velocity profiles in a peripheral artery with a 71 %DS stenosis for the control case (blue) and when a hollow catheter (purple) with an inner diameter of 3.81 mm and an outer diameter of 4.18 mm is positioned 11 mm from the minimum luminal area. (b) Centerline velocity profiles in a coronary artery with a 71 %DS stenosis for the control case (blue) and when a hollow catheter (purple) with an inner diameter of 1.32 mm and an outer diameter of 1.98 mm is positioned 10.34 mm from the minimum luminal area. The shaded area indicates the 95% confidence interval.
Fig. 7.
Forward viewing 3-D intravascular velocity measurements in a peripheral artery with a 43 %DS stenosis. Three flow rates are tested: 50 mL/min, 100 mL/min, and 150 mL/min. The z-direction is in the direction of the flow, with z = 0 at the tip of the catheter. Velocity maps are shown at three depths (columns): the upstream region from the stenosis (7.2 mm from the tip of the catheter), at the location with the minimum luminal area (9.25 mm from the tip of the catheter), and the region downstream from the stenosis (11.3 mm from the tip of the catheter). Three inlet flow velocities are shown (rows): 50 ml/min, 100 ml/min, and 150 ml/min. For all flow rates velocity magnitudes reach maximum values where the area of the blood flow is the smallest, in the stenotic throat region, and the profiles are parabolic.
Fig. 8.
Centerline velocity profiles in a coronary artery phantom with a 54 %DS stenosis for the control case (purple) and when a hollow catheter (blue) with an inner diameter of 1.32 mm and an outer diameter of 1.98 mm is positioned: (a) 6.1 mm (b) 10.1 mm (c) 14.1 mm from the minimum luminal area. The shaded area indicates the 95% confidence interval.
Table 1

Experimental cases tested

<table>
<thead>
<tr>
<th>Vessel diameter (mm)</th>
<th>Distance to minimum luminal area (mm)</th>
<th>Flow rate (mL/min)</th>
<th>Catheter design tested</th>
<th>Imaging transducer</th>
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<tr>
<td>#1 6.33</td>
<td>8.5</td>
<td>363 [71]</td>
<td>Hollow vs. Solid</td>
<td>Linear array</td>
</tr>
<tr>
<td>#2 6.33</td>
<td>6.8, 11.6, 16</td>
<td>363 [71]</td>
<td>Hollow (O.D.=4.18 mm, I.D.=3.81 mm)</td>
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<tr>
<td>#3 6.33</td>
<td>9.25</td>
<td>50, 100, 150</td>
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<td>FV US</td>
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<tr>
<td>#4 4.74</td>
<td>6.1, 10.1, 14.1</td>
<td>200 [72, 73]</td>
<td>Hollow (O.D.=1.98 mm, I.D.=1.32 mm)</td>
<td>Linear array</td>
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Table 2
Absolute velocity difference between cases with and without catheter in three regions

<table>
<thead>
<tr>
<th>Vessel diameter (mm)</th>
<th>Distance to minimum luminal area (mm)</th>
<th>Absolute velocity difference between cases with and without catheter (cm/s)</th>
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<tr>
<td></td>
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<td>Upstream region</td>
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<tr>
<td>6.33</td>
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<td></td>
<td>11.6</td>
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<td>4.74</td>
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<tr>
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<td>10.1</td>
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<tr>
<td></td>
<td>14.1</td>
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Table 3

Velocity measurements at the center with FV vs linear array transducer (cm/s)

<table>
<thead>
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<th>Flow rate (mL/min)</th>
<th>Transducer type</th>
<th>Distance to minimum luminal area (mm)</th>
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<tr>
<td></td>
<td></td>
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</tr>
<tr>
<td>50</td>
<td>FV</td>
<td>10.06 ± 1.25</td>
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<td></td>
<td>Linear array</td>
<td>11.94 ± 2.06</td>
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<tr>
<td>100</td>
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<td>150</td>
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