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ARFI Ultrasound for *In Vivo* Hemostasis Assessment Postcardiac Catheterization, Part I: Preclinical Studies

Russell H. Behler[1], **Mallory R. Scola**[1], **Timothy C. Nichols**[2,3,4], **Dwight A. Bellinger**[3], and **Caterina M. Gallippi**[1]

Caterina M. Gallippi: cmgallip@bme.unc.edu

[1]Joint Department of Biomedical Engineering, The University of North Carolina at Chapel Hill, Chapel Hill, NC 27599

[2]Division of Cardiology, The University of North Carolina at Chapel Hill, Chapel Hill, NC 27599

[3]Department of Pathology and Laboratory Medicine, The University of North Carolina at Chapel Hill, Chapel Hill, NC 27599

[4]Department of Medicine, The University of North Carolina at Chapel Hill, Chapel Hill, NC 27599

Abstract

The world wide prevalence of cardiovascular disease leads to over seven million annual percutaneous coronary catheterization procedures, the majority of which exploit femoral artery access. Femoral puncture sites (‘arteriotomies’) can be associated with severe vessel complications after sheath removal if hemostasis is not properly achieved. Hemostasis onset is routinely determined by examination for bleeding at the skin puncture; however, clotting along the puncture path can obscure subcutaneous bleeding, and therefore hemostasis is blindly assessed. We hypothesize that hemostasis assessment can be un-blinded by Acoustic Radiation Force Impulse (ARFI) ultrasound. In this first of a two-part series, we present *in vivo* ARFI hemostasis imaging data obtained in relevant canine models of femoral artery puncture. Above arteriotomies, ARFI-induced displacements were large (3.5 to > 5.0 μm) relative to surrounding soft tissue soon after needle removal, which was consistent with our expectation for pooled extravasated blood. ARFI-induced displacements above arteriotomies decreased in magnitude (to ~ 2 μm) some time after needle removal and suggested the onset of hemostasis. This preclinical investigation served as proof of concept and justification for a pilot human study, which is presented in part two of this series.

Keywords

Acoustic radiation force impulse (ARFI) ultrasound; canine model; cardiac catheterization; femoral artery; hemostasis

Introduction

Diagnosis and treatment of coronary artery disease leads to over seven million annual angiograms and percutaneous coronary interventions by catheterization world-wide. The majority of catheterization procedures gain access to coronary arteries by inserting a sheath through the femoral artery. After sheath removal, the femoral artery puncture site, known as the ‘arteriotomy’, is generally treated by manual compression and prolonged immobilization to achieve hemostasis.[1] If hemostasis is in complete, severe vessel complications, including hematomas, psuedoaneurysms, fistulas and groin infections, may follow. The reported incidence of such complications ranges from 3.5 to 26%, with the majority occurring within 48 hours after catheterization.[2] 20 to 40% of patients who experience such complications

require surgical repair.[3] Because the consequences of incomplete hemostasis are severe, manual compression and immobilization times may be prolonged to prevent re-bleeding. However, unnecessary delays may increase patient discomfort, extend time to discharge and increase medical expense.[4]

Currently, the onset of hemostasis is assessed by visual inspection of bleeding from the femoral access site at the skin surface. However, this is not an indication of subcutaneous bleeding that may be masked by clotting at the skin surface or along the femoral puncture path. Sustained hemostasis is assessed by a lack of complications such as hematoma formation after 2 to 6 hours of immobilization, but ideally, rebleeding would be detected and treated before complications arise. Vascular complications rates could be lowered and timely manual compression and ambulation facilitated by a medical imaging technology capable of *in vivo*, noninvasive, subcutaneous hemostasis assessment following sheath removal.

Acoustic Radiation Force Impulse (ARFI) ultrasound – an imaging technology that exploits energy in acoustic waves to interrogate the mechanical properties of tissue – is well suited to this application. ARFI has been demonstrated in previous work for inducing blood streaming in response to radiation force excitation in human carotid arteries, *in vivo*,[5] and sonorheometry is a related acoustic radiation force application for measuring blood coagulation times.[6] Coagulation time has also been evaluated by alternative ultrasonic means.[7-9] In addition to diagnostics, ultrasound has also been employed therapeutically to arteriotomies in rabbits.[10] This body of past work supports ARFI's relevance to *in vivo*, noninvasive assessment of subcutaneous hemostasis at femoral arteriotomy following cardiac catheterization.

The first in a two-part series, this paper presents our initial preclinical studies performed in relevant canine models of femoral artery puncture. In part two of the series, we present clinical results from our pilot human investigation.

Materials and Methods

All procedures were approved by the University of North Carolina at Chapel Hill Institutional Animal Care and Use Committee (IACUC). ARFI imaging was performed using a Siemens SONOLINE Antares™ imaging system specially equipped for modifiable beam sequencing and a VF7-3 linear array transducer (Siemens Medical Solutions USA, Inc. Ultrasound Division). First, two conventional two-cycle A-lines were acquired for references. These two A-lines were followed by a single 300-cycle (70 μs) ARFI excitation impulse centered at 4.21 MHz with an F/1.5 focal configuration. The excitation impulse was followed by an ensemble of 60 (5.5 ms) conventional A-lines at a center frequency of 6.15 MHz and a prf of 11 kHz. This pulse sequence was repeated with wiperblading (which entailed translating the imaging focus from the far left of the imaging field of view, to the center of the field of view, to one position right of the far left, to one position right of center, etc) in 40 lateral locations spaced 0.53 mm apart for a 2.1 cm lateral field of view. The focal depth was positioned on the near arterial wall at 18 mm.

Imaging was performed in the left and right femoral arteries of 4 beagles with no known clotting disorders, all of approximately 9-11 kg mass. The dogs were fully anesthetized with isoflurane to effect (usually ~2%) and ventilated during the procedure. With ultrasound image guidance, an 18-gauge catheter needle was inserted into the femoral arteries, puncturing the near arterial wall. The imaging transducer was used to apply pressure above the arteriotomy. To accommodate the shallow depth of the dogs' femoral arteries, a 1 cm acoustic stand-off pad was employed. Figure 1 illustrates the experimental set-up. ARFI and B-Mode data were acquired at baseline, at the time of arteriotomy, and at 5 to 7 s intervals following needle removal, for a total serial imaging time of 3 min.

Acquired raw rf data were transferred to a computational work station for processing and analysis. One-dimensional axial displacements were measured along each acquired ensemble using normalized cross-correlation with an interpolation factor of 4, a search window length of 80 μm, and a kernel length of 1.5λ. The method of axial displacement tracking is explained with extensive detail by Pinton et al.[11] Physiological motion was rejected using a linear filter.[12] Two-dimensional parametric images of peak ARFI-induced displacement, displacement at a given time point after excitation, time to recovery from ARFI-induced displacement and time-to-peak displacement were rendered. One spatially-matched B-Mode frame was acquired immediately before each ARFI data collection.

Results

Imaging results achieved in all four examined dogs were generally consistent. Representative results are presented in figure 2, which illustrates spatially-matched ARFI and B-Mode images acquired in the left femoral artery of a female, 9.5 kg beagle. Panel (a) shows the spatially-matched B-Mode image (top) and parametric image of ARFI-induced peak displacement (PD) (bottom) taken at baseline. The top and bottom femoral artery walls are positioned at approximately 17 and 20 axial mm, respectively (boxed). Note that in the base line PD image, the near arterial wall and surrounding soft tissue displace roughly 2 to 2.5 μm (light blue/green, as per adjacent colorbar). Panel (b) shows the spatially-matched B-Mode (top) and ARFI PD (bottom) images acquired with the puncturing needle in place. The red vertical lines denote the arterial diameter. The needle appears as a hyperechoic diagonal structure in the B-Mode image (arrow). The needle is also apparent in the ARFI PD image as a diagonal structure that exhibits relatively low displacement in response to radiation force excitation (arrow, ~0.25 μm, dark blue). At the intersection of the needle with the near arterial wall (circled), the ARFI PD image shows an area of heightened displacement (>5 μm, dark red, saturated colorscale). We hypothesize that this large displacement corresponds to extravasated blood displacing in response to radiation force excitation as the artery bleeds into the surrounding soft tissue. Note that there is no corresponding indication of bleeding in the matched B-Mode image.

Panel (c) shows matched B-Mode and ARFI images acquired 46 s after the puncturing needle was removed. Once again, the B-Mode image (top) offers no indication of hemostatic status. However, the ARFI PD image again shows a focal region of relatively large displacement (circled, >5 μm) at the arteriotomy. In addition, increased displacement relative to the baseline image is observed in the soft tissue above the near arterial wall (arrow), which is suggestive of ARFI-induced displacement of pooled extravasated blood. Panel (d) shows B-Mode and ARFI PD images acquired 93 s after the removal of the puncturing needle. As in the previous time points, the B-Mode image offers no information regarding hemostatic status. However, the ARFI PD image shows that induced displacement at the arteriotomy is smaller than at previous time points (circled, ~2.5 μm, light green), suggesting that clotting at the arteriotomy may have occurred. In addition, the relatively large displacements in the soft tissue above the arteriotomy are now dispersed (arrow), suggesting that the pooled extravasated blood in the soft tissue has diffused away from the arteriotomy and that bleeding has ceased.

Discussion

Our preclinical results obtained in the left and right femoral arteries of four dogs indicate that ARFI ultrasound is efficacious for monitoring hemostasis at femoral arteriotomies. Parametric images of ARFI-induced PD show heightened displacement at the location of the arteriotomy and in the soft tissue surrounding the arteriotomy as bleeding occurs. This heightened displacement is consistent with our expectation that pooled extravasated blood will displace farther in response to radiation force excitation than surrounding soft tissue. Similarly, observation of diminishing and diffusing ARFI-induced PDs at and above the arteriotomy 93

s after needle removal suggested that bleeding had ceased. No information regarding hemostatic status was provided by the matched B-Mode images.

While we chose to represent three-dimensional ARFI results in the form of two-dimensional parametric ARFI-induced PD images, it should be noted that parametric images of ARFI-induced displacement at a given time point (up to 1 ms) after excitation achieved comparable discrimination of extravasated blood (data not shown). However, extravasated blood was not well-identified in parametric images of time to recovery from ARFI-induced displacement, which appeared to be corrupted by high noise in the blood region (data not shown). This result was consistent with expectation that blood does not recover from ARFI-induced displacement. Finally, parametric ARFI images of time-to-peak displacement did not successfully distinguish extravasated blood from soft tissue, as time-to-peak measures were generally coincident with the first time point after excitation.

We did not validate ARFI estimations of time to hemostasis because we are not aware of a proven alternative method for detecting slow subcutaneous bleeding. Clotting in the puncture path rather than at the arteriotomy itself could have caused cessation of bleeding at the skin surface while bleeding continued from the artery. In future work, we will consider comparing ARFI results to alternative experimental hemostasis imaging methods such as contrast enhancement with a bubble-bursting pulse sequence. We will also consider an opened-leg imaging protocol that would allow us to clamp the artery to prevent bleeding after puncture. Despite this study limitation, these preliminary results yielded proof of concept and ample justification for a pilot human investigation.

Conclusions

Preclinical studies in relevant canine models of femoral artery puncture support that ARFI ultrasound is a viable imaging method for *in vivo*, noninvasive monitoring of hemostasis at femoral arteriotomies. This work serves as justification for a pilot human study involving patient volunteers undergoing diagnostic percutaneous cardiac catheterization.

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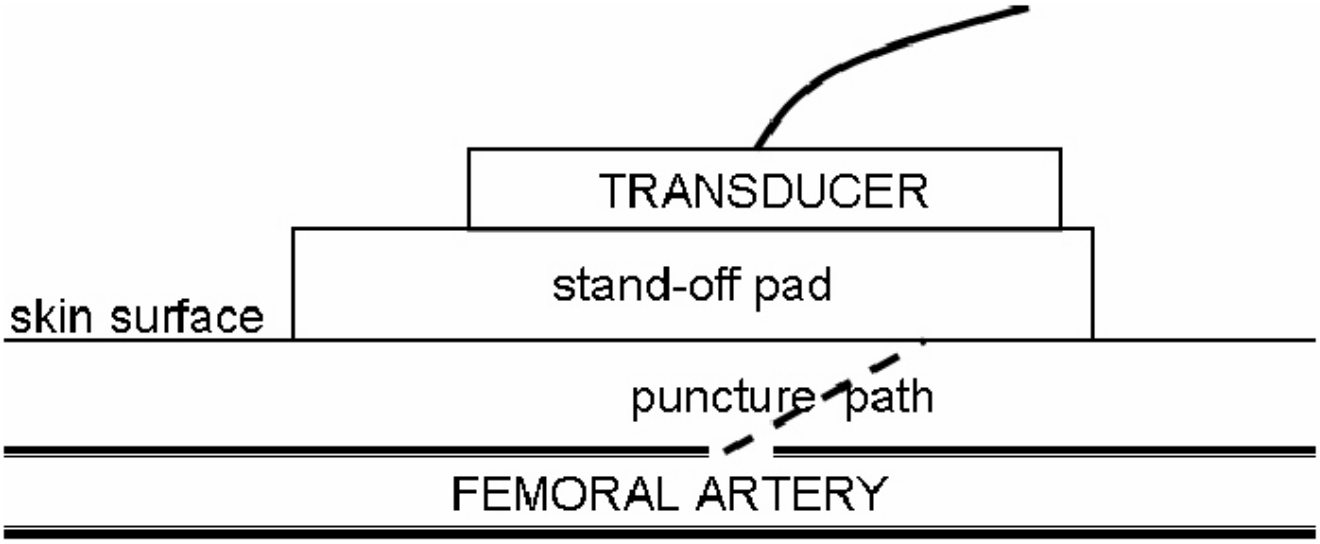

FIG. 1.

Experimental set-up for ARFI imaging of hemostasis at femoral arteriotomy in canine model. Four beagles were fully anesthetized and ventilated during the procedure. The left and right femoral arteries were punctured with a 18 gauge needle. ARFI and B-Mode data were collected at baseline, during arterial puncture, and at 5-7 s intervals following needle removal for a total serial imaging period of 3 min. To perform imaging, the ultrasound transducer was positioned above a 1 cm stand-off pad. The transducer and pad were centered above the arteriotomy, with the skin puncture site and the puncture path within the lateral imaging field of view. Figure not drawn to scale.

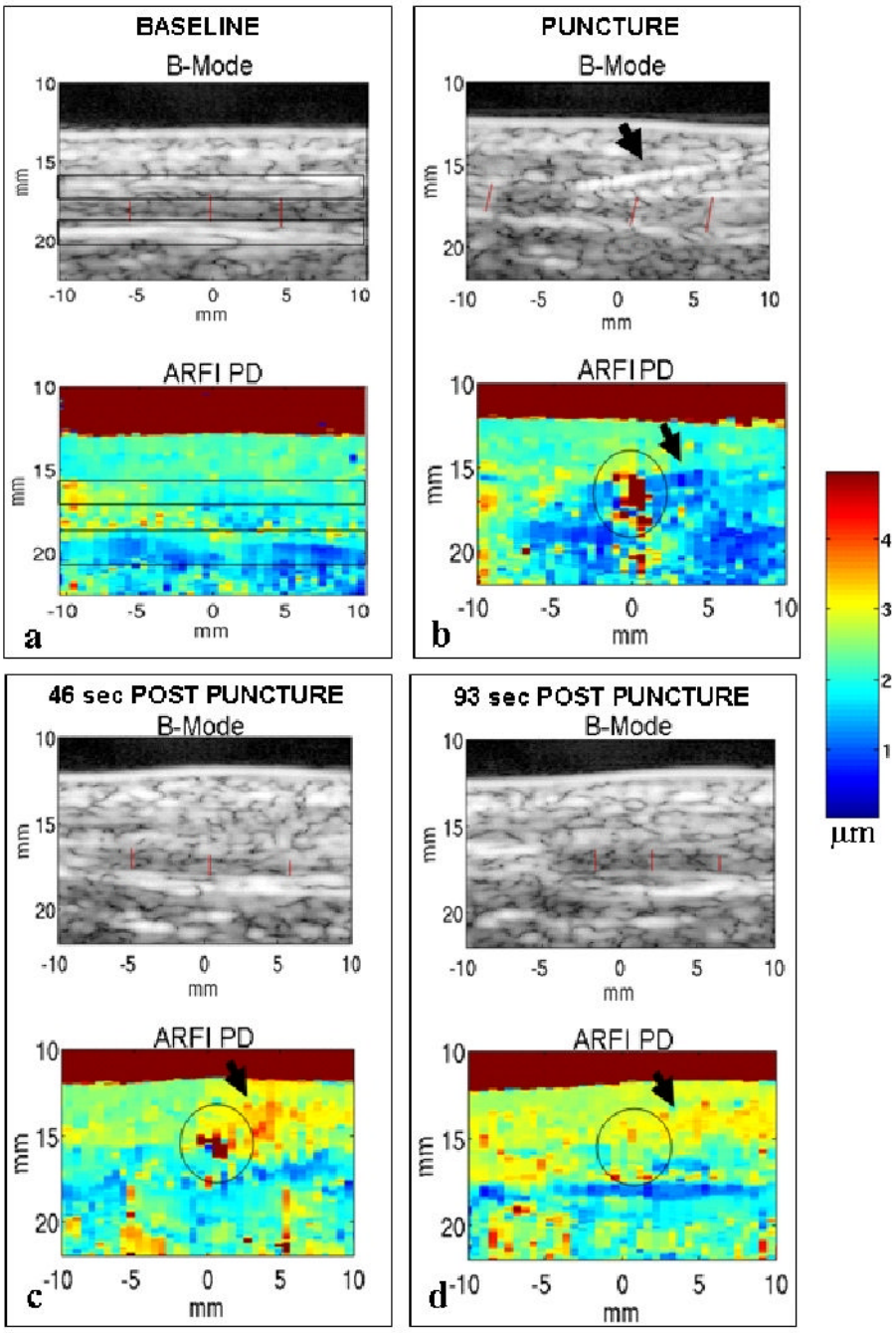

FIG. 2.

Matched B-Mode and ARFI-induced peak displacement (PD) images in the left femoral artery of a female, 9.5 kg beagle. Prior to puncture (panel (a)), the artery appears intact in the B-Mode (top) image (red lines denote arterial diameter). The ARFI PD image (bottom) shows that the arterial walls exhibit a generally uniform response to ARFI excitation (arterial walls boxed). Panel (b) shows results acquired during femoral artery puncture with a 18 gauge needle, which is in place during imaging (arrows). In the ARFI PD image, the dark red region suggests blood displacing in response to ARFI excitation at the position of the arteriotomy (circled). Panel (c) shows data acquired 46 s after the puncturing needle was removed. The ARFI image shows a focal region of large PD (dark red, circled) at the arteriotomy, with a larger region to the upper

right of heightened PD (arrow). These regions are consistent with pooled extravasated blood displacing in response to ARFI excitation. In panel (d), 93 s after the puncturing needle was removed, no large PD is apparent at the arteriotomy (circled), and large displacements observed in the adjacent soft tissue are smaller and more dispersed (arrow), which suggests that bleeding has stopped at the arteriotomy.