In vivo demonstration of photoacoustic image guidance and robotic visual servoing for cardiac catheter-based interventions

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Abstract—Cardiac interventional procedures are often performed under fluoroscopic guidance, exposing both the patient and operators to ionizing radiation. To reduce this risk of radiation exposure, we are exploring the use of photoacoustic imaging paired with robotic visual servoing for cardiac catheter visualization and surgical guidance. A cardiac catheterization procedure was performed on two in vivo swine after inserting an optical fiber into the cardiac catheter to produce photoacoustic signals from the tip of the fiber-catheter pair. A combination of photoacoustic imaging and robotic visual servoing was employed to visualize and maintain constant sight of the catheter tip in order to guide the catheter through the femoral or jugular vein, toward the heart. Fluoroscopy provided initial ground truth estimates for 1D validation of the catheter tip positions, and these estimates were refined using a 3D electromagnetic-based cardiac mapping system as the ground truth. The 1D and 3D root mean square errors ranged 0.25-2.28 mm and 1.24-1.54 mm, respectively. The catheter tip was additionally visualized at three locations within the heart: (1) inside the right atrium, (2) in contact with the right ventricular outflow tract, and (3) inside the right ventricle. Lasered regions of cardiac tissue were resected for histopathological analysis, which revealed no laser-related tissue damage, despite the use of 2.98 mJ per pulse at the fiber tip (379.2 mJ/cm² fluence). In addition, there was a 19 dB difference in photoacoustic signal contrast when visualizing the catheter tip pre- and post-endocardial tissue contact, which is promising for contact confirmation during cardiac interventional procedures (e.g., cardiac radiofrequency ablation). These results are additionally promising for the use of photoacoustic imaging to guide cardiac interventions by providing depth information and enhanced visualization of catheter tip locations within blood vessels and within the beating heart.

1. INTRODUCTION

Cardiac interventional procedures, such as diagnostic electrophysiology and radiofrequency ablation, are often performed to diagnose and treat cardiac arrhythmias. During these procedures, a catheter is inserted into the femoral vein or artery in the patient’s thigh and navigated into the heart using fluoroscopic guidance [1], [2]. Once inside the heart, it is necessary to utilize image guidance to reach points of interest. A combination of intracardiac echocardiography and fluoroscopy is typically used to provide real time localization of the catheter tip inside the heart [3].

There are several challenges with these two primary image guidance methods for cardiac interventions. First, due to the projection method of fluoroscopic acquisitions, it is often difficult to determine the depth of the catheter in the image. In addition, fluoroscopy utilizes ionizing radiation, exposing both the patient and operators. For example, Lickfett et al. [4] found that the mean fluoroscopy duration for atrial fibrillation procedures was greater than 60 minutes, resulting in greater than 1.0 Gy of peak skin radiation dose to the patient. While this radiation dose does not exceed the safety limits, repeated exposure increases lifetime risk of excess fatal malignancies [4], [5].

In intracardiac ultrasound imaging, the ultrasound array elements are located at the catheter tip, which is the frame of reference for acquired images. This moving reference frame provides excellent local views of the anatomy as the catheter is advanced, but it requires skilled operators [6] and does not provide a more global reference frame. These limitations require the additional use of fluoroscopy (in combination with electromagnetic tracking and electrical mapping) for global positioning of the catheter. For global localization of the catheter tip position based on ultrasound signals, it would be more ideal to use a transthoracic ultrasound probe, but transthoracic ultrasound images are known to suffer from several image artifacts, including acoustic clutter [7] and shadowing from the ribs [8]. Therefore, it is difficult to consistently locate the catheter tip in these transthoracic ultrasound images. In addition, the catheter tip can often be difficult to resolve with respect to its shaft and this tip is particularly difficult to visualize when it has similar echogenicity to the surrounding tissue [9]–[12].

Other imaging modalities to assist with catheter tracking include magnetic resonance imaging (MRI) [13] and computed tomography (CT) [14]–[16]. These modalities use preoperative images for registration with intraoperative fluoroscopic imaging. While they are capable of providing successful results, these methods still require the use of intraoperative fluoroscopy and, in the case of CT, add additional radiation exposure to the patient prior to the cardiac intervention. In addition, both CT and MRI rely on preoperative imaging, which do not take into account motion during surgery. Another

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possibility is all-optical ultrasound, which is being explored as a promising, MRI-compatible method for simultaneous visualization of cardiac radiofrequency ablation lesions and catheter tip tracking [17]–[19], yet independently shares the limitations of intracardiac ultrasound with respect to its local reference frame.

Photoacoustic imaging has recently emerged as a novel imaging technique capable of achieving submillimeter resolution in real time without utilizing ionizing radiation [20], [21]. This imaging technique relies on the illumination of a region of interest with a pulsed laser. The pulsed laser light is then absorbed by photoabsorbers within the tissue (such as hemoglobin), resulting in a small mK rise in temperature due to vibrational and collisional relaxation. The temperature rise results in rapid thermal expansion, generating an acoustic pressure wave. This pressure wave can be received by an ultrasound probe and reconstructed into an image [20], [21].

Endogenous contrast in photoacoustic images is primarily derived from differences in the optical absorption spectrum of different tissue types [21], [22], such as differences between blood and surrounding soft tissue. Photoacoustic imaging has multiple medical applications, with one focus being its potential to guide a variety of surgeries and procedures, including neurosurgeries [23], spinal fusion surgeries [24], hysterectomies [25]–[27], prostatectomies [28], fetal surgeries [29], minimally invasive robotic surgeries [26], [30], and liver biopsies [31], [32]. In addition, photoacoustic imaging has been used to distinguish between ablated and healthy myocardial tissue after a radiofrequency ablation [33]–[35]. Bouchard et al. [33] demonstrated 6-10 dB of contrast between ablated regions and normal tissue using a wavelength of 750 nm in ex vivo porcine cardiac tissue but with limited penetration depth. Dana et al. [34] later performed similar experiments in vitro with an increased imaging depth of up to 3 mm, visualizing ablation lesions with submillimeter accuracy and providing 3D visualizations of ablated and non-ablated myocardium in excised tissue. Iskander-Rizk et al. [35] later implemented a dual wavelength (790 nm and 930 nm) approach to identifying radiofrequency ablation regions, achieving a diagnostic accuracy of 97%.

Building on the demonstrated potential of photoacoustic imaging to characterize cardiac radiofrequency ablation lesions [33]–[35], we are exploring photoacoustic imaging as an additional guidance method to reduce fluoroscopy exposure during cardiac interventions, which require catheter tip visualization for navigation to and within the heart. In addition to the known challenges with using ultrasound alone to guide catheter placement (i.e., poor image quality of vessel visualization in the presence of acoustic clutter, which raises uncertainty about the catheter tip location), another challenge is the expectation that the ultrasound probe will be held by hand. We propose to overcome both of these challenges with a robotic photoacoustic system that holds the ultrasound probe and autonomously centers the probe on photoacoustic signals from the catheter tip, using the photoacoustic-based robotic visual servoing approach presented in our previous publications [32], [36].

In this paper, a novel method for autonomous catheter tip visualization and tracking with photoacoustic-based visual servoing is demonstrated. To the authors’ knowledge, this paper also presents the first known demonstration of the feasibility of acquiring photoacoustic images within an in vivo heart. We also show example photoacoustic images acquired during specific time points throughout catheter navigation to and within the heart. Finally, we performed a histopathological analysis on excised cardiac tissue to explore possible tissue damage caused by the laser energies used to acquire the in vivo photoacoustic images.

II. METHODS

A. Photoacoustic Imaging System

Our photoacoustic imaging system consisted of a Phocus Mobile laser (Optotek, Carlsbad, CA, USA), an E-CUBE 12R ultrasound scanner (Alpinion Medical Systems, Seoul, South Korea), and a Sawyer robot (Rethink Robotics, Boston, MA, USA). Unless otherwise stated, an Alpinion SP1-5 phased array ultrasound probe was attached to the end effector of the robot to acquire ultrasound and photoacoustic images. This probe was calibrated to the robot using the method described by Kim et al. [37]. A 1 mm core diameter optical fiber was coupled to the laser source on one end with the other end inserted into the hollow core of a 5F inner diameter, 7F outer diameter, 28 inch long, non-steerable cardiac catheter (St. Jude Medical, St. Paul, MN, USA). The tips of the fiber and catheter were coincident with each other, and a photograph of this fiber-catheter pair is shown in Fig. 1.

The ultrasound probe had a center frequency of 2.5 MHz, a bandwidth of 1 to 5 MHz, a selected transmit frequency of 3.5 MHz, and a lens with fixed elevation focus at approximately 70 mm depth. The mean ± one standard deviation of five lateral resolution measurements per target was 0.34 ± 0.02 mm, measured as the full width at half maximum (FWHM) of two line targets in a CIRS 054Gs phantom (Computerized Imaging Reference Systems, Inc., Norfolk, VA, USA). The mean ± one standard deviation of five lateral resolution measurements per
target, measured as the FWHM of line targets in the same phantom located at 18 mm and 78 mm axial depths (with foci at 20 mm and 80 mm, respectively), was $0.87 \pm 0.06$ mm and $2.71 \pm 0.25$ mm, respectively. These depths were chosen because they were the closest available depths in the phantom corresponding to the mean target depths during the \textit{in vivo} experiments described in Section II-C. The elevation resolution of these two line targets was measured after rotating the robot-held ultrasound probe by $90^\circ$ (to align the lateral dimension with the length of the line targets), translating in the direction corresponding to the elevation dimension of the probe, then acquiring and stacking the resulting ultrasound images. The mean $\pm$ one standard deviation of five elevation resolution measurements per target, measured at axial depths of 18 mm and 78 mm (with foci at 20 mm and 80 mm, respectively), was $8.10 \pm 0.68$ mm and $3.18 \pm 0.43$, respectively.

The first near-infrared window for maximum optical penetration in biological tissue is 650 - 900 nm. Despite this range of suitable wavelengths for the endogenous hemoglobin chromophore, a fixed laser wavelength of 750 nm was chosen to generate a photoacoustic response from blood in the experiments described in Sections II-B, II-C, and II-G.

\section*{B. Investigating Source of Photoacoustic Signals}

Considering that the laser fluence is generally greatest at the fiber tip, we hypothesized that the photoacoustic signals obtained with the photoacoustic imaging system described in Section II-A originate from the fiber tip. To test this hypothesis, two \textit{ex vivo} experiments were performed to determine the source of the photoacoustic signals within a catheterized blood vessel. In the first experiment, the hollow core of a plastisol phantom was perfused with whole human blood. In the second experiment, the blood was removed and replaced with a porcine aorta inserted into the hollow core of the plastisol phantom, and the aorta was perfused with whole human blood. This second experiment enabled us to test our hypothesis in the presence of tissue, which introduces acoustic clutter that complicates catheter tip visualization in ultrasound images and makes it difficult to visually maintain the catheter tip within the plane of the ultrasound probe, similar to challenges expected \textit{in vivo}.

For each \textit{ex vivo} experiment, an Alpinion L3-8 linear array ultrasound probe was positioned with its imaging plane centered along the length of the hollow core of the phantom. The fiber-catheter pair shown in Fig. 1 was inserted in the blood, and the 1 mm core diameter optical fiber emitted an average 2.8 mJ per pulse (approximately 365.5 mJ/cm$^2$ fluence at the fiber tip). Photoacoustic images were acquired with the fiber tip in three positions relative to the catheter tip: (1) proximal, (2) coincident, and (3) distal, as illustrated in Fig. 2. Assuming that our hypothesis is true, when the fiber tip is coincident with the catheter tip, the photoacoustic signals from the fiber tip can be approximated as coincident with the location of the catheter tip.

\section*{C. Navigating a Cardiac Catheter in an In Vivo Pig}

The robot described in Section II-A was used to maintain continuous sight of the catheter tip by visually servoing photoacoustic signals from the catheter tip, as described in previous publications for a needle tip [32], [36] and summarized in more detail in Section II-D. We evaluated the performance of our visual servoing system and assessed photoacoustic signal visualization in an \textit{in vivo} setting consisting of two female pigs weighing 43 kg (first pig) and 40 kg (second pig). The first pig was primarily useful with regard to determining initial \textit{in vivo} feasibility, while the second pig was useful with regard to refining our methodology and confirming initial observations. The fiber-catheter pair shown in Fig. 1 was navigated toward the heart in these experiments after obtaining vascular access through the femoral vein in both pigs and through the jugular vein in the second pig, using an ultrasound-guided micropuncture technique. All studies and procedures (described in more detail below) were approved by the Johns Hopkins University Animal Care and Use Committee.

After each pig was fully anesthetized with isoflurane, two 9F vascular sheaths were placed in the right femoral vein and artery. An additional sheath was placed in the jugular vein of the second pig. Once each sheath was secured in place, a bolus of heparin (5,000 United States Pharmacopeia units) was administered. The fiber-catheter pair was inserted into the femoral vein sheath in both pigs and the jugular vein sheath in the second pig and advanced toward the heart. An example of the experimental setup is shown in Fig. 3.

For the first pig, preoperative fluoroscopic guidance was used for an initial mapping of the catheter path from the femoral vein in the direction of the heart. Five checkpoints along the catheter path (i.e., Positions 1-5) were marked on the skin surface with posterior-anterior (PA) fluoroscopic images obtained at each of the checkpoints. These same checkpoints were marked on the catheter at the entry point into the vascular sheath. The distances from Positions 1-2, 2-3, 3-4 and 4-5 were approximately 6 cm, 3.5 cm, 5.5 cm, and 4 cm, respectively, spanning a total distance of 19 cm.

The catheter was returned to Position 1 and the Alpinion SP1-5 phased array ultrasound probe (held by the robot) was placed in the general area where Position 1 was marked, with the lateral dimension aligned in the direction of the

![Fig. 2. (left) A schematic diagram of the \textit{ex vivo} experimental setup to investigate the source of photoacoustic signals within a catheterized blood vessel and (right) a corresponding photograph of this setup.](image-url)
external markings (i.e., to ensure that the lateral dimension of the probe would be roughly aligned with the long axis of the catheter-fiber pair). The catheter was manually navigated toward Position 5 with visual servoing of the photoacoustic signal enabling the ultrasound probe to autonomously remain centered on the photoacoustic signal from the catheter tip. The average laser energy per pulse was 2.67 mJ, and the fluence at the fiber tip was approximately 340 mJ/cm². This energy was chosen because it was the minimum energy required for successful catheter tip segmentation.

In addition to fluoroscopic images, fiber tip localization errors were investigated with an EnSite™ Precision Cardiac Mapping System (Abbott, Abbott Park, IL, USA) in the second pig. This mapping system has a reported 3D tracking accuracy of 0.45 ± 0.49 mm and a 3D navigation accuracy of 0.34 ± 0.16 mm [38]. Tracking accuracy was defined as the error between an induced catheter displacement and the corresponding measured displacement. Navigation accuracy was defined as the error in navigating a catheter back to a defined location. Due to its proximity to the chest cavity and our familiarity with operating the mapping system for cardiac applications, we chose to test our procedure on the jugular vein, which was first mapped to create a 3D vessel model. Three visual servoing trials were then performed while navigating the fiber-catheter pair within the jugular vein over a total distance of approximately 4 cm.

In the first visual servoing trial for the second pig, the cardiac catheter was positioned near the entry point in the jugular vein. The ultrasound probe was manually placed to visualize the photoacoustic signals with the lateral dimension of the probe roughly aligned with the long axis of the catheter-fiber pair. This purposeful placement ensures that the direction of maximum motion is not aligned with the worst resolution dimension of the visual servoing system (i.e., the elevation dimension of the ultrasound probe). Visual servoing ensued as the fiber-catheter pair was manually navigated toward the heart, stopping at 8 random positions during insertion. Then, the fiber-catheter pair was retracted, stopping at an additional 5 random positions during retraction. At each stop, an electromagnetic (EM) catheter connected to the mapping system approached the fiber-catheter pair from the opposite direction, entering from the right femoral vein to touch the tip of the fiber-catheter pair fiber in the jugular vein. This connection point was confirmed by acquiring right anterior oblique (RAO) fluoroscopic images. The position of catheter-to-catheter contact was logged with the mapping system and considered as the ground truth catheter tip location for 3D localization errors. The EM catheter was then withdrawn, and visual servoing proceeded to the next random position.

In the second visual servoing trial, the fiber-catheter pair was visually servoed during insertion with no stops, and the average robot velocity was approximately 0.97 mm/s. Similarly, in the third trial, the cardiac catheter was visually servoed during retraction with no stops, and the average robot velocity was approximately 1.8 mm/s. A total of 92.1% and 91.3% valid labels were produced by the validity check defined in Section II-D2 during these second and third trials, respectively. This similar performance between the two trials quantifies the smooth, uninterrupted motion that we observed when not making random stops to assess localization errors.

During these three visual servoing trials in the second pig experiment, the average laser energy per pulse was 0.75 mJ, and the fluence at the fiber tip was approximately 95.4 mJ/cm² (which was the minimum energy required for successful catheter tip segmentation). This energy is lower than that used during visual servoing in the first pig experiment, likely due to the shallower imaging depth of the jugular vein compared to the femoral vein.

D. Visual Servoing of Cardiac Catheter Tip

Our visual servoing method consists of catheter tip segmentation, segmentation comparisons and validity checking, followed by probe centering and post-processing, as described in more detail below. During the interim period between the first and second pig experiments described in Section II-C, our segmentation comparison and probe centering software were updated. Therefore, two alternative methods are reported for each of these procedures.

1) Catheter Tip Segmentation: The catheter tip was segmented from the photoacoustic image using a series of standard image processing techniques, with the initial technique being binary thresholding. This threshold was dynamically

![Fig. 3. An ultrasound probe was attached to the end effector of the Sawyer robot and placed in a starting position near the jugular venous catheter sheath. As the catheter was manually advanced toward the heart, the robot advanced the ultrasound probe to autonomously maintain continuous visualization of the advancing catheter tip (see Supplementary Video 1). Probe motion was based on catheter tip coordinates identified in real-time photoacoustic images.](image-url)
selected based on the maximum intensity in the photoacoustic image. Second, dilation and erosion were performed with a 3x3 kernel to remove single-pixel regions and connect nearby segments that became disconnected during the binary thresholding process. This second step helped to ensure that the segmented catheter tip signal was displayed as a single connected component (rather than multiple smaller components of the same signal), thereby increasing the performance of the third step, which was connected component labeling. After this third step, the pixel area was calculated for each label and the frequency of each area measurement was displayed as a histogram. The mean area was computed and regions with areas of more than three times the mean were selected. If only one region met this criterion, it was assumed to be the catheter tip, and the centroid of that region was calculated as the catheter tip position. Otherwise, the algorithm assumed that the catheter tip was not visible in the image frame. Example outputs of this segmentation step are shown in Fig. 4.

2) Segmentation Comparisons and Validity Check: For robustness, the segmentation results from five frames were assessed for spatiotemporal continuity using two different comparison methods. In the first method, five images were acquired after the robot stopped moving. Each of the acquired images was then segmented to obtain an estimate of the catheter tip position. If the five estimated catheter tip positions were within 10% of the mean position, then the mean estimated catheter tip position was labeled as valid. The mean estimated catheter tip position and its validity check result were then forwarded to the robot.

In the second comparison method, instead of waiting for the robot to stop moving, each acquired image was segmented and compared to the four preceding images with the robot. The commanded velocity was then converted into the robot base frame as \( B\vec{p}(n) \) using the following equation, where \( E^T U \) is the fixed transformation from the instantaneous ultrasound probe frame, \( U \), to the robot’s end effector, \( E \), (obtained from the calibration process), and \( B^T E(n) \) is the instantaneous transformation from the robot’s end effector to its base, \( B \).

\[
B\vec{p}(n) = B^T E(n) E^T U \vec{p}(n)
\]  

The robot was then commanded to move the ultrasound probe to the position \( B\vec{p}(n) \) to center the probe over the estimated position of the catheter tip. We refer to this method as position-based visual servoing.

In the second method, instead of moving the probe to the position \( B\vec{p}(n) \), the robot was commanded to move its end effector with a velocity \( U\vec{v}(n) \) computed using a proportional-integral-derivative (PID) controller. The PID controller was provided with \( U\vec{p}(n) \) as an input, and computed the required velocity \( U\vec{v}(n) \) in the probe frame according to the following equation, where \( K_p, K_I, \) and \( K_d \) are the proportional, integral, and derivative gains of the controller, respectively, and \( \Delta t \) is the time difference between the current and previous estimated positions.

\[
U\vec{v}(n) = K_p U\vec{p}_x(n) + K_I \sum_{k=0}^{n-1} U\vec{p}_x(k) \Delta t + K_d \left( U\vec{p}_x(n) - U\vec{p}_x(n-1) \right) / \Delta t
\]

The commanded velocity was then converted into the robot base frame using the following equation.

\[
B\vec{v}(n) = B^T E(n) E^T U \vec{v}(n)
\]

We refer to this method as velocity-based visual servoing.

For both methods (i.e., position- and velocity-based visual servoing), if the catheter tip position was continuously determined to be invalid for more than one second (based on the validity check defined previously in Section II-D2), then the robot was commanded to search for the catheter tip in a pre-programmed pattern until either the catheter tip was reacquired or the system timed out. The position- and velocity-based probe centering methods were respectively implemented during the first and second pig experiments described in Section II-C.
4) **Post-Processing:** The acquired data was post-processed to remove data points that were either deeper than the field of view of the photoacoustic images or shallower than the target was expected to appear. These erroneous data points were introduced after losing visualization of the catheter tip and incorrectly detecting electronic or thermal noise as the photoacoustic target. In particular, for the first pig experiment, points shallower than 6 cm and deeper than 10 cm in the photoacoustic image were removed, and for the second pig experiment, points deeper than 4 cm were removed. In addition, because robot positions were continuously recorded whether or not the ultrasound probe was in contact with the skin to acquire images, data points obtained while the probe was not in contact were also removed.

**E. Validation of Catheter Tip Locations**

The accuracy of the catheter tip locations identified by the visual servoing algorithm was evaluated using both fluoroscopy and the mapping system described in Section II-C.

To validate with fluoroscopy in both pig experiments, the 2D catheter tip positions acquired with the robot, \( \vec{p}_n \), were transformed into a fixed frame, \( U_1 \), to obtain \( \vec{p}_{x,y}(n) \), where \( U_1 \) is the same as \( U \) (i.e., the moving probe frame) at a particular time \( n_1 \). The transformation between frame \( U_1 \) and the photoacoustic system, \( F \), was estimated using a subset of \( U_1\vec{p} \) and the corresponding catheter tip positions identified with fluoroscopy. The full set of robot positions (i.e., \( U_1\vec{p}(n) \)) was then transformed into frame \( F \) as \( F\vec{p}(n) \) and overlaid on the fluoroscopic image. A spline was fit to the position of the catheter in the fluoroscopic images. A 1D root mean square error (RMSE) between the catheter spline positions and \( F\vec{p}(n) \) was then calculated. For the second pig experiment, two separate 1D RMSE measurements were calculated in order to demonstrate the similarity when using (1) all points within \( F\vec{p}(n) \) and (2) the subset of points within \( F\vec{p}(n) \) that were simultaneously acquired with the mapping system.

To validate with the mapping system, the 3D catheter tip positions acquired with the robot, \( \vec{p}_n \), were transformed into a fixed frame, \( U_2 \), to obtain \( \vec{p}_{x,y,z}(n) \), where \( U_2 \) is the same as \( U \) (i.e., the moving probe frame) at a particular time \( n_2 \), and the \( x \), \( y \), and \( z \) dimensions of \( \vec{p}_{x,y,z}(n) \) correspond to the elevation, lateral, and axial dimensions of the ultrasound probe. The 3D rigid body transformation, \( U_2T_M \), from the mapping system frame, \( M \), to frame \( U_2 \), was calculated using Horn’s quaternion-based algorithm [39] using a subset of \( U_2\vec{p} \) and the corresponding catheter tip positions from the mapping system. The full set of catheter tip positions in the mapping frame, \( M\vec{p}(n) \), were transformed into the fixed probe coordinate frame as \( U_2\vec{p}(n) \) using the equation:

\[
U_2\vec{p}(n) = U_2T_M M\vec{p}(n) \tag{4}
\]

The 3D RMSE was then calculated between \( U_2\vec{p}(n) \) and \( U_2\vec{p}(n) \) using only the points within \( U_2\vec{p}(n) \) that were simultaneously acquired with each \( U_2\vec{p}(n) \) position.

Note that the accuracy of catheter tip localization with visual servoing relies on the resolution of the photoacoustic imaging system which is similar to the resolution of the ultrasound system [40]. In particular, when validating catheter tip positions, the depth-dependent resolution measurements reported in Section II-A are expected to influence our overall error measurements. In addition, the accuracy of the mapping system reported in Section II-C is also expected to introduce error in catheter tip localization measurements.

**F. Confirmation of Vessel Location with Doppler Imaging**

Color Doppler, an ultrasound modality typically used to visualize blood flow, was used to confirm vessel locations for the first pig experiment (as opposed to the mapping system, which was unavailable during the first pig experiment and provided vessel confirmation in the second pig experiment). A bolus of water was injected through the vascular sheath immediately prior to initiating color Doppler imaging, which was then implemented by tracking radiofrequency lines from a single location over multiple acquisitions (defined as one ensemble package).

The color Doppler images were obtained from a pulse sequence with a 0.6 kHz pulse repetition frequency (PRF), an ensemble package of 12, a focus of 8 cm, and a total image depth of 12 cm. The 0.6 kHz PRF was selected to sufficiently sample the relatively high flow velocities (i.e., 7 cm/s). The red color in the displayed Doppler images represents flow toward the probe and the blue color represents flow in the opposite direction. These color Doppler images were overlaid on B-mode images to enhance interpretability.

**G. Visualization of Photoacoustic Signals within In Vivo Heart**

In addition to visualizing the catheter tip within the right femoral vein, the catheter tip was also visualized at two positions within the heart of the first pig: (1) inside the right atrium and (2) in contact with the right ventricular outflow tract (RVOT). The ultrasound probe was manually positioned then held in place with the robot for each of these three positions. The optical fiber was held in place for a total of 23 minutes while the catheter was navigated and images were acquired at each position. Matching ultrasound, photoacoustic, and fluoroscopic images were acquired at these three positions. The average laser energy per pulse was 2.98 mJ and the fluence at the fiber tip was approximately 379.2 mJ/cm².

To provide additional confirmation of signal differences observed while in contact with the endocardium, the catheter was navigated through the femoral vein toward the heart of the second pig and was visualized with and without endocardial contact with the right ventricle, as confirmed with an injection of the contrast agent iohexol during fluoroscopic imaging. To quantify differences in signal appearance, contrast was measured as follows:

\[
\text{Contrast} = 20\log_{10} \left( \frac{\mu_{signal}}{\mu_{background}} \right) \tag{5}
\]

where \( \mu_{signal} \) and \( \mu_{background} \) are respectively the mean values within regions of interests (ROIs) corresponding to the photoacoustic signal and background regions of delay-and-sum.
beamformed radiofrequency data. The ROIs were located at the same axial depth, and each ROI was the same size of approximately 1.2 mm x 0.3 mm. The average laser energy per pulse was 2.25 mJ, and the fluence at the fiber tip was approximately 286.2 mJ/cm² for these measurements.

H. Assessing Possible Laser Damage to Cardiac Tissue

In the experiments described in Sections II-C and II-G, the laser fluence exceeded the 25.6 mJ/cm² laser safety limit defined for skin at a wavelength of 750 nm [41]. However, no safety limits currently exist for lasers in direct contact with blood vessels or cardiac tissue. Assuming that the laser will be in contact with cardiac tissue longer than it will be in contact with the vein in cardiac catheter-based interventions, we assessed possible laser-related damage to the heart that could have been caused by the energy applied to obtain photoacoustic images of the catheter tip within the heart. In addition, the fluence was highest in the heart of first pig. Therefore, the heart of the first pig was removed for histopathological analysis.

Immediately after cardiac tissue resection, lasered regions were identified by visually comparing the excised heart with fluoroscopic images and marking the lasered regions with blue tissue dye. These marked regions of the heart were then fixed in 10% neutral buffered formalin. These tissue specimens were then processed and embedded in paraffin, cut to 5 µm-thick slices, and standard haemotoxylin and eosin (H&E) staining was applied to perform microscopic examination and assess possible laser-related pathology. Standard histopathological processing and readings were performed by co-author S.B, a board-certified veterinary pathologist.

The following five regions of the heart were analyzed at 200x magnification: (1) the anterior wall of the RVOT (i.e., endocardial surface where laser was in contact with the tissue, as approximated from the fluoroscopic image), (2) a control region in the RVOT (including both the endocardial and epicardial surfaces) near region 1 (i.e., >1 cm away from region 1), (3) the superior portion of the interventricular septum (IVS) adjacent to the location of the fiber tip in the RVOT, (4) a control region from the IVS inferior to region 3 (i.e., >1 cm away from region 3), and (5) a control region from the epicardial surface of the left ventricular free wall, where no photoacoustic imaging was performed.

III. RESULTS

A. Ex Vivo Visualization of Photoacoustic Signals

Fig. 5 shows photoacoustic images overlaid on ultrasound images of the fiber-catheter pair within the ex vivo blood phantom. The top row shows images in the presence of blood. The bottom row shows images when this blood is replaced with an ex vivo aorta filled with blood and when the catheter tip is slightly outside of the image plane (based on the ultrasound image and knowledge of the catheter tip geometry shown in Fig. 1). Therefore, in addition to identifying the source of the photoacoustic signals, this experiment also shows a range of photoacoustic signal appearances that are possible in vivo. The photoacoustic signals from the catheter tip remain well-visualized in the presence of tissue, which further emphasizes the expected benefits of using photoacoustic imaging to approximate the location of the cardiac catheter tip in the presence of acoustic clutter and out-of-plane motion.

A diffuse photoacoustic signal was observed when the optical fiber was proximal to the catheter tip, as shown in Fig 5(a,d). A more concentrated photoacoustic signal was observed at the fiber tip when the fiber tip was coincident with or distal to the catheter tip, as shown in Figs. 5(b,e) and 5(c,f), respectively. There were minimal qualitative differences in the photoacoustic signals obtained with the coincident and distal optical fiber positions. Similar images were obtained when the fiber tip was placed to touch the vessel wall. Therefore, the results of this ex vivo experiment demonstrate that the source of the photoacoustic signal in the photoacoustic-guided catheterization procedures described in this paper is the optical fiber tip, which supports our hypothesis in Section II-B. In addition, because we fixed the fiber to be coincident with the catheter tip for the duration of our experiments (see Fig. 1), it is reasonable to conclude that visualization of the fiber tip is synonymous with visualization of the catheter tip.

B. Localization Errors

To visualize the 3D locations determined by the visual servoing system during the first pig experiment, Fig. 6(a) shows the segmented catheter tip locations relative to the 3D probe locations. The probe was oriented with the elevation, lateral, and axial dimensions corresponding to the X-, Y-, and Z-dimensions, respectively. Figs. 6(b), 6(c), and 6(d) represent the projection of the probe and target points on the Y-Z, Y-X, and X-Z planes, respectively. Fig. 6(b) also shows that the robot operated over a distance of 23.8 cm in the Y-direction with an average catheter depth of 7.90 cm.

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Fig. 5. Ultrasound and photoacoustic images of the fiber-catheter pair within the ex vivo blood phantom (top) and within an ex vivo aorta filled with blood (bottom). The optical fiber tip was placed in three positions relative to the catheter tip: (a,d) proximal, (b,e) coincident, and (c,f) distal.
Fig. 6. (a) 3D scatter plot of the ultrasound probe locations (red) and segmented photoacoustic signal locations (blue) during visual servoing. The planes show the locations of Positions 1-5 as marked on the skin surface. The corresponding 2D projections of these points are shown on the (b) Y-Z plane, (c) Y-X plane, and (d) X-Z plane. The lines in the Y-Z and Y-X planar views depict the locations of Positions 1-5.

Fig. 7. Posterior-anterior fluoroscopic images of the cardiac catheter at Positions 1, 2, and 3. The yellow line shows the position of the catheter at the time that each fluoroscopic image was acquired. The catheter tip positions found while visual servoing are shown in red. These positions are registered to the images by matching the pointer positions with the the positions of the planes shown in Fig. 6.

Fig. 8. 3D scatter plots of the mapping system-based positions (i.e., $U_2 r(n)$) and catheter tip positions (i.e., $U_2 p(n)$) obtained during (a) insertion and (b) retraction of the fiber-catheter pair. These positions are overlaid on a model of the jugular vein produced by the EnSite™ mapping system.

Fig. 7 shows the segmented catheter tip positions detected with visual servoing in red, overlaid on the ground truth fluoroscopic images. The position of the catheter at the time that each fluoroscopic image was acquired is shown in yellow. The metal pointer, placed on the skin surface to identify and mark the location of the catheter tip relative to the skin surface, is shown in the fluoroscopic images. The 1D RMSEs calculated between the detected source positions and the catheter trajectory from Position 1 to 2 and Position 2 to 3 were 2.28 mm and 1.63 mm, respectively. Note that these errors were obtained by comparing serially acquired data (i.e., the ground truth fluoroscopic acquisition was followed by the visual servoing data), resulting in two independent trajectories and larger measured errors when visual servoing from Position 1 to 2. In particular, Fig. 7 demonstrates a variation in the catheter path as it is inserted into the vessel, as the red dots associated with Position 1 are closer to the Position 1 pointer.
The ultrasound probe was manually moved from Position 3 to Position 4 to test the capability of the proposed system to recover from a perturbation [36]. Although the system successfully recovered from this perturbation, there were less data points from Positions 4-5, as shown in Fig. 6. In addition, the fluoroscopic image frame of reference changed for Positions 4 and 5 (as Position 3 was near the edge of the fixed fluoroscopic reference frames shown in Fig. 7). Thus, it was not possible to report tracking errors at these last two positions using the method reported in Section II-E.

To overcome challenges introduced by the varying reference frames and the serially acquired data in the first in vivo experiment, ground truth data from the mapping system were acquired simultaneously with the robotic tracking data during the second in vivo experiment. Fig. 8 shows the segmented catheter tip locations in blue relative to 13 catheter tip positions in red and a vessel model in gray, both acquired with the mapping system during insertion (Fig. 8(a)) and retraction (Fig. 8(b)). The X-, Y-, and Z-dimensions correspond to the elevation, lateral, and axial dimensions of the ultrasound probe, respectively. The robot operated over a total distance of 4.06 cm in the Y-direction with a mean catheter depth of 1.54 cm.

Fig. 9 shows similar information overlaid on the fluoroscopic image, which was acquired at the onset of retraction. The trajectory of the fiber-catheter tip is highlighted in yellow. The segmented catheter tip positions coinciding with the mapped points detected during retraction are shown in red. The ultrasound probe and the tip of the Ensite™ mapping catheter are also visible in the fluoroscopic image.

The 1D errors measured during insertion and retraction in the second pig experiment are summarized and compared with results from the first pig experiment in Table I. The largest 1D errors were obtained when visual servoing from Position 1 to 2 in the first pig experiment. In the second pig experiment, larger 1D RMSE values were obtained during insertion rather than retraction. While the errors for the first pig experiment can be approximated to align with the elevation dimension of the ultrasound probe because of the PA fluoroscopy view, the 1D errors reported for the second pig experiment do not have a direct relationship to one of the primary dimensions of the ultrasound probe because of the RAO fluoroscopy view.

Three refinements introduced with the second pig experiment were simultaneous robotic and ground truth acquisitions, 3D localization error reporting within the ultrasound image coordinate system, and data point visualization relative to a mapped vessel, as shown in Fig. 8. Table II summarizes 3D RMSE errors within the elevation (X), lateral (Y), and axial (Z) dimensions of the ultrasound probe. The 3D errors range from 1.24 mm to 1.54 mm and are largest in the lateral (i.e., Y) dimension, which has errors that range from 1.06 mm to 1.18 mm. These lateral dimension errors exceed the $0.87 \pm 0.06$ mm lateral resolution of our ultrasound probe (measured near the mean 1.54 cm depth of the photoacoustic signals), indicating that there are additional sources of error, such as the mapping system accuracy. Similarly, the $0.63$ mm axial (i.e., Z) dimension error obtained during insertion exceeds the $0.34 \pm 0.02$ mm axial resolution of our ultrasound probe (while the Z-dimension errors obtained during retraction are within one standard deviation of the axial resolution). The errors in the elevation dimension are within the elevation resolution of the ultrasound probe.
ultrasound probe. Table II also shows that greater errors were obtained during insertion when compared to errors obtained during retraction, which is similar to the results obtained with fluoroscopy as the ground truth.

C. In Vivo Visualization of Photoacoustic Signals within Vein

An example of the photoacoustic signals acquired at Position 1 is shown in Fig. 10(a) with the corresponding color Doppler image shown in Fig. 10(b). In general, B-mode images alone provided poor visualization of the catheter tip at Positions 1-5. In contrast, the benefits of photoacoustic imaging are observable with the visualization of the catheter tip overlaid on the B-mode image in Fig. 10(a). The color Doppler image enhances visualization of the blood vessel location.

Registration of the photoacoustic signals to the Doppler image was performed using ultrasound images that were independently acquired and simultaneously co-registered to each modality (i.e., photoacoustic or color Doppler). Specifically, the photoacoustic signal in Fig. 10(a) was segmented at a threshold of -12 dB using Canny edge detection [42], and this segmented profile was overlaid in magenta on the co-registered Doppler image of Fig. 10(b). This display method demonstrates that the photoacoustic signals from the fiber tip coincided with the location of the vessel wall in this example.

D. In Vivo Visualization of Catheter within the Heart

In addition to visualizing the catheter tip within the femoral and jugular veins, the catheter tip was also visualized at three

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**Fig. 10.** (a) Photoacoustic signal of the cardiac catheter at Position 1 overlaid on the corresponding ultrasound acquisition. (b) The segmented photoacoustic signal (magenta) was overlaid on the co-registered color Doppler and B-mode images at Position 1.

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**Fig. 11.** (a,d) Fluoroscopic images (b,e) ultrasound images and (c,f) photoacoustic images overlaid on the corresponding ultrasound images, each showing the catheter tip located within the right atrium (top) or in contact with the right ventricular outflow tract, i.e., RVOT (bottom). The ultrasound and photoacoustic images were acquired with a subcostal acoustic window and provide depth information that is not present in the fluoroscopic images. In addition, the catheter tip location and its contact with the endocardium is more apparent in the photoacoustic image when compared to the ultrasound image.
positions within the heart. Matching ultrasound, photoacoustic, and fluoroscopic images were acquired at these three positions.

The first catheter tip position was inside the right atrium of the first pig. The corresponding fluoroscopic image, ultrasound image, and photoacoustic image (overlaid on the ultrasound image) are shown in Figs. 11(a), 11(b), and 11(c), respectively, with a subcostal probe position. The catheter tip is visible in the ultrasound image, as indicated by the arrow in Fig 11(b). This position is better visualized in the photoacoustic image of Fig. 11(c), however, photoacoustic reflection artifacts are also present outside of the heart. These minor reflection artifacts appear with a lower amplitude than the signal from the catheter tip (i.e., approximately 10 dB below the catheter tip signal), and they are likely caused by the echogenic myocardium.

The second catheter tip position was in contact with the RVOT of the first pig. Figs. 11(d), 11(e), and 11(f) show the corresponding fluoroscopic image, ultrasound image, and photoacoustic image (overlaid on the ultrasound image), respectively. The catheter is difficult to visualize with ultrasound alone (Fig. 11(e)). However, with the addition of the photoacoustic signal overlay (i.e., Fig. 11(f)), the tip of the catheter is more clearly identified by the presence of photoacoustic signal. In addition, we observed that the photoacoustic signal in Fig. 11(c) has a different geometric appearance than that presented in Fig. 11(f). It was also possible to display the photoacoustic signals in Fig. 11(f) with a lower dynamic range than that in Fig. 11(c). These observed differences in signal appearance were investigated in more detail with the third catheter position.

The third catheter position was inside the right ventricle of the second pig. Fig. 12 shows example photoacoustic images overlaid on co-registered ultrasound images of a catheter in contact and not in contact with the endocardium. Unlike the results presented in Fig 11, these results are shown for the same region of the heart (i.e., the right ventricle, as confirmed with fluoroscopy). Figs. 12(a) and 12(b) were normalized to the brightest pixel in each image. For each case (i.e., contact vs. no contact), photoacoustic signal contrast was measured in six frames at similar time points in the cardiac cycle (as determined by the similarity of the ultrasound images). The mean contrast was 48.8 dB and 29.8 dB with and without contact, respectively, demonstrating a mean contrast increase of 19 dB when the catheter was in contact with the endocardium.

In order to visualize the measured contrast difference, the photoacoustic image in Fig. 12(c) was created from the same data used to create that in Fig. 12(b) and displayed with an alternative normalization method. Rather than normalizing by the brightest pixel in the image, Fig. 12(c) was normalized by the brightest pixel within the data that created the two photoacoustic images. This normalization method demonstrates decreased photoacoustic contrast when compared to Fig. 12(a), while maintaining visibility of the catheter tip. In general, this alternative normalization method can be used to visualize

Fig. 13. Example histology results from (a) the superior IVS and (b) the anterior wall of the RVOT. Both images were taken at 200x magnification.
(rather than only quantify) the observed contrast differences after confirming contact during an interventional procedure.

E. Safety Assessment of Intracardiac Photoacoustic Imaging

No pathologic changes were noted on the endocardial surface of the sample taken from the lasered region of the RVOT. Similarly, no pathologic changes were noted on the endocardial surfaces of the RVOT control or the IVS regions. Representative histologic sections of the lasered RVOT and the IVS are shown in Fig. 13.

Despite no pathological changes to the endocardial tissue, inflammation was seen on the epicardial surface of the control regions taken from the left and right ventricles. However, the observed inflammation was restricted to the epicardium and subepicardial tissues with no involvement of the myocardium or endocardial surfaces (i.e., the primary regions receiving laser energy).

IV. DISCUSSION

A. Promise of Proposed Photoacoustic & Robotic Technology

The work presented in this paper demonstrates the first use of a photoacoustic imaging system to guide cardiac catheters in vivo. In traditional cardiac catheter guidance, fluoroscopy is used to steer the catheter to the desired location. However, fluoroscopy contains limited depth information due to the planar projection images and is also a source of ionizing radiation. In contrast, photoacoustic imaging provides no harmful ionizing radiation and also has the potential to provide depth information to cardiac electrophysiologists from a global reference frame (i.e., the reference frame associated with an external ultrasound probe). This global reference frame is more efficient with regard to orienting users, as opposed to the more local and transitory reference frame that would be provided with an internal catheter ultrasound probe or transesophageal echocardiography.

The ex vivo experimental results in Fig. 5 confirmed that the photoacoustic signals correspond to the tip of the fiber-catheter pair. In addition, the diffuse signals shown in Figs. 5(a) and 5(d) were not observed in vivo, providing additional support that the optical fiber maintained its position of being coincident with the catheter tip during the two in vivo experiments. During these in vivo experiments, photoacoustic imaging provided catheter tip visualization at depths that contain significant acoustic clutter in traditional ultrasound images alone. In the first in vivo experiment, color Doppler images demonstrated that the photoacoustic signals from the catheter tip coincided with the location of the vessel wall (e.g., see Fig. 10). Similar confirmation of signal locations relative to the vessel wall was provided by the 3D vessel mapping in the second in vivo experiment (e.g., see Fig. 8).

The proposed approach to assist cardiac electrophysiologists with visualizing cardiac catheter tips and guiding these catheters to the heart with minimal assistance from fluoroscopy was validated with both fluoroscopy and 3D mapping. The detected catheter tip locations were overlaid on the matched preoperative and interoperative fluoroscopic images, as shown in Figs. 7 and 9, respectively. Similarly, detected points are shown alongside the ultrasound probe positions in Fig. 6 and the mapped points in Fig. 8. As demonstrated by these examples, visual servoing is advantageous as it provides a spatially and temporally consistent global frame of reference, while enabling real-time visualization of relative anatomical structures. In addition, the system has the capability to search for the catheter tip, as demonstrated by the perturbation step between Positions 3-4 in Fig. 6 which further indicates the possibilities of servoing more complex geometries.

B. Localization Error Insights

Catheter path deviations significantly contribute to the large fluoroscopic errors observed in the first pig experiment, considering that the associated fluoroscopic images were acquired prior to the visual servoing experiment. This serial acquisition of ground truth data followed by robotic data appears to have the most influence on the localization measurements obtained from Position 1 to Position 2. In particular, the catheter path prior to Position 1 appears to change when inserting the catheter from Positions 1 to 2 to 3, as demonstrated in Fig. 7. When fluoroscopic images were obtained simultaneously with visual servoing (i.e., during the second pig experiment), 1D errors were lower than those obtained during the first pig experiment, as reported in Table I. Therefore, the localization error results from the second experiment are more representative of the expected localization errors with our proposed system.

The observed catheter path deviations can be explained by vessel sizes that are larger than the 2.33 mm outer diameter of the catheter (see Figs. 8 and 10 where the vessel diameters are approximately 7 - 9 mm and 1 cm, respectively, at the site of visual servoing) and larger localization errors with insertion compared to retraction (see Tables I and II). During insertion, the catheter path is undefined and more likely to encounter obstacles such as vessel walls and branches which lead to path deviations, as demonstrated in Fig. 8(a). During retraction, the catheter path is more well-defined by its previous locations, as demonstrated in Fig. 8(b). Therefore, the results in Table I from the second pig experiment suggest that when a 3D mapping system is unavailable, fluoroscopy can potentially be used as a reliable ground truth in future in vivo experiments if localization error measurements are obtained during catheter retraction.

The segmentation algorithm is not included as a source of localization error, because the series of steps reported in Section II-D1 (i.e., binary thresholding, erosion, dilation, connected component labeling, and the subsequent decision processes to estimate the catheter tip position) were designed to minimize the catheter tip position estimation error. However, one potential method to improve the accuracy of the catheter tip segmentation is to use a deep learning approach as an alternative to standard beamforming methods [43]–[45]. For the same phased array ultrasound probe used in our experiments, these methods report sub-millimeter mean source
The robot positioning accuracy is also not reported as a source of error because our previous publication [36] explains that the probe positioning accuracy depends on the robotic control accuracy, and not the localization (or tracking) error, considering that the robot will move wherever it is programmed to move. The robotic control accuracy is therefore directly related to the probe centering accuracy, which was previously reported as 0.44 - 0.98 mm [36].

C. Benefits of In Vivo Intracardiac Catheter Tip Visualization

With ultrasound images alone, it is difficult to visualize the tip of the catheter when it is in contact with the endocardium, as shown in Fig. 11(e). However, knowledge of the catheter tip location and its contact with the endocardium is critical when performing multiple cardiac interventional procedures, including ablation. With the introduction of photoacoustic imaging, the tip of the cardiac catheter and its contact with the endocardium can be identified with greater certainty in a global reference frame, as demonstrated in Figs. 11(c), 11(f), and 12.

The quantitative differences in signal contrast observed when the catheter was in contact with the endocardium demonstrates the potential of using amplitude-related metrics as an indicator of tissue contact. Iskander-Rizk et al. [46] reported a similar change in signal appearance when imaging with a custom RF ablation catheter, noting the magnitude of the photoacoustic signal is larger when the catheter is in contact with tissue than when away from the tissue. Similar to [46], we hypothesize that the increase in signal magnitude is due to the increase in fluence at the tissue surface, when the photoacoustic effect is generated from both the light source and the surrounding tissue (and possibly blood).

D. Future Outlook for Clinical Translation

In order to advance the proposed approach to clinical utility in an interventional suite, three key modifications would be required. First, due to space constraints, technologies such as table- or body-mounted robots [47]–[52] and wireless ultrasound probes [53]–[55], as well as miniaturized light delivery systems [30] would help to free the floor space that is currently required for our prototype system. These technologies would also assist with limiting the number of currently required wired connections between system components. With the inclusion of these technologies, it is conceivable that a photoacoustic-guided approach has the potential to be less intrusive than a fluoroscopy system, which also requires additional safety precautions that do not exist for our proposed approach (e.g., mobile lead shields). Second, optical fibers with smaller diameters would enable greater flexibility to bend with the shaft of steerable catheters while still meeting laser energy and wavelength requirements. While explorations of system optimizations at the intersections of required fiber diameters, wavelengths, and energy levels is outside of the scope of this paper, these investigations will be the focus of future studies. Third, the acoustically coupled ultrasound probe and the robotic arm must be sterile or otherwise contained in sterile sleeves (e.g., see the plastic fluorescein sleeve in Fig. 3 or the sterile ultrasound probe covers currently used during surgery) and may be used with a customized cardiovascular incise drape containing a continuous echoluent slot (e.g., similar to those used in cardiovascular surgery [56]) in order to maintain sterility within the operating room. Alternatively, the system could be miniaturized (e.g., body-mounted robot [47]–[51] attached to wireless ultrasound probe [53]–[55]) to fit under the sterile drape.

In addition to the updates required to make this system adaptable to an interventional suite (or similarly any operating room that would benefit from the proposed photoacoustic-guided catheterization procedures), there are some additional software and technical updates that could be implemented to enhance clinical utility. For example, coherence-based beamforming could be implemented to improve ultrasound image quality [57]–[62], and force control could be implemented to maintain probe contact with the skin [63]. Building on work that utilizes a robotic 3D ultrasound catheter guidance system with force control to maintain consistent contact with the heart [64], a system that combines catheter force control with photoacoustic imaging of the catheter tip may also be developed in the future to expand clinical capabilities.

One possible limitation of the proposed approach is the use of fluence levels that exceed the 25.2 mJ/cm² ANSI safety limit for skin at 750 nm [41], which led us to perform histopathological analyses on endocardial tissue that interfaced with the laser for an extended period of time. Despite the unexpected pathological finding (i.e., inflammation) on the epicardial surface of the control regions, there was no discernible difference between pathology found in the control or lasered regions of the endocardium or myocardium, and no other pathology was noted in the tissues examined. In addition, there were no changes to either side of the IVS. Therefore, it is unlikely that the epicardial pathological observations were related to the application of the laser. Our understanding is that this epicardial inflammation was potentially caused by a pre-existing infection contracted by the pig prior to our study, and we were unable to replicate this finding on a pig heart that did not exhibit similar symptoms of an infection. Additional studies are needed to determine laser safety limits for cardiac tissue. Nonetheless, the absence of pathological changes to the lasered and control endocardial tissue indicates that the applied energy of 2.98 mJ per pulse (which corresponds to 379.2 mJ/cm² fluence at the fiber tip) has potential for cardiac interventional applications.

V. CONCLUSIONS

This paper introduces in vivo cardiac photoacoustic imaging for potential guidance of multiple cardiac interventions, demonstrating two primary benefits. The first benefit is the addition of depth information to fluoroscopy without requiring multiple projections when guiding catheters to and within the
heart. The second benefit is the enhanced visualization of blood vessel locations at depths that are obscured by clutter when using ultrasound imaging alone. We successfully located the tip of a cardiac catheter at multiple positions within the in vivo, beating heart and at multiple positions along the insertion path. The 3D RMSD was 1.54 mm and 1.24 mm during insertion and retraction, respectively. These results are promising for photoacoustic-based catheter tip localization in procedures such as cardiac radiofrequency ablation. In addition, our histopathological analysis showed no signs of laser-related damage to the sections of heart tissue that were in direct contact with the laser (e.g., endocardium and myocardium), which is promising for the overall introduction of photoacoustic-guided cardiac interventions.

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