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● *Original Contribution*

ACOUSTICALLY ACTIVE INJECTION CATHETER GUIDED BY ULTRASOUND: NAVIGATION TESTS IN ACUTELY ISCHEMIC PORCINE HEARTS

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Abstract—Catheters are increasingly used therapeutically and investigatively. With complex usage comes a need for more accurate intracardiac localization than traditional guidance can provide. An injection catheter navigated by ultrasound was designed and then tested in an open-chest model of acute ischemia in eight pigs. The catheter is made "acoustically active" by a piezo-electric crystal near its tip, electronically controlled, vibrating in the audio frequency range and uniquely identifiable using pulsed-wave Doppler. Another "target" crystal was sutured to the epicardium within the ischemic region. Sonomicrometry was used to measure distances between the two crystals and then compared with measurements from 2-D echocardiographic images. Complete data were obtained from seven pigs, and the correlation between sonomicrometry and ultrasound measurements was excellent ($p < 0.0001$, $\rho = 0.9820$), as was the intraclass correlation coefficient (0.96) between two observers. These initial experimental results suggest high accuracy of ultrasound navigation of the acoustically active catheter prototype located inside the beating left ventricle. (E-mail: Belohlavek.marek@mayo.edu) © **2014 World Federation for Ultrasound in Medicine & Biology.**

Key Words: **Acoustic catheter, Ultrasound navigation, Pulsed-wave Doppler.**

INTRODUCTION

There is a continuing trend toward minimally invasive procedures, such as catheter-based aortic valve replacement or coronary angioplasty. Specialized steerable injection catheters are being developed for local delivery of drugs or cells (Minguell et al. 2011). One of the challenges is the accuracy of delivery to a specific anatomic location. This is especially the case with delivery of agents to the heart. As typically used, fluoroscopic guidance is hampered by limitations in depicting local anatomy and the relationship of the delivery catheter to the target of interest because of the planar representation of a complex 3-D space. Electromechanical mapping of the left ventricular (LV) endocardial surface (Emmert et al. 2013) is limited in that successful delivery of the agent is inferred and not definitively visualized. Magnetic navigation (Lindsay 2006) and remote robotic guidance (Schmidt et al. 2009) systems require specialized external equipment and do not eliminate exposure to ionizing radiation if complementary imaging by fluoroscopy is used. Magnetic resonance imaging provides excellent anatomic views, but is available only in some institutions because of the high cost. Furthermore, the magnetic resonance imaging systems require a specialized room, can induce claustrophobia and eliminate from the procedure many patients with pacemakers and intracardiac defibrillators (Friday and Kubal 1990) or the use of catheters with metallic components.

We have previously reviewed ultrasound-based navigation systems for placement of catheters or biopsy needles and presented our navigation principle based on a catheter with an acoustically active tip (McMahon et al. 2012). The tip of this catheter emits a specific acoustic signal that is unambiguously identified using a conventional ultrasound imaging system operating in the pulsed-wave (PW) Doppler mode. Our initial tests in a water tank, during which the ultrasound system operator was blinded to the actual position of the catheter,

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indicated that the average final distance of the catheter tip from a point target after 10 navigation trials was 2.4 ± 1.2 mm (McMahon et al. 2012). These results were encouraging and supported the purpose of our development—that a falsely recognized tip of a catheter in ultrasound scans can be prevented and that a "true" tip can be accurately guided by ultrasound imaging by creating a catheter with its tip acting as an acoustic "beacon."

In the present study, we first introduce our custom development of a working prototype of an injection catheter with an acoustically active tip. Then, we present the results of identification and guidance of the tip of this catheter, which is placed inside the left ventricle of an open-chest pig by scanning in the PW Doppler mode from outside of the heart with a commercial ultrasound system. The accuracy of identification of the catheter tip in a beating heart is quantitatively tested against sonomicrometry, which serves as the reference method of the distance of the catheter tip from a point target represented by another piezo-electric crystal sutured on the LV epicardial surface. A calibrated, signal-attenuating gelatin pad is interposed between the ultrasound transducer and cardiac surface in all these tests to simulate signal loss by a chest wall.

METHODS

Basic principle of navigating the acoustically active catheter by ultrasound

The physical principle of our navigating method has been previously described (McMahon et al. 2012). Briefly, when an ultrasound signal is reflected from a vibrating surface (in our case the vibrating piezo-electric crystal located at the tip of the custom catheter), the reflected signal has two main frequency components. One component has a frequency equal to the summation of the insonation and vibration frequencies, whereas the other component has a frequency equal to the difference between the two frequencies (Censor 1972, 1984). These two frequency components are contained in the acoustic field received by the same transducer that insonated the catheter. The ultrasound imaging system interprets the two reflected signal components as positive and negative Doppler shifts and displays them on a PW graph as uniquely recognizable horizontal lines above and below the baseline, respectively (Fig. 1). The locations of the lines on the PW graph correspond to the positive and negative values, respectively, of the vibration frequency of the acoustic tip.

On the basis of our experience in the previous *in vitro* studies (McMahon et al. 2012), the signal on the PW graph diminished rapidly and disappeared completely when the acoustic tip moved only a few millimeters out of the scan plane or out of the PW sample window located within that plane. This property contributed to the very precise identification and navigation of the catheter tip within a 3-D space. In the current *in vivo* animal studies, the tip of the prototype catheter was never static because of cardiac and respiratory motions. Therefore, instead of continuous positive and negative horizontal lines, the PW graph displayed interrupted lines or line segments for those periods during the cardiac

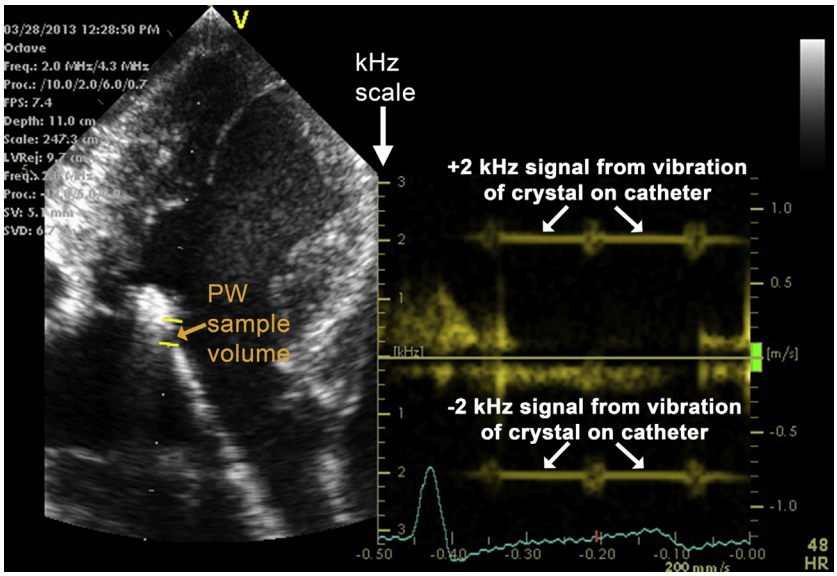

Fig. 1. Catheter tip identification. Pulsed-wave (PW) Doppler was used to identify the actual tip location. When the sample volume of PW Doppler was placed on the exact position of the crystal attached near the catheter tip, both a synchronized sound was heard and a horizontal line appeared in the PW graph at the ± value of the frequency transmitted by that crystal (±2 kHz in this example).

and respiratory cycles when the tip occurred exactly within the scan plane and the PW sample window. By simultaneous use of the B-mode scan, which depicted the catheter as a blurred bright object, and the PW graph, the catheter tip could be reliably identified and steered to the desired location within the left ventricle.

Animal studies

The animal studies were approved by the Institutional Animal Care and Use Committee. We used eight male domestic pigs weighing between 65 and 94 kg (mean weight: 81 ± 10 kg). Anesthesia was induced by intramuscular injection of tiletamine hydrochloride and zolazepam (Telazol, 5.0 mg/kg), xylazine (2.0 mg/kg) and glycopyrrolate (0.02 mg/kg), and maintained by inhalation of isoflurane (1%–3%) and intravenous fentanyl (4 μg/kg/h). Each animal was intubated and mechanically ventilated (Narkomed 6000, Draeger Medical, Telford, PA, USA). Cut-down of the right carotid artery was secured with 14Fr or 9Fr sheaths for insertion of the acoustically active catheter; the sheaths were filled with heparin. Aortic pressure was monitored with a high-fidelity catheter (Millar Instruments, Houston, TX, USA) placed via the left carotid artery or femoral artery, whereas the left jugular vein or femoral veins served as routes to administer fluid and medications. The chest was open by mid-sternotomy, and the heart placed on a pericardial cradle to allow instrumentation and ultrasound scans from various angles. Each animal was heparinized (activated clotting time > 350 s). An injection catheter with an acoustically active tip was inserted via the right carotid artery through the aortic valve into the LV cavity. To ensure that the acoustic catheter and its tip were not damaged during insertion, the navigation signal generated by the crystal at the acoustic catheter tip was checked by epicardial PW ultrasound scanning and by a testing reception with a sonomicrometric crystal temporarily attached to the epicardial LV surface. The acoustic catheter was manipulated to various locations within the left ventricle during most of these tests using a steerable introducing sheath to verify functionality throughout the left ventricle.

In all but one pig, an acute ischemia was induced in an apical region of the anterior wall by placing an occlusive snare around the left anterior descending coronary in the vicinity of its second diagonal branch. An intravenous bolus of lidocaine was administered and followed by a continuous infusion of lidocaine to manage ischemia-induced arrhythmias. The location of the ischemic region was determined by ultrasound scans as the extent of akinetic or dyskinetic myocardial wall in apical and short-axis projections, and visually by the extent of pale epicardial surface. The center of the ischemic region was approximated, and a sonomicrometric crystal was sutured onto the epicardial surface at that location to serve as a point target for quantitative analysis of spatial tip identification and catheter guidance accuracy.

Acoustic catheter prototypes

The first two pigs were considered pilot studies and were slightly different from the last six animals in the following ways.

In the first pilot pig, a straight 14Fr introducing sheath (Fig. 2a) was inserted through the aortic valve, and then a prototype of the acoustically active catheter was inserted. In only that pig, the prototype catheter was unique in that it was a combination of a steerable ablation catheter with a crystal at its tip and a second tube with a 22-gauge needle at its end for injection. These two parts were bound together into one catheter by heat shrink tubing, glue and Teflon tape. With that first prototype, the ablation catheter, rather than the sheath, was entirely used for steering within the LV cavity. The disadvantages of this prototype included somewhat limited steerability caused by bonding of its two component parts; also, its relatively thick diameter was impractical for insertion via the carotid artery and manipulation because of a very tight fit within the arterial lumen.

In the second pilot pig, there was again a unique situation, in which both the catheter type and steerable introducing sheath were used only in that pig. This particular prototype catheter was designed and constructed by one of the authors (D.Z.) and consisted of two tubes (one for injection, the other as a conduit for wiring) bound together. The tubes were flexible in their distal parts, but not steerable (Fig. 2b). Navigation was enabled by a steerable sheath, which was initially guided into the LV cavity by ultrasound imaging and through which the catheter was then inserted. As another testing novelty, this catheter prototype included a small corkscrew part surrounding the needle, which could be screwed into the myocardium, thus securing the needle in place. This catheter was thinner than the first one, but more technically complex, which eventually limited its reliability, and the prototype broke down by the end of the experiment. In addition, unmanageable arrhythmias complicated and prematurely ended this second pilot study. As a consequence, no ischemia was induced; no epicardial crystal was placed; and thus, no reference data could be obtained for quantitative analysis of targeting accuracy.

For the remaining six pigs, a Unison (Greatbatch Medical, Clarence, NY, USA) 9Fr steerable sheath was used (Fig. 2c). We also used the same style of catheter prototype for the remaining studies in which there was a single tube. The wire to the crystal passed through the same (2-mm internal diameter) tube, which was fitted with a needle and used for transendocardial dye (diluted food color) injection. The needle and crystal were attached to the distal end (Fig. 2c). The steerable sheath,

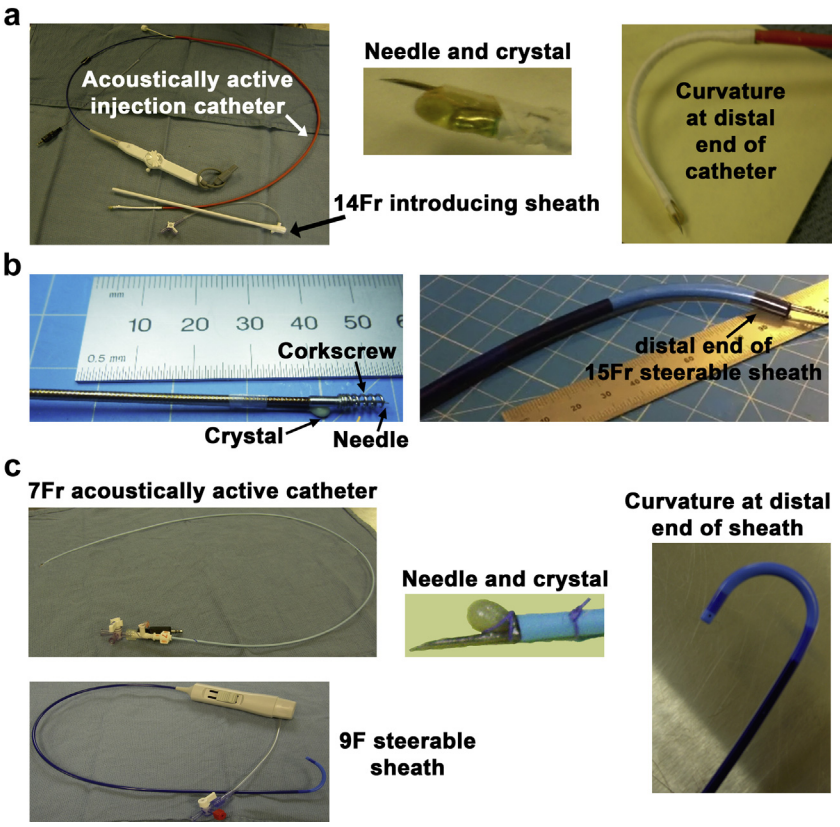

Fig. 2. Acoustically active catheter prototypes. (a) For the first pig, we used a prototype of a steerable injection catheter and a straight 14Fr introducer (left). The orange material seen in the photograph was heat shrink tubing used to bind together a separate injection tube with needle, a steerable ablation catheter with piezo-electric crystal attached and the wiring for that crystal. The other panels are close-up views of the needle and crystal at the tip and the approximate amount of curvature available at the distal end of that prototype. (b) For the second pig, we used a prototype style of injection catheter with a corkscrew surrounding the needle along with a 15Fr steerable introducing sheath. The distal ends of the prototype catheter and its steerable sheath are also seen. (c) for pigs 3 through 8, we used a prototype of an injection catheter with one 7Fr tube shared by the wiring to the crystal and also used for injection to transport a colored dye. That catheter prototype, a close-up view of its distal end (needle and crystal) and its 9Fr steerable introducing sheath are depicted.

whose distal segment could bend more than 90°, was used for manipulating the tip of the catheter toward the desired location inside the LV cavity.

Echocardiography and electronic instrument settings

A Vivid 7 (GE Healthcare, Milwaukee, WI, USA) was used in this study. An M4S phased array sector probe was used in all guidance tests. A 7L linear probe was used for high-resolution close-up views and initial guidance of the catheter into the left ventricle through the ascending aorta and aortic valve. Figure 3a illustrates insertion of a guide wire into the left ventricle and initial placement of a catheter sheath into the LV outflow tract. After guide wire removal, Figure 3b illustrates insertion of a catheter prototype into the LV cavity with the crystal and needle exposed. For further manipulation, we retracted the catheter and its tip into the sheath so the needle was not exposed.

Two-dimensional sector scans with the M4S probe guided initial navigation of the catheter inside the left ventricle toward the approximate location of the target. Final precise guidance to the target was performed by using acoustic navigation in the PW Doppler mode as described in this article. The PW Doppler frequency was set at 2.0–2.7 MHz, and sample volume size was set at 4.0–6.1mm. The active tip crystal was driven by a continuous sinusoidal wave with a frequency in the audio range 1–3 kHz and amplitude of 20 V. When the crystal (tip of the catheter) was within the PW sample volume, the acoustic energy produced by crystal vibrations was recognized by the ultrasound machine and created clearly identifiable horizontal lines in PW graphs (Fig. 1). An in-house made gelatin pad, which was calibrated to 8-dB signal attenuation at 1 MHz, was interposed between the M4S probe face and cardiac surface in all initial and acoustic navigation scans to simulate attenuation by a chest wall (Von Bibra et al. 1999).

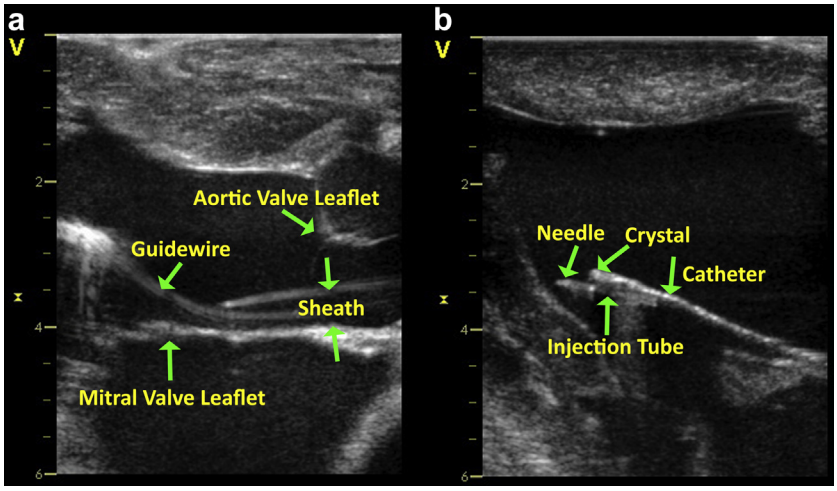

Fig. 3. Insertion of catheter. (a) A 14Fr straight sheath was successfully inserted from the right carotid artery following a guide wire. (b) The active tip catheter was placed through the sheath into the left ventricle. The crystal and the needle part were visible, as indicated by labels.

Distance measurements by sonomicrometry and echocardiography

To elucidate the accuracy of acoustic navigation, we used the sonomicrometry system (Sonometrics, London, ON, Canada) as the reference measure for the distance between the catheter tip and the target. A sonomicrometric crystal was sutured on the epicardial surface of the ischemic area as a target. Both crystals, that is, the "target" and the one on the catheter tip, were connected by a thin wire to a sonomicrometry system. Based on available product information, these crystals are coated by a spherical lens made of epoxy with an external diameter of approximately 2 mm. For the purpose of sonometry, they operate with signals on the order of kilohertz and megahertz and behave as nearly omnidirectional transmitters and receivers of such signals. Minimal and maximal distances over three cardiac cycles were recorded, and the average was calculated as the reference measure by sonomicrometry. The testing measurement was the distance between the catheter tip and the target crystal, as displayed on an ultrasound screen or off-line using EchoPAC software (GE Healthcare, Milwaukee, WI, USA). When the clear horizontal line was present on the PW Doppler screen and the epicardial crystal was visualized clearly as well, the distance between the sample volume (a crystal on the catheter tip) and the epicardial crystal was measured on the 2-D image. The reference (sonomicrometric) and testing (echocardiographic) measurements were not performed concurrently to avoid any ultrasound signal interference. The initial testing measurements by ultrasound were done in the operating room based on the consensus of two individuals experienced in ultrasound image analysis (M.B. and E.M.M.). Repeated testing measurements (for reproducibility evaluation) were performed using an off-line setting by another author (M.K.), who was blinded to the initial results. The repeated measurements are averages of three distances obtained at different phases of a cardiac cycle when the tip and target crystals, as well as the navigation PW Doppler signal, were all clearly identifiable. In all tests, we used commercially available crystals (Sonometrics) at the tip and at the epicardial target location.

Statistical analysis

The distance data are expressed as means ± standard deviations. Correlation and agreement between the testing measurements by ultrasound and the reference measurement by sonomicrometry were assessed using the Spearman correlation coefficient, Wilcoxon signed rank test, and Bland-Altman plot. Reproducibility of the ultrasound measurements was assessed using an intraclass correlation coefficient between initial online measurements and repeated off-line measurements.

RESULTS

We present qualitative results, which indicate insertion of the prototype catheter into the left ventricle, including generation of an acoustic navigation signal, and quantitative results, which document the spatial accuracy of acoustic tip identification and distance from a point target. The quantitative results were obtained from seven of the eight pigs used in this study.

Catheter insertion and navigation signal generation

Catheter insertion was successfully performed in all animals. The outside diameter of the 9Fr steerable

sheaths was almost the same as the lumen diameter of the carotid artery in our animals, and therefore, lubrication was used for smooth insertion and manipulation with the sheath. In the first pig, the aortic valve leaflet was injured because of catheter insertion using a 14Fr introducer, but no other aortic injury related to acoustic injection catheter insertion was observed. The navigation signal generated by the 2-mm crystal at the acoustic catheter tip and attenuated by the interposed gelatin pad was detected by PW Doppler in all animals.

Acoustic tip identification and navigation toward the center of ischemia

Figure 4 illustrates an example of the echocardiographic distance measurement between the two crystals (one on the acoustic injection catheter inside the left ventricle and one on the epicardial surface) in the ultrasound system. The correlation between sonomicrometry and ultrasound measurement was significant ($p < 0.0001$, $\rho = 0.9820$) (Fig. 5a). There was no significant difference between sonomicrometry and ultrasound measurements ($p = 0.4688$). The Bland-Altman plot (Fig. 5b) indicated neither a proportional bias nor a fixed bias.

The intraclass correlation coefficient between initial measurements and second measurements was 0.96 (95.00% confidence interval: lower = 0.8086, upper = 0.9937), reflecting the very good reproducibility of repeated measurements.

Transendocardial injection

On completion of distance measurements, a color dye was injected transendocardially into the myocardium, and the animal was euthanized. Figure 6a documents the position of the catheter inside the heart, which was dissected *in situ*, a pale ischemic area with a color patch that resulted from transmural spread of the dye and an attached crystal. In Figure 6b the left ventricle was dissected to reveal the dye location, as viewed from inside the cavity. In Figure 6c is an example from a different animal, where dye injection formed a spot centered within the anterolateral LV wall. Dye injections were accomplished in four of the seven completed studies and documented not only that the catheter needle was navigated to the desired location, but most importantly, that the dye injection was effective, that is, neither too shallow nor too far toward epicardium (perhaps perforating the myocardial wall), in which case there would not be a well-contained deposit. In the remaining three animals, the needle in our prototype either broke away or was plugged by tissue or a blood clot (despite heparinization).

DISCUSSION

This article describes the development of an acoustically active intracardiac injection catheter prototype and the high accuracy in spatial navigation of its tip by extracardiac PW Doppler scans with a conventional ultrasound transducer. Navigation is based on an acoustic signal

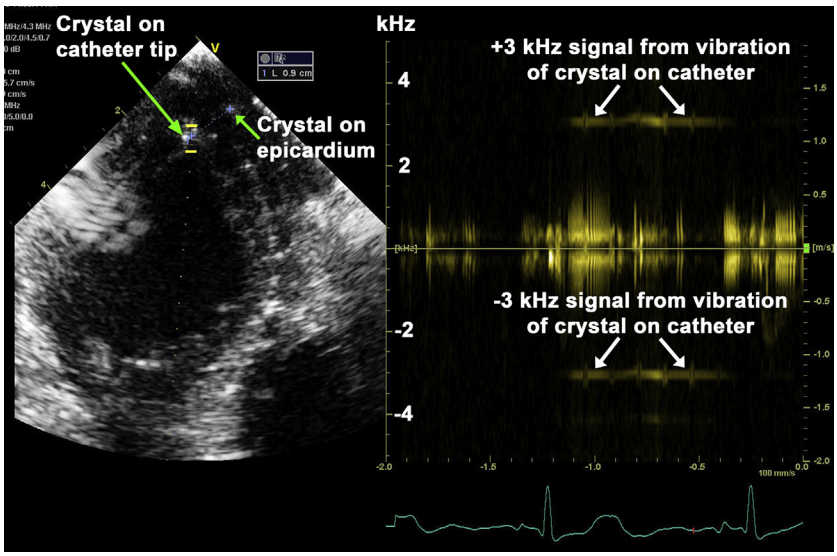

Fig. 4. Navigation of the catheter tip and measurement by the ultrasound system. The catheter tip (and the attached acoustically active crystal) was placed within the pulsed-wave (PW) Doppler sample window (left). This was verified by the appearance of a unique Doppler shift signal in the Doppler graph (right). This process was iterative as the PW Doppler window was successively moved toward the closest transmyocardial distance from the point target (another crystal sutured on the epicardium). Simultaneous with the appearance of the horizontal PW signal, the distance between the two crystals was measured on the 2-D image in the ultrasound system (left).

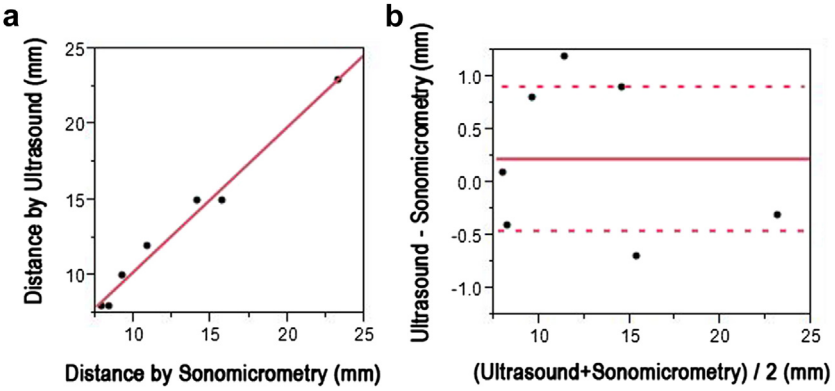

Fig. 5. Comparison of distance measurements between ultrasound and sonomicrometry systems. (a) Correlation plot of the distances measured by ultrasound and sonomicrometry ($p < 0.0001$, $\rho = 0.9820$). (b) Difference between distance measurements by ultrasound and sonomicrometry are plotted against the average of ultrasound and sonomicrometry measurements. The mean differences and 95% limits of agreement are illustrated (*solid line* and *dashed lines*).

produced by a piezo-electric crystal placed at the tip of an acoustically active injection catheter prototype. The crystal vibrates at a frequency on the order of kilohertz. These vibrations interact with an insonation signal, which is on the order of megahertz and generated by a conventional echocardiographic transducer. The reflected signal, which is a result of an interaction between the insonation signal and the vibrating surface of the crystal, is received by a regular clinical echocardiography system. The received signal is interpreted by the ultrasound system as a Doppler shift. When the system is set to the PW mode, it displays a horizontal line in the PW Doppler graph when the catheter tip is located exactly within the scan plane and the PW Doppler sample. By appropriate adjustment of the crystal vibration frequency, the horizontal line is clearly and uniquely identifiable in the PW Doppler graph. By aiming

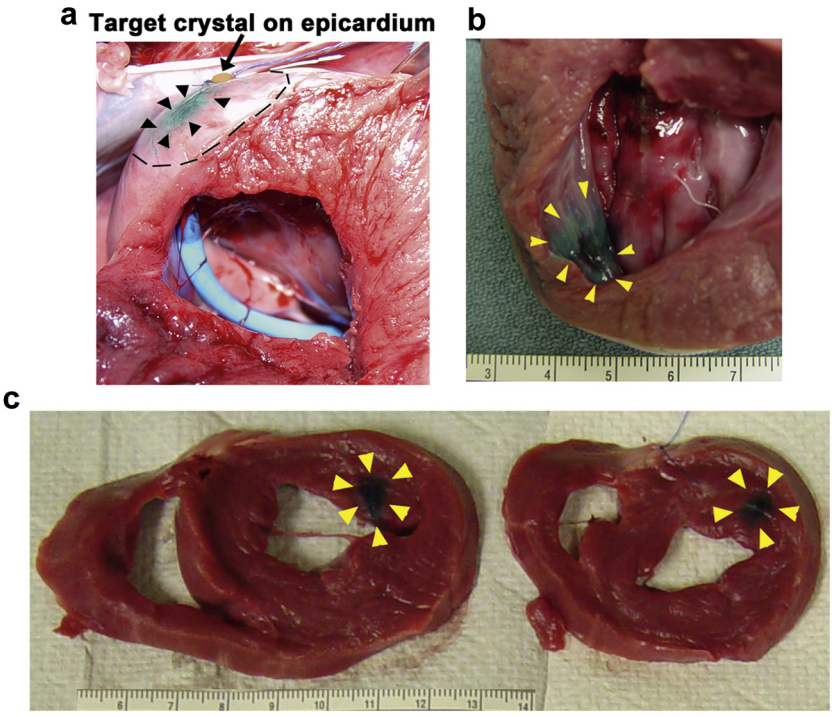

Fig. 6. Dissected heart with colored dye injected: (a) A colored dye was successfully injected into the middle of the anterior myocardium. The anatomic orientation of the catheter sheath, the injected color dye (area within *black arrowheads*) and the target crystal (*arrow*) within the ischemic area (approximately delineated by a *dashed line*) are all apparent from a photograph of pig 4, whose heart was first partially dissected *in situ*. (b) Injected color dye on the endocardial surface (excised heart from pig 4). (c) Color dye formed an intramyocardial deposit (slices from excised heart of pig 1).

the scan plane and moving the PW Doppler sample (within the scan plane), we can identify, track and navigate the tip of the acoustically active catheter.

Ultrasound navigation of minimally invasive procedures

To our knowledge, the first attempt to use ultrasound for navigation of catheter-based procedures was published in 1988 (Landzberg et al. 1988; Langberg et al. 1988). The authors described successful tests of a "transponder" catheter system in dogs. A piezo-electric crystal attached to a catheter tip would first passively receive an insonation signal when an external ultrasound transducer was scanning across the heart and its signal interrogated the crystal. At that moment, the transponder system responded by generating an ultrasound signal that was transmitted from the crystal. This signal was received by the ultrasound imaging system and generated a marker within the ultrasound image that indicated the location of the catheter tip. The communication of the transponder with the ultrasound machine required synchronization of the two systems and significant modifications of the imaging circuitry in the latter. The use of the transponder system for ultrasound visualization of biopsy needles has also been reported (Winsberg et al. 1991). Our navigation method, although also based on a piezo-electric crystal, does not require any modification of the ultrasound imaging system, because it uses a PW Doppler sample window as an "indicator" of the location of the catheter tip when the Doppler shift signal produced by crystal vibrations is detected. In other words, our approach is principally different as it does not transmit an ultrasound signal but, rather, a signal in the audible frequency range. Any ultrasound system capable of PW Doppler scans can be readily used, and no modifications are needed.

Our method is also different from ultrasound navigation of venipuncture needles (Bold et al. 1998; Gratz et al. 1994) or guidance of placement of central arterial or venous lines (Keenan 2002). Those systems use Doppler signals too, but to determine whether the needle is within a vessel and whether the vessel is an artery or vein. Finally, navigation by real-time 3-D color Doppler scans of interventional devices, based on the vibration of the interventional instrument or a portion of it, has been reported (Fronheiser et al. 2008). The mechanical vibrations need to be strong enough to induce an effect of a moving object and, thus, visualization of the instrument by a color Doppler overlay. We speculate that the vibrations are attenuated by surrounding tissues or would cause a mechanical injury to the tissues. Separating the depiction of the device from color Doppler signals produced by blood flow or other physiologic motions would be challenging. It is noteworthy that although we currently use planar projections, our method identifies and navigates the catheter tip in the 3-D space of the LV cavity as well, by angulating the scan plane and moving the PW Doppler sample within that plane to detect the catheter tip and guide it to an anatomic target.

Intraventricular steering of the catheter prototype

There is at least one commercially available steerable injection catheter, Myostar (Biosense Webster, Diamond Bar, CA, USA), which would be relatively easily adaptable for our navigation tests with a miniature piezo-electric crystal at its tip, but this catheter was not available at the time of the current experimental study. Therefore, we developed a prototype of our own, which progressed through trials and errors with various materials and through three different designs described earlier. The final design using the Unison steerable sheath could direct the tip to any intracavitary location within the mid-and, especially, apical LV segment. Guiding the tip toward a basal portion of the left ventricle was challenging because it required a sharp bend and was further complicated by the restricted space in the outflow tract or a tendency to get tangled in chordae tendinae. For these reasons, we elected to target the distal left anterior descending coronary artery territory. During initial intraventricular manipulation, the catheter tip was not exposed from the distal end of the steering sheath.

Acoustic navigation to the target and its spatial accuracy

Acoustic navigation was used once the distal end of the steering sheath (with the catheter prototype inside) was manipulated to the vicinity of the target region. The tip of the catheter (and, therefore, the needle and the crystal) had to be exposed to prevent dampening of crystal vibrations and allow transendocardial injection; guiding the tip of our prototype along the endocardial surface with the needle exposed led to minor hemorrhagic injuries visible in Figure 6b. A miniaturized design that would allow control of needle exposure independently of steering, like in the commercial Myostar catheter, was beyond our manufacturing capabilities.

The acoustic navigation was carried out by using a dual display feature that included B-mode anatomic scanning at an approximately 8-Hz frame rate (Fig. 4, left), which was sufficient for tracking the acoustic catheter movement, and a PW Doppler spectral plot (Fig. 4, right). The approach to the target then consisted of two iterative steps: (i) the tip of the catheter was identified by scanning across the distal catheter end and receiving the Doppler shift signal produced by the vibrating crystal, and (ii) the PW Doppler sample window was placed at the closest transmyocardial distance from the point target (a sonomicrometric crystal) sutured to the epicardial side of the ischemic region. These two steps had to be repeated

several times because during manipulation, the catheter tip easily got out of the scan plane. Although the crystal on the epicardium was relatively easy to visualize, as it was surrounded by an acoustic coupling gel, the crystal at the catheter tip was blurred together with the rest of the catheter tip, making the acoustic identification critically important. Also, typically partial oblique projections of the bent catheter often mimicked the appearance of the catheter tip, that is, depicted a false tip, thus further emphasizing the need for reliable detection of the true tip of the catheter.

The results of distance measurements, which are summarized in Figure 5, document excellent correlation and agreement compared with the reference data. The transmyocardial distances obtained on-line during the animal experiments were closely reproducible by those obtained during blinded off-line measurements. Ideally, the distance would be zero or close to zero if the crystal at the catheter tip and the target crystal were in contact or nearly touching each other, as during our previous *in vitro* validation (McMahon et al. 2012). But that was technically not possible in the current setting because there was the thickness of the myocardial wall between the two crystals. Endocardial placement of the reference crystal was considered but abandoned because, based on our practical experience, such a crystal is difficult to visualize by B-mode ultrasound and would mechanically interfere with dye injection. On close inspection of the graphs in Figure 5, it is apparent that two measured distances are approximately 14–15 mm and one distance is about 23 mm. Considering that the LV wall is thinner than these measurements, the interpretation is that the catheter tip could not be manipulated to the nearest transmyocardial distance, that is, perpendicular to the endocardial surface. We found that the anatomic conditions were such that the catheter was significantly bent and its tip kept snapping away from the ideal location as the heart was beating, or manipulation with the tip was limited by trabecules. Thus, another interpretation of our quantitative results is that we may not have been able to place the tip in the ideal location because of technical or anatomic obstacles (which could be the case also with future clinical applications), but even in those cases, the close correlation and agreement with the reference documented that we knew exactly where the tip was (which is, again, critical for future clinical use).

Clinical relevance

The acoustically active injection catheter was developed and tested because of the need for targeted delivery of cells or therapeutic agents. Our prototype and the initial animal tests described here document that ultrasound can be used not only for general B-mode imaging of catheter manipulation, but also, in PW Doppler mode, for accurate targeting toward the desired location. Our navigation method, although currently tested in a setting of intracardiac navigation and intramyocardial injection, is anticipated to be useful for guidance of minimally invasive procedures anywhere in the human body as long as ultrasound imaging can be used and the interventional device will accommodate the vibrating crystal. Moreover, the fact that no modification to an ultrasound system is needed significantly supports clinical translation of the presented navigation approach, because essentially any current echocardiography system has the PW Doppler mode.

The current experimental study suggests that acoustical navigation in a beating heart is feasible. However, only further preclinical tests and future clinical trials will indicate whether transmission of the guidance signal is reliable and navigation sufficiently accurate in a human beating heart. Using the Doppler mode, which has routinely been used in clinical echocardiography, and designing the method with prospective use of simultaneous biplane, multiplane or multidimensional scans are prerequisites that will help overcome the possible technical hurdles.

Limitations

The main limitation of the current catheter prototype is that the crystal identifies its tip, but not the tip of the needle. Although the latter would be ideal, there are several technical obstacles, including the difficulty and problematic logistics of placing the crystal at the tip of the needle. In our setting, the length of the needle was constant, and therefore, the actual depth of injection could be approximated.

The present study design allowed for $n = 7$ data points, which is a relatively small sample size. However, we used a very conservative statistical approach and, therefore, consider the results as representative of a larger sample and reliable. Capitalizing on the current focused study, we plan to extend our experimental investigations in which all 16 standard LV perfusion segments (Lang et al. 2005) will be furnished, in a beating heart, with reference crystals, and the ability to guide the acoustic catheter to all these locations will be systematically defined.

The qualitative analysis was limited by technical issues with needle endurance. The best solution would be use of a commercially manufactured injection catheter, once available, because only attachment of a piezoelectric crystal would be required.

The open-chest setting was needed to accommodate animal instrumentation. Although this setting closely replicates the human cardiovascular system and its proportions, it excludes transthoracic ultrasound signal attenuation. To address this, we used an attenuation pad, which closely simulates the amount of signal loss caused by transthoracic transmission. Our future plans include experimental studies designed with a closed-chest setting.

CONCLUSIONS

We developed an acoustically active intracardiac injection catheter prototype and tested its ability to deliver material to a desired location within the LV wall. We document that its tip inside the LV cavity can be accurately navigated toward a point target surrounded by ischemic myocardium by using conventional extracardiac PW Doppler ultrasound scans.

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REFERENCES

Bold RJ, Winchester DJ, Madary AR, Gregurich MA, Mansfield PF. Prospective, randomized trial of Doppler-assisted subclavian vein catheterization. Arch Surg 1998;133:1089–1093.

Censor D. Scattering by time varying obstacles. J Sound Vibrat 1972;25: 101–110.

Censor D. Harmonic and transient scattering from time varying obstacles. J Acoust Soc Am 1984;76:1527–1534.

Emmert MY, Wolint P, Winklhofer S, Stolzmann P, Cesarovic N, Fleischmann T, Nguyen TD, Frauenfelder T, Boni R, Scherman J, Bettex D, Grunenfelder J, Schwartlander R, Vogel V, Gyongyosi M, Alkadhi H, Falk V, Hoerstrup SP. Transcatheter based electromechanical mapping guided intramyocardial transplantation and in vivo tracking of human stem cell based three dimensional microtissues in the porcine heart. Biomaterials 2013;34:2428–2441.

Friday PJ, Kubal WS. Magnetic resonance imaging: Improved patient tolerance utilizing medical hypnosis. Am J Clin Hypn 1990;33: 80–84.

Fronheiser MP, Idriss SF, Wolf PD, Smith SW. Vibrating interventional device detection using real-time 3-D color Doppler. IEEE Trans Ultrason Ferroelectr Freq Control 2008;55:1355–1362.

Gratz I, Afshar M, Kidwell P, Weiman DS, Shariff HM. Doppler-guided cannulation of the internal jugular vein: A prospective, randomized trial. J Clin Monit 1994;10:185–188.

Keenan SP. Use of ultrasound to place central lines. J Crit Care 2002;17: 126–137.

Landzberg JS, Franklin JO, Langberg JJ, Herre JM, Scheinman MM, Schiller NB. The transponder system: A new method of precise catheter placement in the right atrium under echocardiographic guidance. J Am Coll Cardiol 1988;12:753–756.

Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, Picard MH, Roman MJ, Seward J, Shanewise JS, Solomon SD, Spencer KT, Sutton MS, Stewart WJ. Recommendations for chamber quantification: A report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr 2005;18:1440–1463.

Langberg JJ, Franklin JO, Landzberg JS, Herre JM, Kee L, Chin MC, Bharati S, Lev M, Himelman RB, Schiller NB, Griffin JC, Scheinman MM. The echo-transponder electrode catheter: A new method for mapping the left ventricle. J Am Coll Cardiol 1988;12: 218–223.

Lindsay BD. Perspectives on the development of a magnetic navigation system for remote control of electrophysiology catheters. Europace 2006;8:231–232.

McMahon EM, Jiamsripong P, Katayama M, Chaliki HP, Fatemi M, Belohlavek M. Accurate guidance of a catheter by ultrasound imaging and identification of a catheter tip by pulsed-wave Doppler. Pacing Clin Electrophysiol 2012;35:44–50.

Minguell JJ, Lorino R, Lasala GP. Myocardial implantation of a combination stem cell product by using a transendocardial MYOSTAR injection catheter: A technical assessment. Acute Card Care 2011;13: 40–42.

Schmidt B, Tilz RR, Neven K, Julian Chun KR, Furnkranz A, Ouyang F. Remote robotic navigation and electroanatomical mapping for ablation of atrial fibrillation: Considerations for navigation and impact on procedural outcome. Circ Arrhythm Electrophysiol 2009;2: 120–128.

Von Bibra H, Voigt JU, Froman M, Bone D, Wranne B, Juhlin-Dannfeldt A. Interaction of microbubbles with ultrasound. Echocardiography 1999;16:733–741.

Winsberg F, Mitty HA, Shapiro RS, Yeh HC. Use of an acoustic transponder for US visualization of biopsy needles. Radiology 1991; 180:877–878.