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Septic Shock due to Implantable Cardiac Defibrillator Related Infection

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Abstract

Infection is an important complication of cardiac device implantation. We report the case of a 61 year old patient presenting with septic shock caused by cardiac device infection (CDI) three-weeks after device implantation. At initial presentation, there was an absence of both localising signs and echocardiographic evidence of CDI. Later, Staphylococcus aureus was cultured from blood and the pre-pectoral pocket. 48 hours after admission the device and leads were explanted in theatre by simple traction. Despite appropriate antibiotics and full supportive care (including haemofiltration, ventilation and inotropic support), the patient died on day six. Cardiac device infection may present with septic shock in the absence of localising features. A high index of suspicion is required, particularly for early CDI.

Introduction

Mortality and morbidity associated with cardiac device infection (CDI) is likely to increase as the indications for device therapy in cardiac disease broaden [1]. Septic shock is a rare presentation of CDI. Early explantation and antimicrobial therapy can avert an adverse outcome but clinical suspicion must be high particularly if, as in the illustrated case (below), there is an absence of both localising signs and echocardiographic evidence of infection (at presentation).

An 61-year-old male presented with a 10 day history of general malaise with fever, flu-like symptoms, mild abdominal pain and watery diarrhoea. He had received a course of antibiotics 12 days previously for sinusitis. His past medical history included type II diabetes mellitus treated with gliclazide.

Three-weeks previously he underwent dual chamber implantable cardioverter defibrillator (ICD) implantation (Boston Scientific Teligen™ 100 dual chamber ICD). He was presenting with palpitations and, ventricular tachycardia (VT) was documented. Further investigation revealed moderate to severe left ventricular systolic dysfunction (estimated ejection fraction by echocardiography 30%) and extensive coronary artery disease. The coronary artery disease was not amenable for revascularisation and managed medically. A VT stimulation study was positive. The ICD was implanted in the left pre-pectoral pocket with single-dose cefuroxime 1.5g intravenous antibiotic prophylaxis.

On his latest presentation his blood pressure was 85/40mmHg and pulse 115bpm. He was afebrile.

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There were neither cardiac murmurs nor clinical stigmata of infective endocarditis. His generator site at presentation was not swollen and there were no signs of induration or inflammation.

He had a thrombocytopenia and anaemia (platelets 67, Hb 11.0g/dl) but his white cell count was normal. There was renal impairment with urea and creatinine of 18.4 and 376 mmol/l respectively. His cardiac rhythm was atrial fibrillation. There was no consolidation of lung fields on chest x-ray and both leads of the ICD were in satisfactory positions.

The initial working diagnosis was gastroenteritis with dehydration, precipitating acute kidney injury and atrial fibrillation. Clostridium difficile infection was considered because of the recent antibiotic exposure.

In the initial hours following presentation he received fluid resuscitation in the accident and emergency department, but remained hypotensive and anuric. He was transferred to the critical care unit where infusions of noradrenaline, enoximone and dopexamine, and con tinuous veno-venous haemofiltration were commenced. His respiratory function deteriorated and he required intubation. Empirical antibiotics (cefuroxime and metronidazole) were given.

The differential diagnosis was now considered to be CDI, or an intra-abdominal focus of sepsis.

A CT scan of his abdomen was performed, which demonstrated significant free fluid, particularly around the pancreatic head. A subsequent exploratory laparotomy confirmed free fluid, but was otherwise unremarkable.

Blood cultures grew a gram positive cocci (day two). An ultrasound scan revealed a small fluid collection around the ICD, which was aspirated and this also grew gram positive cocci on culture. The antibiotic regime was adjusted to vancomycin, clindamycin and linezolid, pending sensitivities of the organism. Transthoracic echocardiogram did not identify any vegetations on the valves nor on the ventricular leads although shielding by the distal coil of the ICD ventricular lead made interpretation difficult. 48 hours after admission the ICD system was explanted in theatre in its entirety. There was purulent fluid released from the generator site. The organism in the blood culture and collection around the ICD was identified as Staphylococcus aureus. The antibiotic regime was changed to flucoxicillin monotherapy administered intravenously.

By day six the patient had remained noradrenaline dependent, had shown no recovery in renal function and had developed an ischaemic liver injury. His temperature was persistently > 39°C despite appropriate antibiotic treatment. Finally, through sepsis and high-dose noradrenaline, his fingers and feet had become critically ischaemic and no longer viable. After discussion with the patient’s family, care was withdrawn.

Discussion

There are relatively few reports in the literature describing septic shock as the mode of presentation for CDI and no previous detailed report, as far as we are aware, of Staphylococcal aureus as the causative organism.

The main learning points from this case are that (i) vigilance and high suspicion of index is required for CDI, (ii) clinical localising signs and echocardiographic evidence of infection may be absent at presentation, and (iii) prompt explantation of the entire device (generator and leads) is important. In the case described, CDI was not considered at first presentation because of the absence of clinical localising signs. Explantation of the device was carried out, but only after the patient had developed established multi-organ failure.

Criteria of a CDI, as opposed to secondary infection of the device, as indicated by Chamis et al. [2] are fulfilled in this case. There was no other source of bacteraemia identified, there was positive culture from the generator site and the implantation was less than one year ago. However, there were no strong pointers to CDI at presentation and the delay in diagnosis is likely to have contributed to the adverse outcome.

The presentations of CDI are diverse. Pocket infection may present with pain, swelling and discharge, while pacemaker lead endocarditis may present with systemic features (e.g. fever)
and pulmonary features (e.g. cough, shortness of breath). The absence of localising features at presentation in this case remains unexplained.

The rate of CDI rates varies between 1.6% to 6.7% [1;3;4]. In a large retrospective series of CDI the overall infection rate was 1.6% and the rate of confirmed pacemaker endocarditis was 0.3% [1]. The most commonly identified pathogens are those of the Staphylococci family - usually S. aureus or S. epidermidis. Other organisms - including fungi [5] - are occasionally implicated.

In a comprehensive series of 33 patients with ‘definite’ pacemaker endocarditis (based on surgery or autopsy histologic findings or bacteriologic findings or electrode-tip wire vegetation), three patients presented with septic shock [6]. All three patients had lead vegetations, with two out of the three cases surviving. Time to explantation and its possible influence on outcome was not detailed.

Explantation of device has been shown to be important [2] for outcome and it is fair to say that this is time dependent. Our case highlights the possibility of fulminant sepsis in CDI with Staphylococcus aureus bacteraemia in the absence of localising signs or symptoms at presentation and in the absence of (transthoracic) echocardiographic evidence of vegetations. A high index of suspicion is important, particularly for early CDI (<1 year) [2].

References

Cardiac Image Registration: Rotational Error Correction and Gated Stabilization for Cardiac Motion

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Abstract

Background: Dynamic motion of the heart due to cardiac and respiratory cycles, and rotation from varying patient positions between imaging modalities, can cause errors during cardiac image registration. This study used phantom, patient and animal models to assess and correct these errors.

Methods and Results: Rotational errors were identified and corrected using different phantom orientations. ECG-gated fluoroscopy images were aligned with similarly gated CT images in 9 patients, and accuracy assessed during atrial fibrillation (AF) and sinus rhythm. A tracking algorithm corrected errors due to respiration; 4 independent observers compared 25 respiration sequences to an automated method. Following correction of these errors, target registration error was assessed. At 20 mm and 30 mm from the phantom model’s center point with an in-plane rotation of 8 degrees, measured error was 2.94 mm and 5.60 mm, respectively, and the main error identified. A priori method accurately predicted ECG location in only 38% (p=0.0003) of 313 R-R intervals in AF. A posteriori method accurately gated the ECG during AF and sinus rhythm in 97% and 98% of 375 beats evaluated, respectively (p=NS). Tracking algorithm for ECG-gated motion compensation was identified as good or fair 96% of the time, with no difference between observers and automated method (chi-square=25; p=NS). Target registration error in phantom and animal models was 1.75±1.03 mm and 0 to 0.5 mm, respectively.

Conclusions: Errors during cardiac image registration can be identified and corrected. Cardiac image stabilization can be achieved using ECG gating and respiration.

Key Words: Imaging, ablation, atrium, registration, atrial fibrillation.
area of current interest [1-9]. Gating to both the cardiac cycle and respiration could potentially help reduce these errors. Another source of error could be due to different patient positions at the time of imaging and during the interventional procedure. Although for the purpose of this study a 2D-3D registration model was used, these errors can be common to both 3D-3D and 2D-3D image registration. One important difference, however, between 3D and 2D registration is that fluoroscopic images are conic projections. In contrast, computed tomography (CT) images represent the synthesis of many X-ray projections obtained circumferentially around an object. Therefore, during CT-fluoro fusion (CT-FF), in addition to the errors described above, fusion and visualization of 3D images with conic projections from 2D fluoroscopy can cause image distortions and need to be taken into account.

This study was designed to identify and evaluate corrections for a) in-plane and out-of-plane rotational errors that would reflect changes in patient position, b) cardiac cycle motion, and c) LA motion during respiration. Finally, following correction of these errors, any target registration error in the phantom and animal model was identified by marking or delivering ablation points to the implanted beads using only registered images.

Methods

The study included the use of phantoms, patient data and an animal model. The initial part of the study used phantom and patient data to assess rotational errors and cardiac motion as well as motion due to respiration. A subsequent part of the study assessed target registration error in the phantom and an animal model, where implanted beads were targeted for ablation using the registered images.

The Institutional Review Board approved the study and all patients gave informed written consent. Animal studies were performed at the Aurora Sinai Medical Center Research Laboratory (accredited by the American Association for Accreditation of Laboratory Animal Care) and approved by the institute’s Research Subcommittee for Animal Studies.

Imaging and Segmentation

Phantoms were scanned in a normal fashion with CT, while canine model and patients were scanned with contrast-enhanced, ECG-gated CT scan (LightSpeed® Ultra, GE Healthcare, Waukesha, WI). The process of imaging and segmentation of the LA has been described previously in detail [10-12]. Retrospective ECG-gated reconstruction of the axial slices was performed at the point in the cardiac cycle that yielded the best image quality, approximately 70% to 80% phase location. The native slice acquisition thickness was 1.25 mm. Left atrium, superior vena cava (SVC), and coronary sinus (CS) were segmented using CardEP™ software (GE Healthcare, Waukesha, WI), which has been described in detail in the literature. Postprocessing software allowed these data segments to be seen separately or together.

Registration

Registration was performed on the registration platform (Advantage™ Windows workstation, GE Healthcare, Waukesha, WI) as previously described [4]. Essentially, prior to registration, a 6F decapolar catheter (St. Jude Medical Inc., St Paul, MN) was placed in the CS. A transformation process that linked the catheter imaged on the fluoroscopy system to the SVC and CS segmented from the CT images was used to register the 3D-CT model with the 2D fluoroscopy images. A multielectrode basket catheter with 64 unipolar electrodes (Constellation®, Boston Scientific Corp., Natick, MA) and a mapping and ablation catheter (ThermoCool®, Biosense Webster Inc., Diamond Bar, CA) were placed in the superior pulmonary veins (PVs) after transseptal catheterization in the patient part of the study. The fluoro images were transferred to the registration platform. Similarly, the appropriate ECG signals were identified and transferred from the CardioLab™ (GE Healthcare, Waukesha, WI) to the registration platform. Fluoro images were also gated to the ECG as the CT images.

Conic vs. Parallel Projection

In order to fuse the 3D-CT model data with the 2D fluoro projection image, the 3D-CT model data must first be projected into a 2D image that can
be registered with the fluoroscopic image. Typically, 2D projection images are created from a 3D-CT image dataset by a parallel projection process, which is analogous to 2D projection imaging with the X-ray source infinitely distant from the anatomical object and detector. Parallel projection has the advantage of preserving the integrity of distances measured between objects in an x-y plane (perpendicular to the central X-ray) at any depth in the z direction (parallel to the central ray) in the anatomy. However, X-ray projection imaging embodies an inherent projection distortion due to the fact that the X-ray source is a finite distance from the anatomy being imaged. As a result, objects closer to the source are magnified more than objects more distant from the source in the pro-

Figure 1: Representation of the distortion due to conic projection of the 3D model during 3D-2D cardiac image registration. See text for details.
jected image, and there is no way to resolve these ambiguities without knowing the positions of the objects of interest along the z-axis. Figure 1 is a representation of the problem that could occur from overlaying 3D parallel projection images of CT on 2D conic projection images seen on fluoro. If \( a_1 \) and \( a_2 \) are two points located 20 mm from the center (straight line), these points will be projected as \( X_1 \) and \( X_2 \), resulting in an error on the location of a point in the image. For measurements of projection distortion using 3D-CT models, values of 20 mm and 30 mm were used. The difference in markings in the upper scale on the CT images versus scale marks on the fluoro images was measured, as indicated in Figure 1, to assess the conic projection error. Custom-designed post-processing software was used to correct this error.

**Phantom Studies**

Phantom studies were designed to address the following: in-plane and out-of-plane rotation error and target registration error using rigid-body registration process. For those studies not assessing the target registration error, a custom phantom constructed of 1-inch (2.54 cm) thick plexiglass plates and two scales Figure 2 was used. The scales were essentially printed circuit boards with two perpendicular rulers (marked in centimeters) and five concentric circles (with 1-inch increments in radii) traced into each of them. The scales were placed such that one was rotated 45 degrees in plane relative to the other and separated by two of the plexiglass plates. The plexiglass had pegs that fit tightly into a pattern of holes in the plates and

**Figure 2:** Custom phantom used in the study. A representation of the phantom depicting top and side views along with measurement scales (Panel A). Scales, which are circuit boards separated from each other by plexiglass (Panel B). Fluoro image of the phantom (Panel C). See text for more details..
length of the 10-mm mark along the scale that was at the right calibration height. CT markings were scaled and aligned with fluoro markings, and the 1-cm caliper length on the CT image matched the 1-cm mark on the fluoro image. For the purpose of this study, two distances, 20 mm and 30 mm, were used from the center point of the image. For target registration error, the plastic model of the LA used was Angiogram Sam® (Medical Plastics Laboratory Inc., Gatesville, TX).

In-plane and Out-of-plane Rotation Error

For the purpose of this study, in-plane rotation was defined as any rotation in a horizontal plane about the vertical axis going through the center of scales. In the phantom model, by adjusting the VR opacity bounds, it was possible to visualize just the scales and filter out everything else, including the plexiglass plates.

Out-of-plane alignment of the phantom on the CT and fluoro tables was accomplished using a spirit leveler. For in-plane alignment, precise lines were marked on the fluoro table and the phantom was aligned with these markings [Figure 2]. Lower scale was 4 inches (10.16 cm) above the fluoro table, and upper scale was 6 inches (15.24 cm) above the fluoro table. In both CT and fluoro images, the length of the 1-cm caliper was measured and compared to the markings on the appropriate scale. The length of the 1-cm caliper matched the

Figure 3: “A priori” (Panel A) and “a posteriori” (Panel B) ECG-gating technique.
the phantom. Out-of-plane rotation was defined as any rotation about a horizontal axis going through the center of the phantom.

In-plane rotation was achieved by making markings relative to the original alignment markings on the fluoro table with the aid of a common protractor, and aligning the phantom to their markings. Out-of-plane rotation was achieved by raising one end of the phantom using sheets of paper, and verifying the angle of rotation with a common protractor. For this study, in-plane rotation of 8 degrees was applied to the phantom. For the analysis of out-of-plane, a 5-degree rotation was applied to the phantom in the right-to-left and craniocaudal directions, respectively.

Target Registration Error

Eleven glass beads (1 mm in diameter) were attached to the left atrial surface of a cardiac phantom. These glass beads are easily visualized on the CT and CT-FF but not on the fluoroscopy image. The LA, SVC and CS were segmented, and the phantom was positioned on a fluoroscopic table. A 20-pole 7F CS catheter (St. Jude Medical Inc., St. Paul, MN) was placed inside the CS and the fluoroscopic images were acquired. Following this, registration was performed as described previously, using a transformation that superimposed a CS catheter placed inside the phantom during fluoroscopy over the segmented SVC and the CS from the CT model. A mapping catheter was brought into contact with the glass beads (which were not used for registration) using the CT-FF image only. The distance between the catheter, as seen on fluoroscopy, and each bead as it appeared on the CT-FF, was measured to determine the target registration error.

Patients

ECG data from 9 patients was used for the ECG-gating study, while data from 17 patients was used for the respiration motion study.

ECG Gating for Cardiac Cycle Motion

The a priori method used a moving average of the prior 10 R-R intervals to predict the optimum timing for image registration, while the a posteriori method used 75% of the previous R-R interval to select the proper fluoroscopic image within that R-R interval [Figure 3]. Latency was defined as the lag between the time when the correct fluoroscopic image was acquired and the time when the next QRS complex was detected by the software and depicted on the screen.

In atrial fibrillation (AF), the a priori method was triggered to adjust the image for 375 beats; 313 of these were replayed in a posteriori method. In sinus rhythm, the a priori method was triggered to adjust the image for 370 beats, and the a posteriori method was triggered to adjust the image for 377 beats.

Respiratory Motion Compensation

For the respiration motion study, a database was created by recording a series of 25 ECG-gated fluoroscopy image sequences from 17 patients undergoing AF ablation. The results of a two-step validation procedure were used to assess the performance of this respiration tracking. In the first step of the validation procedure, a mathematical evaluation of the algorithm was conducted. The locations of the multielectrode catheter in one of the superior PVs and the mapping and ablation catheter close to the ostium in the other PV were marked on each of the fluoroscopic images through the entire sequence for at least two respiratory cycles. The motion of these catheters represented a reference for respiratory motion. A custom-designed algorithm was applied to each of the sequences in the database. The algorithm picked up location of catheters in the soft tissue (heart) as they moved in real time with the respiration and created a tracking template for moving the CT-fluoro fused image with them. The results of the tracking algorithm were automatically computed using the absolute difference in pixels between it and the reference.

In the second step of the validation process, the same fluoroscopy sequences were registered with their corresponding left atrial CT images, and the motion of the LA throughout the respiratory cycle was tracked. The accuracy of the respiration motion tracking was evaluated clinically by 4 independent operators and categorized as good (perfect tracking), fair (small jumps in the localization
of the catheters), or poor (big jumps once in a
while inducing misregistration of the catheters).
The two methods were then compared for correla-
tion of results.

Animal Studies

A mongrel dog (weight approximately 25 kg) was
used for the target registration phase of this study.
The animal was sedated with intravenous sodium
pentothal (25 mg/kg) and intubated. Anesthesia
was maintained with 1.0% to 1.5% halothane. Us-
ing aseptic techniques, a left lateral thoracotomy
was performed, and two platinum beads 1 mm in
diameter, which would be visible on CT and fluo-
roscopy, were implanted.

Imaging with the CT scanner and experimentation
for target registration was performed on the same
day. Right atrial segmentation was performed us-
ing the contrast-enhanced CT, registered using a
CS catheter placed in the CS and visualized on
fluoroscopy. Radiofrequency lesions were posi-
tioned over two different beads using CT-FF only,
and were motion compensated and ECG-gated. The
operator during the navigation and ablation
part of the experiment was blinded to fluoroscopy
images and only used CT-FF for guidance. A ra-
diofrequency lesion was delivered at each of these
locations (30 Watts for 30 seconds). After all of the
lesions were accomplished, the animal was eutha-
nized. The heart was removed, and the locations
of the lesions were visualized by staining the heart
with 2,3,5-triphenyltetrazolium chloride. The dis-
tance from the implanted beads to their corre-
sponding lesions was measured and the sites were
photographed. If a lesion touched the implanted
pacing electrode, the distance was recorded as 0
mm. In all other instances, the distance from the
center of the lesion to the nearest portion of the
implanted bead was recorded.

Statistical Analysis and Definitions

Results are expressed as mean ± 1 standard de-

viation for continuous data and as percentages
for dichotomous data. Chi-square analysis was
performed between the mathematical and clinical
models to assess motion compensation outcomes.
In the present study, the target registration error
was defined as the distance from the ablation loca-
tion to the implanted beads on the phantom and
animal models that were targeted.

Results

In-plane and Out-of-plane Rotation Errors

In AF, the a priori method was triggered with
38.3% accuracy. When sequences were replayed in
a posteriori, there was 95.8% accuracy, p=0.0003. In
sinus rhythm, the a priori method had 97.5%
accuracy and the a posteriori method 98.2% accu-

racy, p=NS. The a posteriori method introduced an
average of approximately 187 ms of latency into
the registration process during AF and 218 ms
during sinus rhythm. Figure 5 depicts an ECG-gat-
ing window in sinus rhythm and AF, and latency
during registration. Latency, as depicted in the fig-
ure, is the lag between the time when the correct
fluoroscopic image is acquired (green arrow) and
the time when the next QRS complex is detected
(green dot). This suggests that the images can be
seen almost instantaneously.

Cardiac Cycle Gating

In AF, the a priori method was triggered with
38.3% accuracy. When sequences were replayed in
a posteriori, there was 95.8% accuracy, p=0.0003. In
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(green dot). This suggests that the images can be
seen almost instantaneously.

The a posteriori method of ECG gating was thus
significantly more accurate than the a priori meth-

od when patients were in AF, while both meth-
methods were equivalent when patients were in sinus rhythm.

**Respiratory Motion Compensation**

In the first step of the validation process, using 504 images from the database, the tracking algorithm was good in 72% of cases, fair in 24% and poor in 4%. In the second step, clinical evaluation by 4 independent operators reviewing 25 prerecorded sequences rated 69% good, 29% fair and 2% poor. All sequences were replayed using the a posteriori ECG-gating method. The range between the operators’ sequences assessed as good, fair or poor was 60% to 76%, 20% to 36% and 0% to 4%, respectively. There was an 87% reproducibility of the results on a subsequent analysis of 5 sequences by 3 observers. A chi-square analysis comparing the mathematical versus clinical results demonstrated that there was no difference between the two techniques in regard to outcomes using tracking algorithm and operator-based analysis (chi-square=25, p=ns). Of the 25 sequences evaluated, 10 sequences were found during sinus rhythm and 15 during AF. Figure 6 depicts one example of motion compensation during the respiration cycle.

**Target Registration Error**

Table 1 depicts distance in millimeters from the bead to the centroid of the catheter tip recorded in CT-FF on 3 different angulations during target registration, using the rigid-body transformation in the phantom models. The mean distance was 1.75 ± 1.03 mm, range 0.19 to 3.23 mm. All beads could be identified on the CT-FF Figure 7.

An example of the ablation marking and its relationship to the bead in the animal model experiments is depicted in Figure 8. There was no target registration error targeting the beads implanted in the animal model for ablation when the distance between the border of the bead and ablation lesion was used as the measure. When distance between the centroid of the bead and the lesion was used as the measure, the error was 0.5 mm.

**Conic and Parallel Projection**

Measurement at marks distanced 20 mm and 30 mm from the center independently gave an error of 3.46 mm at 20-mm distance and 4.26 mm at 30-mm distance for the upper and lower scales, respectively. The conic projection of fluoro images does cause a relatively significant error in the registered 3D image. For the purpose of explanation, Panel A in Figure 9 is an example of parallel versus conic projection. Figure 9, Panel B depicts a 3D image in parallel image. Instead of the alignment of green and blue dots seen in the conic projection, the parallel projection of the 3D model aligns the green dot with the red dot on the right panel. The

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**Figure 4**: Demonstration of in-plane rotation error and its correction. The fluoro image of the phantom, which has been rotated by 8 degrees (Panel A). The CT-fluoro registered image (Panel B). However, the CT image is not rotated. In Panel C, the CT image has been rotated by 8.5 degrees to correct the in-plane rotational error as, unlike in Panel B, scales on the CT and fluoro image align perfectly.
distance between the blue and green dots represents the error (X1-X2) depicted in Figure 1. Figure 9, Panel C depicts an image in conic projection once the error has been corrected using customized rendering software. In Panel C, the CT has been morphed into a conic projection, thus aligning the blue dot with the green dot. The green dot, being closer to the source, is projected as a larger dot, as is expected in fluoroscopic projections. Figure 10 further depicts the error from parallel projection of the CT and its correction by the rendering software in the phantom study. Upper left panel in Figure 10 is a CT image of the phantom as depicted in previous examples. Upper right panel in Figure 10 is the fluoro image of the same phantom. The CT image has been prepared using a standard rendering tool to perform the projection of the 3D model and, therefore, is done in parallel projection as shown in Figure 10, lower left panel (CT-FF using parallel projection); the solid and open arrow depicts the error from parallel projection. Lower right panel in Figure 10 depicts the same CT-FF using conic projection, where postprocessing software used in the CT-FF corrects the error by scaling or morphing the CT model to be projected appropriately using conic projection.

Discussion

Intermodal registration algorithms assume that the

Figure 5: ECG gating during atrial fibrillation and sinus rhythm using “a posteriori” method. Latency, the time between when the fluoro images are acquired (green arrow) and when the inscribed QRS is detected (green dot), is minimal, thus the images appear almost instantaneously.
images involved represent identical objects, residing in different image spaces [13-16]. The registration transforms one space into the other and then physically aligns the object, via transformations, within that space. The specific type of registration considered here is 2D-3D, however, the errors and their correction discussed herein apply to any of the currently used cardiac registration techniques.

Errors common to intermodal registration can be described as numerical, resulting from computation or measurements. While movements that occur in the same plane will be addressed by most algorithms, movements that occur out of plane due to different positions of the patient, for example due to long interscan times, may be difficult to address and cause other forms of errors. Similarly, cardiac motion during the cardiac cycle and respiration can cause deformations, i.e. nonrigid-body transformations that are continuous may not be predictable [17-19]. This study evaluated these errors in a systemic fashion and assessed techniques to correct them to enable appropriate cardiac image registration.

Rotational Errors

Out-of-plane rotations of the cardiac chambers can occur with changes in the orientation of the body. Errors may occur due to time lapse between the scans, CT or magnetic resonance imaging (MRI) to fluoro or other imaging modalities, and because of differences in imaging table surfaces, such as curvature and cushioning, and different positioning of the patient. It is critical to identify and correct this interscan movement. To help ensure that the cardiac chamber has the same orientation during both imaging sessions, efforts should be made to align the patient identically on the table during both imaging sessions. As demonstrated in the present study, in-plane rotation is more likely to cause these errors if there is variability in patient alignment and posture.

It is expected that the out-of-plane rotation will have the same 3D error since the rotation is really just an in-plane rotation about a horizontal axis in the 3D modality. However, as compared to in-plane rotation, out-of-plane rotational error was found to be minimal in the current study. Identification of these errors is critical and possible, as demonstrated in this study, and can be corrected.

Cardiac and Respiratory Motion Errors

The displacement of the heart due to respiration has also been identified as a source of error in a number of studies [20-21]. It has been determined that translational movement in the craniocaudal direction is the main type of movement experienced by the cardiac chamber due to respiration. Less significant movements include translations and rotations in other directions. A gating technique during CT imaging involves a patient holding his/her breath in expiration for several heart beats, during which time 2D axial slices are sequentially obtained at fixed points of the cardiac cycle. These slices are stacked and interpolated to create a smooth and static 3D-CT image.

The current study took into account these errors and described techniques to correct them. It is possible to create optimal ECG-gated fluoroscopic images and integrate them with similarly acquired CT images. The a posteriori method seems to be more accurate than the a priori method, especially if a patient is in atrial fibrillation. It is possible to track catheters placed inside the heart to compensate for registration errors due to respiration motion. The study validated this technique using patient and animal data. The technique proved quite easy to use in almost all patients. Further study on

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Mean error was 1.75 ± 1.03 mm.
the use of this technique in a larger cohort of patients is needed.

However, target registration errors were minimal and acceptable in both rigid models using a phantom model and in animal models in which cardiac gating and respiration-tracking algorithms were enabled. The study clearly demonstrated that it is

**Figure 6:** Demonstration of motion compensation in an ECG-gated CT-fluoro registered image. Images are taken during maximum inspiration, in-between and during maximum expiration, as depicted by arrows showing the location of the diaphragm. The relationship between the coronary sinus, the coronary sinus catheter, and the multielectrode basket catheter and the pulmonary veins stays stable throughout the respiration cycle.

**Figure 7:** Target registration in a rigid-body registration. Panels A and B are fluoro images and CT images of the phantom in the anteroposterior orientation (AP), respectively. Panels C and D are registered images showing implanted beads and marked ablation points. It can be appreciated that the glass beads are only visible on the CT image or the registered image, thus allowing navigation and targeting of these beads only on the registered image.
possible to take into account errors due to dynamic motion of the heart and largely correct these errors using appropriate algorithms.

**Study Limitations**

Validation is implicitly a quantification of the integrity of a registration application and the par-

**Figure 8:** Target registration error in an animal model. Location of implanted bead and ablation lesion. ECG gating and respiration motion compensation has been performed already prior to targeting the implanted bead on the registered image.

**Figure 9:** Demonstration of conic and parallel projection errors using a 3D model such as CT. Panel A depicts an example of parallel versus conic projection. Panel B depicts a 3D image in parallel image. Panel C depicts a CT image morphed into a conic projection.
ticular choices made in registration algorithm design. The cardiac cycle is not always regular, and there may be changes in the heart’s rhythm from the time of the CT scan to fluoroscopic session. Although some error could be induced due to these changes, the a posteriori method was equally effective in reconstruction of the 3D image with ECG gating whether the rhythm was sinus or AF. Intermodal registration algorithms assume that the images involved in the registration represent identical objects residing in different image spaces. Potential changes in volume from the time of the CT scan to the fluoroscopic session could cause errors. Therefore, it is important that the time lapses between imaging sessions are not too long. Due to ambiguities involved in addressing the nonpredictive and significant nature of cardiac movement, there may be other ways in which the design of validation strategies could be approached. Despite the possible limitations described above, this study addressed the main errors that could occur during the process of cardiac image registration and detailed and evaluated the means to correct them.

Conclusion

Knowledge of the various sources of error possible during registration is key to establishing a gold standard for use of intermodality image registration, since these errors will have to be addressed in the design of any registration algorithms. This study systematically examined three significant sources of registration error – change in patient position during interscan interval, cardiac motion and respiration motion, as well as conic vs. parallel image distortions during 3D-2D image registration – and corrections for these errors using phantom, animal and patient studies. Further-
more, these algorithms were then successfully applied to achieve appropriate target registration.

**Funding Sources**

Equipment for registration platform provided by GE Healthcare. No other funding was provided for the part of the study detailed in this report.

**Acknowledgments**

We gratefully acknowledge the assistance of Brian Miller and Brian Schurrer in the preparation of illustrations and Barbara Danek, Joe Grundle and Katie Klein in editing the manuscript.

**References**

The Cost of Thromboembolic Events and their Prevention among Patients with Atrial Fibrillation

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Abstract

Aim: Atrial fibrillation (AF) is the most common type of cardiac arrhythmia. People with AF have a significantly increased risk of thromboembolic events, including stroke, and the main treatment is therefore aimed at preventing thromboembolic events via anticoagulation with warfarin or acetylsalicylic acid. However, the development of new anticoagulation treatments has prompted a need to know the current cost of AF-related thromboembolic events, for future cost-effectiveness comparisons with the existing treatments. In this study, we estimated the cost of thromboembolic events and their prevention among Swedish AF patients in 2010.

Methods: The relevant costs were identified, quantified, and valued. The complications included were ischaemic and haemorrhagic stroke, gastrointestinal bleeding, and other types of major bleeding caused by AF. Treatments intended to lower the risk of ischaemic stroke were also included. A societal perspective was used, including productivity loss due to morbidity. Patients with a CHADS2 score of 1 or higher were included.

Results: Among the 9 340 682 inhabitants of Sweden, there are 118 000 patients with AF and at least one more risk factor for stroke, comprising 1.26% of the population. Of these patients, 43.3% are treated with warfarin, 28.3% use acetylsalicylic acid, and 28.3% are assumed to have no anticoagulation treatment. The cost of AF-related complications and its prevention in Sweden was estimated at €437 million for 2010, corresponding to €3 712 per AF patient per year. The highest cost was caused by stroke, and the second highest by the cost of monitoring the warfarin treatment. As the prevalence of AF is expected to increase in the future, AF-related costs are also expected to rise.

Conclusion: Thromboembolic events cause high costs. New, easily-administered treatments that could reduce the risk of stroke have the potential to be cost-effective.

Keywords: cost, thromboembolic events, atrial fibrillation, anticoagulation
is also expected to increase in the long term.

Patients with AF often suffer a decreased quality of life,\textsuperscript{3,5} and AF also increases the risk of thromboembolic events such as ischaemic stroke. The treatment of AF often varies for different patients and types of AF. Most AF treatments, however, are given in combination with anticoagulation treatment to prevent thromboembolic events.\textsuperscript{6} The most commonly used anticoagulation treatment today is warfarin (Waran\textsuperscript{®}), which is very effective in preventing stroke. This treatment requires accurate dosing and careful monitoring, to reduce the risk of stroke without greatly increasing the risk of bleeding. Too high a dose carries a risk of serious complications in the form of bleeding, including intracranial haemorrhagic stroke, while too low a dose will fail to protect against thromboembolic events. Hence, the dose is regularly controlled and adjusted, either at a particular anticoagulation clinic or in primary care.

An alternative to warfarin is treatment with acetylsalicylic acid (ASA). ASA prolongs bleeding time, and therefore provides some protection against thrombosis, but also slightly increases the risk of bleeding. ASA is, however, not as effective as warfarin in preventing thromboembolic events.\textsuperscript{7} The Swedish National Board of Health and Welfare recommends that ASA should not be used unless warfarin is contraindicated.\textsuperscript{6} However, less than 50 per cent of all AF patients in Sweden receive warfarin treatment today,\textsuperscript{8} and many patients are without any anticoagulation treatment. In the near future, new anticoagulation treatments will challenge the established treatments. There is therefore a need to know the current cost of AF-related complications, so that cost-effectiveness comparisons can be performed when the new treatments are available.

The risk of ischaemic stroke in an AF patient depends on several factors including age, sex, previous complications, hypertension, and diabetes.\textsuperscript{7} Patients can therefore be classified according to their risk for stroke. The most commonly used risk classification system is CHADS\textsuperscript{2}, which rates the patient on a scale from 0 to 6, relating to the risk based on predefined risk factors.\textsuperscript{9} In CHADS\textsuperscript{2}, incidence of chronic heart failure, hypertension, an age over 75 years, and diabetes each generate 1 point, while previous stroke or transient ischaemic attack generates 2 points.

The aim of this study was to calculate the societal cost of thromboembolic events and their prevention among Swedish AF patients in 2010. The costs and consequences of using self-testing equipment to monitor warfarin were not included, as this is not common in Sweden today.\textsuperscript{10}

\textbf{Material and Methods}

This study can be classified as a cost-of-illness study. The cost calculation included hospitalizations, primary health care, anticoagulation treatment including monitoring costs, and costs of complications (direct and indirect). The complications included were ischaemic and haemorrhagic stroke, gastrointestinal (GI) bleeding, other types of severe bleeding, and minor bleeding. The analysis was undertaken from a societal perspective, including productivity loss due to morbidity. The unit costs for AF patients were calculated on the basis of the county of Östergötland (population 420 000 inhabitants) and then aggregated to a national level. The treatment of AF patients in Östergötland was assumed to be representative of the rest of Sweden. Costs that would occur in the future were discounted at 3 percent annually.

\textbf{Prevalence}

At the end of 2009, the population in Sweden was 9 340 682.\textsuperscript{11} A recent study using the Swedish national register found that 100 557 individuals were diagnosed with either primary or secondary AF.\textsuperscript{12} However, as some individuals with AF are not diagnosed, this figure is not complete. According to a study of AF in England and Wales, the prevalence was 1.24 per cent of the total population (1.21 for men and 1.27 for women).\textsuperscript{1} The same study showed that the incidence of AF increased between 1994 and 1998. Several other studies have shown similar prevalence.\textsuperscript{13, 2, 14} Applying the prevalence data from England and Wales to the age and gender structure of the Swedish population, we estimated the number of patients
with AF in Sweden to be 135 278 (see Table 1).

The fact that different patients have different background risks of stroke also had to be taken into account in the calculations. One study has analyzed the distribution of patients with AF in different CHADS2 scores, using a population of 51 807 patients in the UK who were diagnosed by general practitioners. The results are presented in Table 2, together with estimates of what the corresponding results would be in Sweden. Our calculations included only patients with CHADS2 = 1 or higher, giving an estimate of 117 827 for the prevalence in Sweden. These patients are assumed to be equally distributed between the three CHADS2-score groups 1, 2 and 3-6.

Anticoagulation Treatment

Patients with AF can be divided into three treatment groups depending on their anticoagulation treatment: warfarin, ASA, or no anticoagulation. In Sweden, 43.3 percent of patients with AF are treated with warfarin, around 28% with ASA, and again around 28% with no anticoagulation treatment. Warfarin treatment can be further divided into three groups: well-controlled (international normalised ratio [INR] within therapeutic range more than 70% of the time), non-controlled (INR within therapeutic range less than 70% of the time), and new (warfarin-naïve) patients.

The percentage of patients monitored at the anticoagulation clinics rather than in primary care varies greatly between different regions in Sweden. In this study, however, it was assumed that the county of Östergötland, with 90 percent of patients monitored at the anticoagulation clinics, represented an acceptable estimate for the rest of Sweden.

The percentage of test results lying in the therapeutic range is between 76 and 78 percent in all of the anticoagulation clinics in Östergötland. As both the national average and the average from the Swedish centres in the recent RE-LY trial have 77 percent of tests within therapeutic range, the clinics in Östergötland are representative in this matter. The average number of samples per patient per year at Linköping anticoagulation clinic (the largest hospital within Östergötland) is 16.94. New patients have been removed from these statistics, and it is estimated that it takes about five tests to stabilize a new patient; we therefore assumed a figure of 21.94 for the average number of samples during the first year for new patients. In a non-published study, the number of tests in primary care in Östergötland was found to be 13.7 in 2005. No data were given for new patients, but in the present paper, we estimated the number of new samples in primary care to be 18.71.

A study has shown that the proportion of INR within therapeutic range is similar between the anticoagulation clinics and primary care in Östergötland. In that study, all INR tests during a specific week in 2004 from both anticoagulation clinics (470 samples) and primary care (517 samples) were analyzed.

Costs

All costs were calculated in Swedish kronor (SEK) and adjusted to the 2009 values by using the consumer price index. The costs are presented in Euros (€), using an exchange rate of €1 = SEK9.50.

The cost of warfarin is generated both by the medication itself and by the monitoring that is needed for it to be effective. The price of warfarin is €11.4 for 100 tablets of 2.5 mg. Given a use of 4 mg daily, the annual cost was estimated at €66. The cost of visiting a doctor once a year was also included; according to the price list in the Southeast regional hospital, this is €188. Warfarin monitoring can take place either at the anticoagulation clinic or in primary care, causing different costs. According to the price list for medical laboratory centres in Östergötland in 2010, the cost per sample in an anticoagulation clinic is €20.6. This value is in line with the average values estimated in a study of the cost of monitoring the anticoagulation clinics in Sweden. The patients’ travel costs to get to the clinic have been estimated at €5 per occasion. The productivity loss (indirect costs) arising from the patient’s being unable to work during the monitoring is estimated at €2.9.

The cost per visit for warfarin treatment in primary care is estimated at €61, including a higher cost in 10 percent of the cases due to samples taken in the patients’ homes. In addition to these costs, we assumed that the patients’ travel expenses
and productivity losses are equivalent to those arising from the visit to the anticoagulation clinic.

The cost of ASA treatment in the calculation was set at the price of the medication and one annual medical examination. The pharmaceutical Tromblyl® costs €6.4 for 100 tablets of 160 mg each. With an average daily dose of 160 mg, this corresponds to an annual cost of €23. The cost of a medical consultation has been estimated at €188.

Ghatnekar et al. who studied the cost of stroke in Sweden in 2004, used an incidence based approach in which direct costs amounted to €62 197 and indirect costs to €15 145 in 2009 values. This estimate includes admission costs, re-stroke admission costs, outpatient costs, and costs for social services. These values were used for the cost calculations of both ischaemic and haemorrhagic stroke in this study. A study from the UK found that the average acute care costs one year after stroke come to €7 666, and that the cost of stroke for patients with a history of AF is higher than for patients with no AF history. It is therefore likely that stroke patients with AF are more costly than the average cost of stroke used in the calculation in this study.

Existing data on the cost of bleeding is poor, partly due to the difficulty of defining major and minor bleeding. A study based on registry data estimated the average cost of serious bleeding at €2 773, while a study from Canada estimated the cost of GI bleeding at €3 303, based on the cost of hospitalization and outpatient care [28]. On the basis of these costs, for the purposes of our analysis we estimated the cost of minor bleeding at €32.

Risk of Complications

Patients with AF who are not receiving anticoagulation treatment have an annual risk of stroke of about 6 percent. When patients are divided into different risk groups by CHADS2 score, the annual risk of stroke varies from 1 percent to 18 percent or higher. Treatment with ASA has been shown to reduce the risk of thromboembolic events by 19 percent compared with no treatment, but it also slightly increases the risk of bleeding. The risk of thromboembolic events with ASA or no treatment used in the present calculation was based largely on the scientific basis underlying the Swedish National Board of Health and Welfare’s guidelines for the treatment of AF. The risks of warfarin-related complications were taken from the recent RE-LY trial, which compared the new anticoagulation drug dabigatran with warfarin. As dabigatran is not yet used in patients with AF, its associated costs were not considered here. The warfarin-related risk of haemorrhagic stroke was taken from the intracranial bleeding estimates in the RE-LY study. One sub-study from RE-LY presented the risks of complications divided by the background risk of stroke according to CHADS2. The annual absolute risks of complications arising with different anticoagulation treatments are presented in [Table 3].

Another subgroup analysis from the RE-LY trial studied the risks for complications divided by the different study centres’ average INR level. Centres were divided into quartiles according to their mean time in therapeutic range (TTR). The quartile with the maximum TTR had more than 72.6 percent of the INR within therapeutic range. In our calculation, we assumed that this corresponds to well-controlled warfarin patients. The second-worst quartile was used for non-controlled warfarin patients; here, TTR ranged between 57.1 percent and 65.5 percent. The reason for using this method was that Sweden has a higher rate of INR within therapeutic range than the mean in the RE-LY trial. Risks for stroke and major bleeding divided by well-controlled and non-controlled warfarin therapy are presented in [Table 4]. A weighting of well-controlled and non-controlled warfarin was used for warfarin-naïve patients, in line with the proportion of warfarin patients in Östergötland (77 percent).

Results

Among the 9 340 682 inhabitants of Sweden, we estimated that there are 117 827 patients with AF and at least one more risk factor of stroke, comprising 1.26% of the population. Of the patients, 43.3% are treated with warfarin, 28.3% use acetylsalicylic acid, and 28.3% are assumed to have no anticoagulation treatment. The largest cost was incurred in the patients not given anticoagulation with warfarin, as these patients have a higher risk of stroke. The lowest cost per patient was incurred by those with well-controlled warfarin therapy (see Figure 1).
The total cost of thromboembolic events and their prevention among AF patients in Sweden was estimated at €437 million for 2010 (see Table 5), corresponding to €3 712 per AF patient per year. The highest cost was caused by stroke, and the second highest by the cost of monitoring the warfarin treatment.

Discussion

In this study, we estimated the costs of thromboembolic events and their prevention among AF patients in Sweden. The total societal cost was estimated at €437 million per year. Even though our calculation did not include AF treatments such as antiarrhythmic drugs or ablation, we believe that thromboembolic events and their prevention constitute the major costs related to AF. Most of the data used for the calculation of the costs are confirmed by published studies, but some presumptions have been made which can be seen as a limitation to the quality of the study. For example, the exact prevalence of AF patients in Sweden is not known and the TTR among patients monitored in primary care is not verified. All these presumptions are presented in the material and methods section.

A recent Swedish study estimated the total cost of AF in Sweden to be about SEK6.6 billion (€708 million), which is higher than the total presented in our study. The main reason for this is probably that the other study used a top-down approach including all medical costs faced by patients with AF. However, this will probably be an overestimate since many patients with AF also have other cardiovascular diseases, and shares of these costs could be traced to diseases other than AF. Another reason for the differing totals is that our study did not include any treatment of the AF. Another study has estimated the AF related cost per AF patient in Sweden to €4 866 and in Germany to €3 891. Another study, which included the costs of social services and productivity loss, estimated the costs directly related to AF in the UK at £1 307 million. Translated to Sweden, this corresponds to a total cost of approximately €380 million, which is roughly in line with the cost estimates in the present article. Another study, which estimated the per-patient cost of AF in five European countries, found that the cost was lowest in Poland (€1 010) and highest in Italy (€3 225). Le Heuzey et al. found that the two highest costs associated with AF were hospital admissions (52%) and pharmaceuticals (23%); these results are also in line with those found in this study. All studies have concluded that the cost for AF will increase significantly in the future, due to the increasing prevalence of AF.

We used a societal perspective in calculating the costs. This includes all costs and effects that occur in the society, whether for the patient (or relatives providing informal care), hospital (county), social services (municipality), or productivity losses (state). However, there are some costs that we were not able to include. Informal care provided by relatives to the patient is not included due to lack of data. Furthermore, the relatives of a patient with AF are often also affected in terms of decreased quality of life due for example to worries, and these costs (or loss of quality of life) are not included either in our calculations.

This cost calculation cannot be used to help decision-makers prioritize in this field, as it only estimates the costs and does not evaluate different treatments. The purpose of this type of analysis is rather to show the economic burden of AF and its consequences. However, this analysis can be used as a basis for future cost-effectiveness analyses. Several new anticoagulation treatments are expected to be available within the near future, and this calculation can be used in future comparative studies of different anticoagulation treatments. These new treatments do not need monitoring or patient-specific adjustments, which may reduce the total costs. On the other hand, the prices of the treatments are expected to be higher than for warfarin making the total influences on the costs unpredictable. Most important for the costs is however the treatments’ effectiveness in preventing stroke, as stroke is the main cost driver. Dabigatran (Pradaxa®) is the first of the new upcoming anticoagulation treatments, and once the price of dabigatran is known its cost-effectiveness can be analysed.

Conclusions

Thromboembolic events and its prevention cause high costs in the society, and stroke is the main
cost driver. New and easily-administered treatments that could reduce the risk of stroke have a potential to be cost-effective.

Financial Disclosure

Grants for this study were received from Boehringer Ingelheim (producer of dabigatran/Pradaxa®) and from the county council of Östergötland.

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Abstract

During the past decade atrial fibrillation (AF) ablation has developed from being an experimental treatment option to an evidence based therapy implemented in current guidelines. Irrigated radiofrequency current guided ablations remain the golden standard of pulmonary vein isolation (PVI) procedures. Although practiced more frequently, it remains a demanding procedure requiring skilful operators. Novel technologies such as balloon based catheters or remote navigation (RN) systems have been developed to overcome the pitfalls of manual ablation procedures.

Introduction

During the past decade atrial fibrillation (AF) ablation has developed from being an experimental treatment option to an evidence based therapy implemented in current guidelines. Irrigated radiofrequency current guided ablations remain the golden standard of pulmonary vein isolation (PVI) procedures. Although practiced more frequently, it remains a demanding procedure requiring skilful operators. Novel technologies such as balloon based catheters or remote navigation (RN) systems have been developed to overcome the pitfalls of manual ablation procedures.

Introduction of RN Systems

To date, two different RN systems are commercially available: 1) magnetic navigation (Niobe II™, Stereotaxis, St. Louis, USA) and 2) robotic navigation (Sensei™, Hansen Medical, Mountain View, CA, USA). Both systems and their technical specifications have been introduced in detail elsewhere but the major concepts will be described briefly.

Magnetic Navigation

In brief, the MNS (Niobe II™, Stereotaxis) consists of 2 computer controlled permanent magnets located on either side of the fluoroscopy table which create a steerable, uniform magnetic field (0.08 T) approximately 15 cm inside the patient’s chest. The mapping and ablation catheter is equipped with 3 permanent magnets within the distal shaft of the soft catheter and aligns parallel to the externally controlled magnetic field. The orientation of the magnetic field is manipulated by changing the orientation of the outer magnets relative to each other. All magnetic field vectors can be stored and, if necessary reapplied for automatic navigation.
tion of the magnetic catheter. To enable remote controlled catheter navigation, a computer controlled catheter advancer system (Cardiodrive™, Stereotaxis, Inc.) is required. The video workstation (Navigant 3.0, Stereotaxis, Inc.) allows for precise catheter manipulations and moreover, for an integrated display of the magnetic catheter tip within the 3D electroanatomic (EA) LA map on standard fluoroscopy [Figure 1]. The second generation Niobe II™ system enables tilting both permanent magnets thus allowing increased C-arm angulations to RAO 30° and LAO 40°.

Robotic Navigation

The electromechanical system achieves catheter navigation by two steerable sheathes (Artisan™, Hansen Medical, USA) incorporating an ablation catheter. Outer (14F) and inner sheath (10.5F) are both manipulated via a pull-wire mechanism by a sheath carrying roboter arm ("slave") that is fixed at the patient’s table. The roboter arm is controlled by the commands of the central workstation ("master") positioned in the control room. Catheter navigation is accomplished using a three dimensional joystick (Instinctive motion control™, Hansen Medical, USA) and allows a broad range of motion in virtually any direction. In general, all catheters < 8.5F and all electroanatomical mapping systems may be used. A customized software (CoHesion™) allows for integration of NavX™ (St. Jude Medical, St. Paul, MN, USA) 3D mapping data into the workstation allowing for instinctive navigation in the 3D map.

Since the operator is deprived of any tactile feedback during catheter manipulation the system is equipped with a proximal contact force sensor (IntelliSense™) for online display of calculated contact force values. An optical and a vibrant alarm can be set at an individual contact force level to increase operator’s awareness towards exaggerated forces.

Rationale to Use RN Systems for AF Ablation

The current consensus document on catheter ablation of AF states that electrical pulmonary vein isolation should be the cornerstone of any ablation procedure. It was shown that circumferential PVI...
is more efficient than a segmental PVI approach. However, deploying permanently transmural circumferential lesion is still a challenging task, requiring a skilled operator who is able to achieve stable catheter positions and to perform precise catheter navigation. For patients with paroxysmal AF mid-term single procedure success reported from single centre trials range between 70-80% and decline to 50-60% over time during long-term follow-up. The major determinant for recurrences is PV to LA reconduction across initially complete circumferential ablation lines following non-transmural ablation lesions. The reasons may be multi-factorial, but recent trials suggest that insufficient contact between the catheter tip and ablated tissue may play a dominant role for incomplete ablations. During TOCCATA multicenter study a novel contact force sensing catheter was evaluated and it was shown that 12% of all ablations during PVI procedures were carried out with a contact force of as low as 5g. Furthermore, there was a clear pattern of low-contact predilection sites namely the myocardial ridge between the lateral PVs and the LA appendage being the most critical region. In sub-analyses it was demonstrated that mean contact force during AF ablation was directly related to success during follow-up.

Similarly, contact force determines the safety of an AF ablation procedure. The two most feared mechanical complications of AF ablation are pericardial tamponade and thermal esophageal injury. The incidence as reported in a recent survey is relatively low (1% for tamponade and 0.04% for atrooesophageal fistula, respectively). Nonetheless, the low complication rate is the benchmark for novel technologies and should not be exceeded. Moreover, despite the use of 3D mapping systems both, the patient and the physician are still exposed to scattered X-ray bearing the potential risk for adverse effects during a long professional career.

Clinical Experience of AF Ablation Using Magnetic Navigation

Published data on AF ablation using MN is scarce. This might partly be explained by the lack of an irrigated tip catheter that had been unavailable until late 2007. The initial feasibility study reported on circumferential PV ablation in 40 patients performed with a 4mm solid tip ablation catheter with the endpoint of voltage abatement >90%. The endpoint could be achieved in 38/40 patients and no major complications occurred. However, the procedure times were significantly longer than in a non-randomized control group.

In contrary, in a second feasibility trial true PVI demonstrated with a spiral catheter within the PVs could not be achieved in the vast majority (92%) of patients using the non-irrigated magnetic ablation catheter. Moreover, in one third of the cases significant charring on the tip of the ablation catheter was observed, underscoring the need for an irrigated ablation technology.

If the PVs were disconnected at a more distal level, the solid tip catheter demonstrated efficacy in smaller patient series. While fluoroscopy times were consistently lower using MN as compared to a manual ablation strategy, data on procedure times are controversial. However, no data from prospective randomized trials are available yet.

Chun and co-workers recently demonstrated the feasibility of MN based PVI using the novel irrigated tip catheter. In a prospective fashion 56 patients were treated with the first (n=28; Thermocool NaviStar RMT I) or second (n=28; Thermocool NaviStar RMT II) generation irrigated tip catheter. In total the primary endpoint of complete PVI was achieved in 93% of all patients in both groups. The major improvements of the novel catheter were the higher effectiveness as documented by a significantly reduced procedure time (370 versus 243 min; p ≤ 0.0001) and the decreased incidence of charring on the catheter tip following the ablation procedure (61% versus 0%; p ≤ 0.0001). Notably, two patients treated with the first generation catheter and an evidence of charring experienced embolic events 7 and 14 days after the procedure. No complications occurred with the second generation irrigated tip catheter. During an average follow-up of 426 ± 213 days 70% of all patients remained in sinus rhythm after a single procedure off antiarrhythmic drugs.
Clinical Experience of AF Ablation Using Robotic Navigation

The initial results on AF ablation of a multi-centre feasibility trial using the first generation RN device were published in 2008. In total 40 patients underwent PV antrum isolation with an irrigated tip catheter using a 3D mapping system. In all patients the acute endpoint was achieved leading to a chronic success rate of 86% at one year follow-up off antiarrhythmic drugs. However, the complication rate of 5% (2 patients developed cardiac tamponade requiring pericardiocentesis) raised safety concerns among the electrophysiologic community.

It became evident that most of the severe complications occurred during an initial learning phase and modification of procedural techniques contributed to improve safety [20]. This included the use of a long femoral sheath for introduction of the Artisan catheter to prevent mechanical venous wall stress and vascular access complications. Second, ablation power needs to be lowered and adapted to the improved wall contact in order to avoid steam popping leading to cardiac perforation. The latter also holds true for thermal esophageal complications as recently demonstrated. The excess contact force and relative stiffness of the Artisan sheath may lead to distortion of the cardiac anatomy, thereby decreasing the distance between the map catheter and the esophageal tissue [Figure 2]. The improved heat transfer may lead to an increased incidence of thermal esophageal lesions. According to our experience, ablation power at the posterior wall should therefore not exceed 20 W.

**Figure 2**: Mechanical distortion of the posterior left atrial wall during an AF ablation using robotic navigation. Left panel: Screenshot from the Sensei workstation showing a NavX map in a left lateral (LL) view. The map catheter pokes out of the LA geometry at a contact force of 10-20g towards the esophageal temperature probe (ESO). Right panel: Corresponding fluoroscopic image in LAO 40° demonstrating the map catheter is situated distant from the left PVs on top of the temperature probe (ESO). CS: multipolar catheter in the coronary sinus. Lasso: spiral catheter in the left superior PV.
ever is the relative reduction in the operator’s fluoroscopy exposure by 35%.

Moreover, in a prospectively randomized trial operator’s fluoroscopy exposure was significantly reduced using robotic navigation for AF ablation (7 ± 2.1 versus 22 ± 6.5 minutes; p < 0.001). 25

It is noteworthy, that despite the availability of contact force information only 22.5% of patients who had undergone a segmental PVI procedure using RN demonstrated chronic PVI at 3 months follow-up assessed by an invasive repeat EP study. 28

Data on chronic efficacy is available from numerous observational studies. The success rate lies in the range of 67-91% after a single procedure off antiarrhythmic drugs and variable follow-up intervals (Table 1). 19,20,24-28

In another feasibility trial, catheter stability during PVI was assessed in a semi-quantitative fashion. 26 While catheter stability was excellent at most superior and inferior PV antral sites, catheter dislodgement during ablation occurred in 46% of ablations at the anterior border of the lateral PVs. This is well in line with the aforementioned observations from the TOCCATA study.

Interestingly, the slope of the individual learning curve defined as stable procedural parameters may substantially differ between large volume centres (n=12; [26]) and low-volume community hospitals (n=75; [29]).

A major difference to manual procedures however is the relative reduction in the operator’s fluoroscopy exposure by 35%.

Moreover, in a prospectively randomized trial operator’s fluoroscopy exposure was significantly reduced using robotic navigation for AF ablation (7 ± 2.1 versus 22 ± 6.5 minutes; p < 0.001). 25

Summary

In summary, feasibility of AF ablation using remote navigation systems has been demonstrated in multiple independent clinical trials. In comparison to manual ablation procedures similar acute and chronic success rates were reported, however data on safety and efficacy from prospectively randomized clinical trials (“man and machine”) have not been available yet. Therefore, the question whether the use of RN translates into a better clinical outcome remains unanswered.

It became evident that the use of remote navigation systems requires modifications of the standard manual ablation approach to prevent serious complications. This includes in particular esophageal temperature monitoring and a decrease in ablation power in robotic navigation procedures.

Unfortunately, recent trials could not provide...
compelling data that the use of robotic navigation will overcome the problem of catheter stability at particular LA regions such as the myocardial ridge between the left atrial appendage and the left PVs or will improve the chronic PV isolation rate.  

The major demerit of MN is the extensive procedure time of approximately 4 hours.

Nonetheless, both systems help to reduce the operator’s exposure to scattered X-ray by ~35% during AF ablation procedures.

Future Directions

It remains the electrophysiologist’s dream to perform a completely automated AF ablation procedure from a workstation within the control room. The magnetic navigation system software contains features (NaviLine) to store vectors and to navigate the catheter to and on pre-defined lines. One day, this might enable the operator to perform a circumferential ablation just by clicking the mouse. However, there is still a long road to travel.

In times of limited economical resources novel technologies should prove at least non-inferiority to conventional treatment options. Besides the reduced X-ray burden to the operator, the theoretical advantages of RN still need to be proven in clinical trials.

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