Tracking the motion of intracardiac structures aids the development of future leadless pacing systems

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Abstract

Background: Leadless pacemakers preclude the need for permanent leads to pace endocardium. However, it is yet to be determined whether a leadless pacemaker of a similar design to those manufactured for the right ventricle (RV) fits within the left ventricle (LV), without interfering with intracardiac structures.

Methods: Cardiac computed tomography scans were obtained from 30 patients indicated for cardiac resynchronisation therapy upgrade. The mitral valve annulus, chordae tendineae, papillary muscles and LV endocardial wall were marked in the end-diastolic frame. Intracardiac structures motions were tracked through the cardiac cycle. Two pacemaker designs similar to commercially manufactured leadless systems (Abbott’s Nanostim LCP and Medtronic’s Micra TPS) as well as theoretical designs with calculated optimal dimensions were evaluated. Pacemakers were virtually placed across the LV endocardial surface and collisions between them and intracardiac structures were detected throughout the cycle.

Results: Probability maps of LV intracardiac structures collisions on a 16-segment AHA model indicated possible placement for the Nanostim LCP, Micra TPS, and theoretical designs. Thresholding these maps at a 20% chance of collision revealed only about 36% of the endocardial surface remained collision-free with the deployment of Micra TPS design. The same threshold left no collision-free surface in the case of the Nanostim LCP. To reach at least half of the LV endocardium, the volume of Micra TPS, which is the smaller design, needed to be decreased by 41%.

Conclusion: Due to the presence of intracardiac structures, placement of leadless pacemakers with dimensions similar to commercially manufactured RV systems would be limited to apical regions.

Keywords
cardiac resynchronisation therapy (CRT), collision detection, computed tomography, image registration, intracardiac structures, leadless pacemaker, motion tracking
INTRODUCTION

About one million cardiac pacemakers are implanted every year worldwide. Conventional transvenous cardiac pacemakers with active fixation leads are commonly used to augment the electrical conduction of the heart and treat conditions such as symptomatic bradycardia and high degree atioventricular block. Since their first implantation in 1950s, pacemaker therapy has evolved considerably. Reduction in generator size, increased battery longevity, quality of pacemaker leads, and algorithmic responsive programming have all improved pacemaker implantation and management.

Despite technological advances in conventional transvenous pacemaker therapy, 10% of patients are still affected by surgical complications during the implantation of the device. The leads are prone to dislodgement, fracture, or insulation failure and can also lead to infection, cardiac perforation, venous occlusion, and tricuspid regurgitation. One treatment requiring transvenous lead implantation is cardiac resynchronisation therapy (CRT), where the left ventricle (LV) is paced via an additional transvenous lead in the coronary sinus (CS). However, CRT has been found to fail in 30%–40% of patients with suboptimal lead placement as one of the reasons for nonresponse. Furthermore, an additional 8%–10% of eligible patients do not receive CRT because of anatomical constraints, such as complex CS anatomy and difficulty in navigating the cardiac valves.

The pursuit of leadless pacing options has long been of interest to reduce the complications of traditional CRT. Stimulation of the LV endocardium, which is not constrained to the epicardial coronary venous anatomy, may provide superior hemodynamics and improved CRT response. Nonetheless, the current commercially manufactured leadless pacemakers are limited to perform single-chamber ventricular pacing and their recommended placement in the right ventricle (RV) has not been free of complications. Although comparable to dual-chamber transvenous pacemaker systems, they have shown to result in worsening tricuspid regurgitation and a reduction in ventricular function at 12 months of follow-up primarily due to their mechanical interference on the tricuspid valve or its subvalvular apparatus.

Since leadless self-contained pacemakers can be ideal for endocardial CRT, developing devices that can physically access all regions of the LV endocardium is desirable. Endocardial CRT requires a compact device, which does not interact with the endocardium or intracardiac structures during systole, as collision can cause direct mechanical trauma and lead to cardiac puncture and perforation, which can lead to longer hospital stays, tamponade, or even death. Assuming that manufacturers may want to use similar designs to the RV leadless pacemakers for endocardial CRT, it is worthwhile to assess the ability of these designs to fit in the LV safely.

RV leadless pacemakers were not designed for LV pacing and should not be proposed for use in the LV. However, they demonstrate plausible designs for future leadless systems. In this study, we determine whether a leadless pacemaker of a similar design to those commercially manufactured for the RV can access all regions of the LV endocardium without interfering with intracardiac structures. The two designs in our study are the Nanostim Device from Abbott Medical Inc and Micra Transcatheter Pacemaker System from Medtronic PLC. We also estimate optimal theoretical device designs that maximise access in the LV and target regions of the endocardium, which are associated with improved CRT response. All our assessments are done by retrospectively analysing motion of the LV endocardial wall, the anterior and posterior papillary muscles, the chordae tendineae, and the mitral valve annulus from a data set of 30 patients with a pacemaker already in situ, who were then upgraded to CRT.

METHODS

In this section, we first introduce the clinical data set used in our experiments. We then present an image registration technique optimised for tracking cardiac motion, followed by modelling of the intracardiac structures. We finally conclude with a description of the collision detection algorithm used to assess the possible regions within endocardium for the safe placement of a pacemaker design and describe a process for finding an optimal dimension to reduce the risk of collision.

Clinical data set

Electrocardiogram (ECG)-gated cardiac computed tomography (CCT) scans used in our experiment were performed on 30 patients undergoing CRT upgrade. Data were collected in accordance with relevant guidelines and regulations as part of two clinical trials, which were approved by the West Midlands Coventry & Warwick REC (14/WM/1069) and the London-Harrow (18/LO/0752) ethics committees. All the patients gave written informed consent and the scans were analysed anonymously.

Scans were performed using a Philips Brilliance ict 256-slice MDCT scanner (Philips Healthcare, Amsterdam, Netherlands). Intravenous metoprolol was used to achieve a mean heart rate of 64 ± 7 beats/min. A total of 100 ml of intravenous contrast agent (Omnipaque; GE Healthcare, Princeton, NJ, USA) was injected via a power injector into the antecubital vein. Helical scanning was performed with a single breath-hold technique after a 10–12 s delay. The scanning parameters included: a heart rate dependent pitch of 0.2–0.45, a gantry rotation time of 270 ms, a tube voltage of 100 or 120 kVp depending on the patient’s body mass index, and a tube current of 125–300 mA depending upon the thoracic circumference. Retrospectively ECG-gated image reconstruction was used to generate 10 images per cardiac cycle. All patients were selected for an upgrade to CRT and preprocedural CCT scans were acquired in RV pacing.
2.2 Processing data set scans

Initially, CCT datasets were converted from their original DICOM format into a series of NIfTI images. The dimension of images varied between data sets, but the majority were 512 × 512 voxels with a 0.32–0.48-mm isotropic in-plane resolution. The three-dimensional (3D) stacks had 121–365 slices with a through-plane thickness of 0.8–2 mm. The Hounsfield unit spanned from −1024 to 3071. Each data set consisted of 10 images equally spaced throughout the cardiac cycle with a temporal resolution spanning 72–120 ms depending on the patient’s heart rate.

2.3 LV endocardium motion estimation

Tracking motion can essentially be defined as the nonrigid registration of image sequences. To track the LV endocardium motion, we used an intensity-based temporal sparse free-form deformation registration algorithm with its hyperparameters optimised to minimise a cost function defined as the mean squared error of tracking manually annotated landmarks. This provided us with a smooth deformation field in space and time. Embedding mesh vertices in the field allowed the deformation of the LV endocardium and intracardiac structures. Specifically, the displacement fields, generated by the registration algorithm, were utilised to deform the reference LV endocardium and other intracardiac structures into a series of pointsets corresponding to each phase of the cardiac cycle. The deformation was formulated as a point set transformation algorithm. We utilised a linear function to interpolate the computed control point displacement fields \( \Pi(M, u_0) \) and deform the reference meshes by:

\[
M_{\text{Deformed}} = \begin{cases} 
  m^\text{Reference}_x + \Pi(m^\text{Reference}_x, u_x), \\
  m^\text{Reference}_y + \Pi(m^\text{Reference}_y, u_y), \\
  m^\text{Reference}_z + \Pi(m^\text{Reference}_z, u_z), 
\end{cases}
\]

where \( M = [m_x, m_y, m_z] \) is a point in the set of all mesh-point coordinates. Further technical details of the tracking algorithm can be found in the Supporting Information Appendix.

2.4 Modelling intracardiac structures

A reference image was selected from the first frame of the CCT, representing the LV at the end-diastolic phase and the peak of the R-wave in the ECG. The blood pool of the LV including the papillary muscles was then segmented from this reference image by a clinical expert. Segmentation was performed using a grey-value based region growing tool. The grey values were determined from all point positions plus/minus a margin of 30 Hounsfield units. The 2D region growing segmentation was applied to 5–10 of the long-axis slices. These slices were interpolated to label the LV cavity in 3D with the option for manual correction. After achieving a full segmentation, a marching cubes process generated a smooth 2D endocardial surface from the segmentation. The average resolution of generated surfaces was 1.0 ± 0.2 mm.

The mitral valve annulus and papillary muscles were also manually marked in the end-diastolic frame (Figure 1). The clinical expert segmented the mitral valve annulus using a recommended D-shaped model, tracing the posterior perimeter of the annulus and truncating the anterior horn across a straight line. Points at the tip and the base of each papillary muscle were defined to generate two cylinders of 5 mm in radius. Mitral valve annulus landmarks were connected to the tips of papillary muscles to create cone-shaped geometries, representing the volume enclosed by chordae tendineae. Gmsh (http://gmsh.info) was used to generate finite element meshes from these geometries. The motion of the intracardiac structures and the LV endocardial wall were tracked throughout the cardiac cycle.

In addition to intracardiac structures, two leadless pacemaker designs were modelled: Nanostim LCP (Abbott) and Micra TPS (Medtronic) with dimensions of 42 × 5.99 mm and 25.9 × 6.7 mm for height and diameter, respectively. The two designs were virtually placed on each vertex in the LV endocardial wall and their positions were updated throughout the cardiac cycle for each patient to detect collisions with intracardiac structures.

2.5 Collision detection

Since the leadless pacemakers were modelled using a cylinder, the collision detection algorithm could be simply devised as a function that determined whether a 3D test point from the endocardial wall or intracardiac structures lies within the oriented cylindrical volume on the LV surface mesh. This generated an LV endocardial surface binary mask of positions where the pacemaker could be implanted without impacting the endocardium or intracardiac structures. Details of the algorithm for detecting collision and verification of its correctness can be found in the Supporting Information Appendix.

2.6 Optimised dimensions

To increase access to the LV endocardium with a maximum 20% risk of collision in patients, new pairs of height and diameter were computed for an optimal pacemaker’s design. These new dimensions were subject to preserving the Micra TPS original 800-mm³ volume, as it is the smaller of the two leadless pacemakers considered in this
study. The volume preservation was initially done to keep within current technological constraints of battery size. Specifically, five different height values starting from 5 to 25 mm were selected and the associated diameter was calculated. Every new height and diameter combination provided us with a probabilistic collision map, illustrating potential safe positions for the placement of pacemakers. Considering technological advancements in battery design and anticipation of smaller devices in the future, we also extended the study by relaxing the volume-preserving condition and decreasing the Micra TPS volume incrementally by 10% to increase the percentage of collision-free LV endocardium surface and determine further potentially safe pacing locations.

3 | RESULTS

In this section, we report the collision results of two commercially manufactured designs, followed by our analysis of finding an optimal size for the pacemakers with and without considering current technological restrictions. The patient demographic characteristics used in our experiments are summarised in Table 1.

3.1 | Pacemaker collision models

The Nanostim LCP and Micra TPS models were placed at each vertex of the LV endocardium mesh for each patient and the collision detection algorithm was used to determine if the models would collide with either the LV endocardium or intracardiac structures throughout the cardiac cycle. The results of the intracardiac structures collision tests were visualised by generating average probability maps from the 30 patients' data set on a 16-segment AHA model.

| Table 1 Demographic characteristics |
|-------------------------------------|
| Characteristic | Value | Characteristic | Value |
| Age | 66 ± 12 | QRS duration (ms) | 162 ± 28 |
| Male | 24 (80) | LV end-diastolic volume (ml) | 186 ± 65 |
| LBBB | 15 (50) | LV end-systolic volume (ml) | 128 ± 62 |
| Atrial fibrillation | 8 (26) | LV ejection fraction (%) | 32 ± 9 |

Note: Values are presented as mean ± SD or as n (%). Abbreviations: LBBB, left bundle branch block; LV, left ventricular.
Figure 2 shows the probability of collision maps for each design, where each map shows the percentage of cases where the pacemaker contacted the LV endocardium or intracardiac structures during the cardiac cycle. The results show that a model with similar dimensions to Nanostim LCP can fit within the apical regions without colliding with the internal LV structures. Micra TPS can be placed in the apical, mid anteroseptal, and mid-anterior regions. Thresholding these maps at 20% chance of collision reveals that only about 36% of the endocardial surface remains collision-free with the deployment of Micra TPS model. The same threshold leaves no collision-free surface in the case of the Nanostim LCP.

3.2 Optimised dimensions subject to current technology limitations

Current devices are deployed by a catheter and their minimal volumes are likely restricted by the battery size. To test if changes in design would allow greater regions of the LV endocardium to be accessed, we calculated collision maps for five different designs with constant volumes. The following results illustrate collision probability maps from the entire 30 patients’ data set on a 16-segment AHA model using the new possible dimensions. The simulations were across five different pairs of height and diameter selected to preserve the original 800-mm³ volume of the Micra TPS. Heights larger than the current Micra TPS model were ignored, as these dimensions would further reduce viable implantation areas in the LV endocardium. The probabilistic collision maps for these new dimensions were assessed, as seen in Figure 3.

The Micra TPS catheter is currently inserted via an introducer sheath with an inner diameter of 23 Fr (7.67 mm). Constraining the upper bounds of the diameter of a theoretical pacemaker design to the current dimensions of the introducer sheath and maintaining the original volume of the Micra TPS pacemaker, the height of the device can be reduced to 20 mm. Thresholding our collision detection algorithm to a 20% chance of collision, this theoretical pacemaker design can be localised at 41% of the total endocardial surface. This is in contrast to the original design of the Micra TPS (25.9-mm height × 6.7-mm diameter), where 36% of the endocardial surface could be accessed.

Figure 2  Probability maps from 30 data sets illustrating no collision (blue) and collision (red) on a 16-segment AHA model of the flattened left ventricle when patients are implanted with models similar to (a) Nanostim LCP and (b) Micra TPS

Figure 3  Collision probability maps, where red indicates collision and blue indicates no collision with intracardiac structures. The five maps are from simulations sets built from a grid of possible dimensions for an optimal pacemaker. The grid values include heights and diameters and were selected subject to preserving the original Micra TPS volume. Sets with a height larger than the current Micra TPS model were omitted from the simulations.
To target at least 50% of the LV endocardium without a significant risk of colliding with internal structures, we examined new dimensions without restricting the volume of the virtual pacemaker and without adhering to the current delivery catheter limitations. The new volumes were the result of monotonically decreasing the original Micra TPS volume by 10% in every simulation. Heights larger than the current Micra TPS model were not considered for the simulations. Micra TPS’s original volume can only reach 36% of the entire endocardial surface and is depicted as a dashed line for comparison on the plot. LP, leadless pacemaker

### 3.3 Optimised dimensions without current technology limitations

To target at least 50% of the LV endocardium without a significant risk of colliding with internal structures, we examined new dimensions without restricting the volume of the virtual pacemaker and without adhering to the current delivery catheter limitations. The new volumes were the result of monotonically decreasing the original Micra TPS volume by 10% in every simulation. Heights larger than the current Micra TPS model were ignored, as the previous experiment. Figure 4 illustrates these new dimensions in terms of total volume and the percentage of collision-free endocardial surface. To reach at least 50% of the endocardial surface with less than 20% chance of collision, the height, diameter and volume of the virtual pacemaker need to be reduced to 10 mm, 7.7 mm and 472 mm$^3$, respectively.

### 3.4 Pacemaker collision models in the right ventricle

Leadless pacemakers were originally developed to avoid interaction with the tricuspid valve in the RV. With the background that lead-related adverse consequences can be mitigated by leadless pacing, Beurskens et al.\textsuperscript{10} reported on the impact of leadless pacemakers on the valvular structure. They found that an RV septal position of the leadless pacemaker was associated with increased tricuspid valve regurgitation, compared with an apical position (odds ratio 5.20; \(p = .03\)). They assumed the fivefold increase was due to displacement of the papillary muscles, entanglement with the chordae tendineae, or direct interaction with the leaflets by the leadless pacemakers. Their findings concluded that longer devices might have greater effects on the valve, shorter ones on the muscles, and a further distance from the proximal end of the pacemaker to the valve decreased the risk of dysfunction.\textsuperscript{11}

To extend our study, we applied a similar collision simulation approach to generated models of the RV from the same datasets, as seen in Figure 5. In agreement with Beurskens et al. findings, we demonstrated that placing Nanostim LCP or Micra TPS on the septal wall leads to an endocardial collision. In fact, Nanostim LCP left only 5% of endocardial surface intact with less than 20% chance of collision. Results showed that pacing from the septal wall caused the collision, even in the case of Micra TPS, which allowed for up to 59% of the endocardium to remain collision-free. However, reducing the height of Micra TPS to 15 mm made 85% of the surface accessible with only a 20% chance of collision.

We have only included the results of collision with the RV endocardium, as modelling the entire intracardiac structures relies on confident localisation and tracking of the RV papillary muscles, which was not possible due to the low contrast in the blood pool and presence of artefacts from the pacemakers leads in the database scans. The Supporting Information Appendix contains further details on these RV simulations and the results of other tests we performed.

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**Figure 4** The five maps are from five simulation sets built from a grid of possible dimensions for an optimal pacemaker dimension. The grid values were built by monotonically decreasing the original Micra TPS volume by 10% in every simulation. Heights larger than the current Micra TPS model were not considered for the simulations. Micra TPS’s original volume can only reach 36% of the entire endocardial surface and is depicted as a dashed line for comparison on the plot. LP, leadless pacemaker

**Figure 5** Probability maps from 30 data sets illustrating no collision (blue) and collision (red) on a model of the right ventricle when patients are implanted with (A) Nanostim LCP and (B) Micra TPS
4 | DISCUSSION

In this study, we assessed the physical ability of leadless pacemakers with similar dimensions to those commercially manufactured for the RV to access regions of the LV endocardium without interfering with intracardiac structures. We also estimated optimal dimensions for theoretical pacemakers to maximise access in the LV endocardium with and without considering current technological limitations.

We found that Nanostim LCP design fits within the apical regions and Micra TPS in the apical, mid anteroseptal, and mid-anterior regions of the LV. We further discovered that decreasing the height of Micra TPS to 20 mm and increasing its diameter to 7 mm will maintain device volume but expand the accessible regions within LV endocardium from 36% to 41%. We confirmed that reducing the volume of Micra TPS can increase the access range from 36% to more than 50% of the endocardial surface, potentially allowing for more optimal pacing locations. At volume set as 472 mm³, height as 10 mm, and diameter as 7.7 mm, we predicted complete access across the mid-wall of the LV endocardium. However, the main clinical limitation in deploying the current RV leadless designs in the LV lies in their large dimensions and the risk of stroke from systemic thromboembolism. Previous studies have shown that these devices have a range of endothelialisation, from partial at 19 months to full at 4 months, which can increase the risk of complications.

An imperative determinant of successful CRT for heart failure is the position of the LV pacing lead. LV intracardiac structures limit the placement of currently manufactured designs to primarily apical regions. However, LV leads positioned in the apical region have been associated with an unfavourable outcome in CRT. The myocardial wall is thinner at the apical region, which can also potentially increase the risk of cardiac perforation and lead to tamponade.

Figure 2 shows that current designs are unable to target most of endocardial surface, which can be associated with improved CRT response. Furthermore, current leadless pacemakers have the significant limitation of performing single-chamber ventricular pacing and are not well suited for patients in whom a dual-chamber system or CRT is preferred. In future, developing dual-chamber pacemakers that can sense the atrium to perform stand-alone LV pacing will be desirable.

There are multiple factors that can determine the future design of leadless pacemakers with balancing access, deployment, and battery life amongst the examples. Our results showed that by keeping the volume within current technological limitations, having a pacemaker thicker than 7 mm can subsequently decrease height and increase collision-free access to mid-inferior and mid-anterior walls. However, these dimensions may not be compatible with current device delivery catheters, which were designed for RV pacing. Furthermore, left atrial access is required to reach the LV endocardium, which potentially increases complications and places additional constraints on the delivery catheter’s size. Our results also demonstrated that longer devices are more likely to collide with intracardiac structures regardless of their diameter. Therefore, manufacturing thicker but shorter devices may be beneficial. However, device delivery catheters then need to become of very large calibre, which will increase access risk during the procedure as Micra TPS introducer is already a bore sheath with a 23-Fr inner diameter and a 27-Fr outer diameter.

Limited battery life is another reason for the consideration of design dimensions. Some patients may need more than one pacemaker in their lifetime. As abandonment at the end of battery life is recommended by some manufacturers (eg, Medtronic), size and endothelialisation may become problematic. In this study, we did not consider the current technological limitations of onboard battery design or whether implanting currently available batteries in shorter pacemakers is plausible, but the ultimate solution may be to sacrifice some of the battery longevity to allow for smaller devices to be implanted. This may also alleviate clot formation on the devices and decrease stroke risk.

A recent alternative to the self-contained pacemakers is the use of a remote battery and an accompanying power transmitter. This approach has been adopted by the WiSE-CRT system (EBR Systems, Sunnyvale, California) and has remarkably enhanced access within the LV endocardium owing to ultrasound transmission of pacing impulses to a small electrode, which is only 12.7 mm in height and 2.7 mm in diameter. Despite the apparent advantages of this system, not all patients are suitable for receiving it. A preprocedural screening is required to identify an adequate parasternal acoustic window to allow the power transmitter to function. Furthermore, this system cannot pace the heart independently. Instead, it delivers LV pacing based upon the pacing activity of a co-implanted pacing device, implantable cardioverter defibrillator or CRT system. While an initial study was halted due to safety concerns of these devices, a subsequent study using a second-generation system on a limited cohort of patients showed promising results.

5 | LIMITATIONS

Collision with intracardiac structure was detected using the pre-procedural CCT derived motion. This was performed under intrinsic activation or with RV pacing. Ideally, collision would be detected during biventricular pacing. However, post-implant, retrospectively ECG-gated CCT data sets were not available. Implanting an endocardial pacemaker is likely to increase cardiac contraction, increasing the likeliness of collision. Therefore, the current results can be taken as an upper bound on the areas, which endocardial pacemakers can access.

The methods for precise modelling of intracardiac structures required certain practical assumptions and anatomic mapping decisions. Our models of the mitral valve chordae tendineae and papillary muscles were based on previously validated studies. Furthermore, our collision model did not account for the intracardiac motion of the pacemaker and assumed it would maintain a consistent perpendicular position against the endocardial wall during cardiac contraction. A possible approach to account for this motion would consist of defining the region of potential collision as a semisphere
that encloses the maximum area covered by the motion of the pacemaker. This would have, however, made the computational cost of the study intractable.

6 | CONCLUSIONS

Leadless pacemaker therapy was developed to address the limitations of standard lead-based pacing. RV leadless pacemakers were not designed for use in the LV. Besides, a left ventricular pacing system with physical dimensions similar to RV pacemakers cannot target most regions of the endocardium without interfering with intracardiac structures. The next generation of self-contained leadless pacemakers needs to be able to synchronise independently and become more compact to be implanted safely within the LV endocardium.

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**SUPPORTING INFORMATION**

Additional Supporting Information may be found online in the supporting information tab for this article.

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