Clinical factors and echocardiographic techniques related to the presence, size, and location of acoustic windows for leadless cardiac pacing

Doreen DeFaria Yeh¹, Katy Lease Lonergan², David Fu², Robert W. Yeh¹, Debra S. Echt³, and Elyse Foster²*

¹Massachusetts General Hospital, 55 Fruit St, YAW 5700, Boston, MA 02114, USA; ²Division of Cardiology, Echocardiography Section, University of California, 505 Parnassus Avenue, M14, San Francisco, CA 94143, USA; and ³EBR Systems, Inc., 686 W. Maude Avenue, Suite 102, Sunnyvale, CA 94085, USA

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Aims
Temporary leadless cardiac pacing using ultrasound energy is feasible in patients. An implantable left ventricular stimulation system being developed for cardiac resynchronization therapy transfers energy from a subcutaneous transmitter to an endocardial receiver through tissue free of interfering lung or rib (‘acoustic window’). The aim was to use transthoracic echocardiography to evaluate acoustic window (AW) locations and sizes to determine the implant site for a transmitter, and to investigate clinical predictors of AW location and size.

Methods and results
Inclusion criteria were ejection fraction ≤35%, and New York Heart Association functional class III or IV. Acoustic windows were evaluated in intercostal spaces (ICSs) measured in the supine, right lateral, sitting, and standing position during normal respiration and held inspiration. Among 42 patients, at least one adequate AW (≥2 cm²) was identified in 41, 19 patients had adequate AWs in 2 ICSs and 20 patients had adequate AWs in 3. Acoustic window areas were generally smallest in the lateral position with held inspiration and largest in the standing position with normal respiration. Patients with ischaemic cardiomyopathy compared with non-ischaemic cardiomyopathy had smaller heart size [left ventricular end-systolic volume index (LVESVI) 78 ± 38 mL/m² vs. 104 ± 46 mL/m², P = 0.03] but larger AWs in the right lateral position (11.4 ± 6.5 cm² vs. 7.3 ± 3.4 cm², P = 0.01) and standing position (14.0 ± 7.2 cm² vs. 9.4 ± 3.3 cm², P = 0.02).

Conclusions
Adequate AWs were present in nearly all patients. Despite smaller hearts, ischaemic cardiomyopathy patients had adequate AWs. A simple procedure performed as an adjunct to pre-implant echocardiography can screen patients and identify transmitter implant locations for an ultrasound-mediated leadless pacing system.

Keywords
Leadless pacing • Cardiac resynchronization therapy • Heart failure • Echocardiography • Acoustic window

Introduction
Endocardial right ventricular pacing with intracardiac leads has been in use since the 1950s and more recently epicardial left ventricular pacing with leads in a coronary vein has been routinely used for cardiac resynchronization therapy (CRT).¹² Pacing leads are the most frequent cause of complications related to permanent pacing systems¹² and CRT complication rates for coronary vein leads are ~11–12%.⁴⁵ Additionally, ~30% of patients receiving CRT do not respond to therapy.⁶ Limitations imposed by coronary venous anatomy on the selection of the site for left ventricular stimulation are thought to be a major contributor to the lack of CRT response. An alternative leadless means of delivering left ventricular stimulation provides greater opportunities to optimize the pacing site and reduce lead-related complications. Temporary leadless cardiac pacing mediated by ultrasound energy has been shown to be feasible in patients.⁷ A novel implantable cardiac pacing system based on this concept has recently been developed for the treatment of heart failure (Wireless Cardiac Stimulation-LV System, WiCSadr-LV, EBR Systems, Inc., Sunnyvale, CA, USA) and
a clinical trial using the WiCS-LV system is actively enrolling patients in Europe. The study titled Wireless Stimulation Endocardially for CRT (WiSE-CRT) is evaluating the safety and feasibility in specific subsets of patients with CRT-eligible heart failure. The WiCS-LV system provides left ventricular endocardial stimulation and is used in conjunction with a co-implanted pacemaker, CRT, or implantable cardioverter defibrillator that provides right atrial and right ventricular stimulation.

This cardiac pacing system design incorporates acoustic energy delivery from a subcutaneous transmitter in the chest wall to an endocardially placed receiver electrode. The acoustic energy is then transduced to electrical energy and pacing electrodes provides direct endocardial pacing stimulation. Since acoustic energy is reflected by air and refracted by bone, a suitable acoustic window (AW) must be identified. Recent findings based on temporary pacing studies performed in heart failure patients using this technology demonstrated significant individual variation in the size and location of this AW based on chest computed tomography scan findings. Moreover, the AW size and location varied significantly with patient position and phase of respiration. In that study, the AW was also evaluated using transthoracic echocardiography; however, patients were studied in the electrophysiology lab and tilted only 45° in each direction, not fully representative of more extreme body positions encountered during daily living. The advantage of transthoracic echocardiography is the potential to evaluate and measure the AW under a variety of conditions and body positions.

The purposes of this study were to investigate the use of transthoracic echocardiography to define the AW and to ensure that it would be adequate to accommodate an implantable system in heart failure patients. The specific aims were (i) to identify the locations of the AWs in heart failure patients; (ii) to measure the size of the AWs in a variety of resting positions including supine, sitting, and standing positions during normal and held respiration; and (iii) to investigate correlations between AW size and clinical variables.

Methods

Patients

This was a single-centre non-randomized prospective study of patients with advanced heart failure considered to be potential candidates for CRT based on having an ejection fraction ≤ 35% and New York Heart Association (NYHA) functional class III or IV. QRS duration was not considered in the eligibility criteria because it was less likely to impact the AW findings. Additional inclusion criteria were age ≥ 18 years and referral for clinically indicated transthoracic echocardiography. Written informed consent was obtained by one of the study physicians. Electronic medical records were manually reviewed to obtain baseline patient information including demographics, body mass index and surface area, comorbid medical conditions such as coronary artery disease, other cardiac disease, chronic obstructive pulmonary disease (COPD), and the presence of a biventricular pacer or defibrillator; classification of cardiomyopathy (i.e. ischaemic vs. non-ischaemic), electrocardiographic findings including QRS duration and type of bundle branch block (if present) and NYHA functional class. Classification of cardiomyopathy was based on physician documentation of ischaemic or non-ischaemic cardiomyopathy, or documentation of significant coronary artery disease by cardiac catheterization to explain a reduced ejection fraction. New York Heart Association functional class was determined based on the clinical visit or hospital admission notes immediately prior to the date of AW imaging.

Echocardiographic measurements including left ventricular end-systolic (LVESVI) and end-diastolic volume indices (LVEDVI), left ventricular ejection fraction, left ventricular mass, right ventricular volumes and function were documented from the most recent clinically indicated transthoracic echocardiogram prior to AW imaging, generally obtained during the same hospitalization. The protocol was approved by the Institutional Review Board of the University of California San Francisco.

Acoustic window measurement protocol

A single trained sonographer performed all AW imaging and measurements. The Siemens Sequoia imaging system (Siemens, Mountain View, CA, USA) was used with a cardiac transducer (4V1c, 4.25 MHz) to obtain limited echocardiographic parasternal and apical imaging confirming the presence of cardiomyopathy with reduced ejection fraction. The same imaging system with a vascular linear array transducer (8LS, 6 MHz) was then used to evaluate the near field for assessment of intercostal space (ICS) dimensions.

Intercostal spaces 4, 5, and 6 were interrogated from the mid-sternal line laterally along the left anterior chest wall to detect the cardiac border. Intercostal spaces having a region of acoustic transmission were considered evaluable AWs. Acoustic window dimensions were imaged in each evaluable ICS in the following positions: supine, supine 90° right lateral, sitting, and standing. Acoustic window areas were calculated as length multiplied by width, where the lengths of the evaluable ICSs were measured in centimetres from the medial edge of the AW (left lateral parasternal border) to the lateral border of the AW at the interface of the cardiac border and lung space (see Figure 1). Widths of the ICSs were determined at 1, 5, and 10 cm lateral to the left parasternal border (see Figure 2).

Figure 1 Acoustic window length measurement. Red line depicts lateral distance from the mid-sternal line to the beginning of the lateral edge of the acoustic window in intercostal space on a representative patient. The yellow line depicts the length of acoustic window along intercostal space.
Using a significance level of 0.2 was performed to create final models. Initial variables considered for the model were chosen on the basis of clinical relevance. As a number of variables were not associated with AW measurements, their presence increased the variance of the model coefficients without influencing the point estimates. Thus, a more parsimonious model was chosen on the basis of backward elimination of variables based on significance level. Forward selection was also performed as a sensitivity analysis, and did not influence the final outcome of the model. Thus, only the backward-selected model is shown. A value of $P < 0.05$ was accepted as indicative of statistical significance. All statistical calculations were performed using STATA (Stata Corp. 2008. Stata Statistical Software: Release 10, College Station, TX, USA: StataCorp LP).

**Results**

Table 1 details the characteristics among the 42 patients. The mean ejection fraction was 23 \pm 7\% and 23 patients (54.7\%) had non-ischaemic cardiomyopathies. As compared with patients with ischaemic cardiomyopathy, the patients with non-ischaemic cardiomyopathies were younger and demonstrated larger LVESVs and LVEDVs. Of the 38 patients with NYHA functional class information available, 86.8\% were class III and 13.1\% were NYHA IV. Mean QRS duration was 133 \pm 36 ms; ≥120 ms in 62\% of patients.

The mean duration for complete image acquisition by the study sonographer was 42 ± 10 min and decreased over time. Adequate AWs (an ICS having an AW area of at least 2 cm² in every body position during held inspiration) were identified in 41 of the 42 patients. 2 patients had one ICS with adequate AWs, 19 patients had 2 ICSs with adequate AWs, and 20 patients had 3 ICSs with adequate AWs. The AW lengths and widths in each ICS are tabulated in Table 2. Acoustic window lengths tended to be longest in the sixth ICS and shortest in the fourth ICS. The width of the ICS increased laterally (i.e. widths at 10 cm were generally larger than at 1 cm).

Acoustic window areas were smallest in the supine 90° lateral position during held inspiration (9.2 \pm 0.8 cm²) and largest in the standing position with normal respiration (11.5 \pm 5.9 cm², $P < 0.001$ for the comparison between positions). However, there was significant variation in AW size among individuals; in 11 patients the largest windows were found to be in the supine position and in 10 patients in the sitting position. Additionally, in eight patients the smallest windows were in the supine position and in three in the standing position. In most patients (58.5\%), AWs were generally largest in the fifth ICS; however, in 36.6\% AWs were largest in the sixth ICS, and in 4.9\% AWs are largest in the fourth ICS. There were no specific clinical variables which predicted which ICS were best. In every case, the smallest AW was contained within the largest AW. Variation in the AW length was always within the lateral border of the window. The medial border of the window was always the left sternal border.

Acoustic window sizes for patients with QRS duration ≥120 ms were similar for all AWs ($P = NS$ for all positions). Acoustic window area in the supine 90° lateral position was inversely correlated with LVESVI ($r = -0.40, P = 0.01$) and positively correlated with ejection fraction ($r = 0.34, P = 0.03$). Acoustic window area in the standing position were also inversely correlated with LVESVI ($r = -0.40, P = 0.01$) and positively correlated with ejection fraction ($r = 0.34, P = 0.03$).
Acoustic windows for leadless pacing

Table 1 Study population characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total</th>
<th>Ischaemic</th>
<th>Non-ischaemic</th>
<th>P value&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>42</td>
<td>19</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>51.1 ± 17.8</td>
<td>65.0 ± 13.1</td>
<td>43.6 ± 16.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male sex (%)</td>
<td>81.0</td>
<td>94.7</td>
<td>69.6</td>
<td>0.05</td>
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<tr>
<td>BMI</td>
<td>27.1 ± 6.9</td>
<td>26.6 ± 4.4</td>
<td>27.3 ± 8.6</td>
<td>0.64</td>
</tr>
<tr>
<td>QRS duration (ms)</td>
<td>133 ± 35</td>
<td>136 ± 31</td>
<td>131 ± 38</td>
<td>0.51</td>
</tr>
<tr>
<td>COPD (%)</td>
<td>11.9</td>
<td>10.5</td>
<td>13.0</td>
<td>1.0</td>
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<tr>
<td>NYHA functional class IV (%)</td>
<td>13.2</td>
<td>5.9</td>
<td>19.0</td>
<td>0.36</td>
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<tr>
<td>Echocardiographic parameters</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>23 ± 7</td>
<td>25 ± 8</td>
<td>22 ± 7</td>
<td>0.24</td>
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<tr>
<td>LVEDVI (mL/m²)</td>
<td>122 ± 52</td>
<td>104 ± 46</td>
<td>136 ± 53</td>
<td>0.03</td>
</tr>
<tr>
<td>LVESVI (mL/m²)</td>
<td>93 ± 44</td>
<td>78 ± 34</td>
<td>104 ± 46</td>
<td>0.03</td>
</tr>
<tr>
<td>LV mass index (g/m²)</td>
<td>140 ± 50</td>
<td>123 ± 34</td>
<td>147 ± 59</td>
<td>0.12</td>
</tr>
<tr>
<td>Mean acoustic window areas</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supine</td>
<td>11.0 ± 5.0</td>
<td>12.5 ± 5.9</td>
<td>9.6 ± 3.8</td>
<td>0.07</td>
</tr>
<tr>
<td>90° Right lateral</td>
<td>9.2 ± 5.4</td>
<td>11.4 ± 6.5</td>
<td>7.3 ± 3.4</td>
<td>0.01</td>
</tr>
<tr>
<td>Sitting</td>
<td>11.5 ± 5.5</td>
<td>13.1 ± 6.6</td>
<td>10.2 ± 4.0</td>
<td>0.12</td>
</tr>
<tr>
<td>Standing</td>
<td>11.5 ± 5.9</td>
<td>14.0 ± 7.2</td>
<td>9.4 ± 3.3</td>
<td>0.02</td>
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<tr>
<td>Scan duration (min)</td>
<td>42 ± 10</td>
<td>45 ± 11</td>
<td>39 ± 9</td>
<td>0.07</td>
</tr>
</tbody>
</table>

COPD, chronic obstructive pulmonary disease; NYHA, New York heart association; LVEDVI, left ventricular end-diastolic volume index; LVESVI, left ventricular end systolic volume index.

<sup>a</sup>Comparison between ischaemic and non-ischaemic cardiomyopathy patients.

Table 2 Acoustic window length and widths by intercostal space

<table>
<thead>
<tr>
<th>ICS</th>
<th>Acoustic window lengths (cm)</th>
<th>Widths at</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Supine 90° Right lateral</td>
<td>1 cm 5 cm 10 cm</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>4.0 ± 3.1</td>
<td>3.4 ± 2.9</td>
<td>4.7 ± 3.9 1.1 ± 0.3</td>
</tr>
<tr>
<td>5</td>
<td>6.6 ± 1.7</td>
<td>5.5 ± 2.5</td>
<td>7.0 ± 2.5 0.8 ± 0.4</td>
</tr>
<tr>
<td>6</td>
<td>7.8 ± 1.9</td>
<td>6.4 ± 2.4</td>
<td>7.7 ± 2.6 0.7 ± 0.4</td>
</tr>
</tbody>
</table>

ICS, intercostal space.

correlated with LVESVI ($r = -0.37, P = 0.02$) as well as with left ventricular mass ($r = -0.38, P = 0.02$). After multivariable linear regression, age ($P = 0.007$) and LVESVI ($P = 0.01$) were independent predictors of AW area in the supine 90° lateral position (adjusted $R^2 = 0.28$ for the model) as well as in the standing position ($P = 0.008$ and $P = 0.012$, respectively, adjusted $R^2 = 0.12$). In a secondary analysis, correlations were similar using AW areas calculated using individualized ICS widths (rather than at 5 cm).

Discussion

This study demonstrates that the AW for leadless left ventricular pacing can be mapped using a standard ultrasound system. Importantly, this study demonstrates the AW is adequate in size to accommodate this technology in nearly all patients in a wide range of body positions associated with normal daily activities during held inspiration, which typically represents the smallest windows. The presence of an AW sufficient to enable ultrasound-mediated leadless left ventricular pacing in heart failure patients potentially eligible for CRT was previously demonstrated in patients. However, that study evaluated only 10 patients, and the body positions evaluated were limited. The current study extends the findings from the previous study by identifying a trans-thoracic echocardiography procedure to identify the size and locations of potential implant sites for individual patients, examining a wider range of more extreme body positions and by examining clinical factors of potential patient populations. Since this technology relies upon ultrasound energy transfer from a subcutaneous implanted ultrasound transmitter to a receiver electrode implanted in the left ventricular endocardium to achieve cardiac stimulation, the presence of an adequate AW is essential for its function. The finding that at least one ICS contained an AW sufficient for implanting the transmitter for the WiCS-LV system was identified in 98% of patients suggests that this new technology...
could potentially have widespread utilization. However, a number of other important issues must also be considered that have not been addressed in this research study before this new technology would be widely adopted. These issues include but are not limited to efficient energy transfer and safe implantation of the receiver electrode.

We enrolled 42 adult patients with advanced heart failure who would be potentially eligible for CRT based on ejection fraction and functional class. In 41 patients an adequate AW was identified, and the majority of these patients (95%) two or three adequate AWSs were identified (defined as an ICS having an AW ≥2 cm² in every body position during held inspiration). Also, although position and respiration have significant effects on the AW size and location, these data demonstrate that the majority of patients had windows that were much greater than 2 cm² in all positions (as depicted in Figure 3). Therefore, the implanting physician should have the ability to select among several subcutaneous locations. This may enable the optimization of energy transfer with efficient targeting of the electrode using shorter acoustic beam distances and less beam angulation.

The ability to perform this testing pre-implant enables a more complete evaluation than can be performed at the time of device implantation when the patient’s body positions are constrained by an X-ray table. Some patients had an adequate AW in all ICSs, whereas some patients only had an adequate AW in the fifth and sixth ICS and not in the fourth ICS, or in the fourth and fifth and not in the sixth ICS. One patient only had an adequate AW in the fifth ICS and another only in the sixth ICS, which would impact potential implantation sites at the time of procedure. Since there was significant variability among individuals as to which positions and ICS provided the largest AWs, the pre-implant examination of all candidate AW areas will be critical to ensure appropriate identification of implantation sites.

We evaluated a number of clinical factors and their relationship to AW size. Although this first application of leadless pacing is being used in CRT patients with wide QRS durations, while patients with narrow QRS duration were also included in the current study, AW sizes were found to be similar among patients with both narrow and wide QRS on analysis. As anticipated, patients with ischaemic cardiomyopathy were older, more likely to be male, and had significantly better ejection fractions and smaller left ventricular volumes as compared with patients with non-ischaemic cardiomyopathies. Less anticipated was the finding that patients with ischaemic cardiomyopathy had large AWs. Interestingly, these data might suggest that LVESVI was inversely correlated with AW area (correlation coefficient ≈−0.4 in all positions) and patients with ischaemic cardiomyopathy had significantly larger AWs in the standing and 90° right lateral positions. The one patient who did not have adequate AWs in any ICS was a 53 male with non-ischaemic dilated cardiomyopathy, ejection fraction of 13% and a large LVESVI of 178 mL/m². He did not have a history of COPD or lung disease. The inverse correlation with LVESVI and AW area is weak and the clinical significance of this correlation is unclear, as several patients with very large LVESVI had adequate windows. Therefore pre-implantation echocardiographic assessment of AW size and location is important for all patients regardless of LVESVI.

**Potential implications**

Novel leadless pacing systems mediated by ultrasound energy may prove to be beneficial only if the transmitter implantation site is individualized to allow acoustic energy transduction at all times during daily activity. The identification of adequate AW areas in nearly all patients examined is critical to the clinical application of this technology. The use of echocardiography to identify adequate AWs in this context will need to be further evaluated in clinical trials.

**Study limitations**

There are several technical factors that may influence ultrasound image quality, and thus the accuracy of measured AW size. As ultrasound penetrates through tissue, signal strength is
progressively attenuated due to absorption of the ultrasound energy, as well as by reflection and scattering. Attenuation is frequency dependent, and lower frequencies penetrate deeper into the body than higher frequencies. In this study we utilized near-field imaging typically requiring higher frequencies than standard echocardiographic imaging (6 MHz as compared with 4.2 MHz), thereby minimizing attenuation. It is possible that the presence of COPD with increased lung volume may impair AW imaging, but in the current study there were too few patients with COPD to assess this correlation.

There are several limitations to this procedure that must be considered. First, since the majority of patients enrolled were NYHA functional class III (86.8%), our ability to draw conclusions based on severity of functional impairment was limited. Moreover, patients who are NYHA functional class IV may be less able to comply with the study protocol, limiting AW assessment. However, the study patient population was largely a hospitalized population of heart failure patients, who are generally less ambulatory than outpatients who would be eligible for CRT. Secondly, AW areas were calculated based on the assumption of rectangular area (length multiplied by width). In actuality, the AWs may be of more complex geometry, and our estimates of rectangular area may not accurately estimate the actual area. Thirdly, a single sonographer performed all measurements potentially limiting reproducibility and all AW areas were calculated based on single measurements of length and width such that small errors in these measurements would result in larger errors in the calculation of area. Fourthly, the current study does not evaluate the effects of AW size and location with movement and physical activity. Ultrasound imaging during treadmill exercise would likely provide additional practical information regarding changes in AWs during motion. Additionally, one must take into consideration that ventricular remodelling may occur over time effecting window size, and this change over time cannot be evaluated in the current study. However, our findings suggest that smaller hearts have larger AWs, and so one could speculate that AWs should not be compromised over time if positive remodelling were to occur.

Finally, this study addresses the AW but not the ability to target the electrode, which is critical to the performance of the investigational device. We did not collect this information in our study. However, the transmitter array of the investigational system can steer 45° in all directions to target an electrode in the heart. The design of the array was based on the analysis (unpublished) of computerized tomography scans with 3D reconstructions from a similar heart failure population of 60 patients, in which a 30% steering angle was found to be sufficient to target the lateral left ventricular wall from the AW.

**Conclusions**

A procedure performed as an adjunct to pre-implant echocardiography can screen patients who are potential CRT candidates and identify transmitter implant locations for an ultrasound-mediated leadless pacing system. Adequate AWs were present in almost all patients. Despite smaller hearts, patients with ischaemic cardiomyopathy had adequate AWs and are candidates for this therapy. In the ongoing clinical trial, the results of this pre-implant AW determination can then be confirmed during the implant procedure and during follow-up assessments.

**Conflict of interest:** D.S.E. is an employee and director of EBR Systems Inc., and has an equity position.

**Funding**

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