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First-in-human noninvasive left ventricular ultrasound pacing: A potential screening tool for cardiac resynchronization therapy

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BACKGROUND A screening tool to predict response to cardiac resynchronization therapy (CRT) could improve patient selection and outcomes.

OBJECTIVE The purpose of this study was to investigate the feasibility and safety of noninvasive CRT via transcutaneous ultrasonic left ventricular (LV) pacing applied as a screening test before CRT implants.

METHODS P-wave–triggered ultrasound stimuli were delivered during bolus dosing of an echocardiographic contrast agent to simulate CRT noninvasively. Ultrasound pacing was delivered at a variety of LV locations with a range of atrioventricular delays to achieve fusion with intrinsic ventricular activation. Three-dimensional cardiac activation maps were acquired via the Medtronic CardioInsight 252-electrode mapping vest during baseline, ultrasound pacing, and after CRT implantation. A separate control group received only the CRT implants.

RESULTS Ultrasound pacing was achieved in 10 patients with a mean of 81.2 ± 50.8 ultrasound paced beats per patient and up to 20 consecutive beats of ultrasound pacing. QRS width at baseline (168.2 ± 17.8 ms) decreased significantly to 117.3 ± 21.5 ms ($P < .001$) in the best ultrasound paced beat and to 125.8 ± 13.3 ms ($P < .001$) in the best CRT beat. Electrical activation patterns were similar between CRT pacing and ultrasound pacing with stimulation from the same area of the LV. Troponin results were similar between the ultrasound pacing and the control groups ($P = .96$), confirming safety.

CONCLUSION Noninvasive ultrasound pacing before CRT is safe and feasible, and it estimates the degree of electrical resynchronization achievable with CRT. Further study of this promising technique to guide CRT patient selection is warranted.

KEYWORDS Body surface potential mapping; Cardiac resynchronization therapy; Cardiac stimulation; Noninvasive ultrasound pacing; Patient selection; Temporary pacing; Ultrasound stimulation

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Introduction

Although the benefits of cardiac resynchronization therapy (CRT) have been demonstrated in clinical trials,[1–4] the response rate to CRT in real-world cohorts with guideline-based indications[5] remains suboptimal.[6] Although models have been developed to predict response to CRT,[7–10] the field lacks a noninvasive, real-time, accurate simulation to determine which patients would have a favorable response to CRT and the degree of response to be expected. Some approaches such as the ECG Belt (Medtronic plc., Mounds View, MN; an array of 40 electrodes around the mid torso) provide feedback about the effectiveness of resynchronization only after the left ventricular (LV) pacing lead has been implanted.[11] An ideal approach to predict CRT response would be noninvasive, inexpensive, and highly sensitive and specific, thereby excluding patients who will not benefit while potentially expanding indications to new populations that would benefit from CRT.

Noninvasive ultrasound-based pacing offers an attractive approach to meet this unmet need before implantation of an LV pacing lead. The physiological basis for ultrasound pacing comes from previous studies demonstrating that transcutaneous delivery of ultrasound energy to the heart could cause ectopic activation in small and large animal models.[12–14] For example, one of these studies showed that high-intensity focused ultrasound could cause premature ventricular

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KEY FINDINGS

- Temporary, noninvasive ultrasound pacing of the heart facilitated by ultrasound microspheres is feasible in humans.
- Ultrasound pacing can simulate the results of cardiac resynchronization therapy (CRT) implants when delivered with appropriate timing and to the locations of the expected left ventricular pacing sites in CRT systems.
- CardioInsight electrical mapping demonstrated QRS duration and standard deviation of activation times (parameter of electrical dispersion used in ECG Belt studies) during ultrasound pacing were similar to those actually achieved with clinical CRT in the same patients.
- The findings have clinically important implications related to the use of ultrasound pacing to select the best candidates for CRT.
- The demonstration that ultrasound pacing was safe in moderation in this study could lead to future clinical studies of related ultrasound pacing applications. These include noninvasive electrophysiological studies to induce ventricular tachycardia, termination of ventricular tachycardia in the inpatient cardiology setting, and optimization of myocardial targets for stereotactic body radiation therapy through noninvasive induction of ventricular tachycardia.

complexes and fusion complexes in anesthetized rats.[13] Another study demonstrated that addition of ultrasound microspheres decreased the threshold for cardiac ultrasound stimulation and permitted consistent ultrasound pacing for up to 1 hour in live pigs.[14] Histologic analysis revealed no abnormal findings on the sonicated regions. To our knowledge, ultrasound-based pacing performed in humans has not been reported.

We hypothesized that proper timing and location of an ultrasonic pacing stimulus, combined with a noninvasive system to determine electrical resynchronization, could provide an effective and noninvasive screening tool to identify which patients could benefit from CRT. This hypothesis was tested in the present study by determining the effectiveness of ultrasound pacing to simulate the effect of CRT on cardiac electrical activation before CRT implants.

Methods

Study design

This was a prospective, nonrandomized, single-center, acute feasibility study for patients with an indication for a cardiac resynchronization therapy–pacemaker (CRT-P) or cardiac resynchronization therapy–defibrillator (CRT-D). The study was conducted according to the principles of the Declaration of Helsinki. Subjects with myocardial damage, cardiac or chest surgery, or percutaneous revascularization within the prior 30 days were excluded. Eligible patients were divided into 2 cohorts. The ultrasound pacing cohort included eligible patients with high-quality baseline echocardiography (ultrasound windows with sufficient LV myocardial definition to calculate LV volumes), no contraindications for use of Lumason ultrasound microspheres (Bracco Diagnostics, Milan, Italy), and sinus rhythm with resting heart rate <120 bpm at the time of the procedure. The control cohort included eligible patients who failed ≥ 1 criteria for the ultrasound pacing cohort or who did not elect to undergo the ultrasound pacing procedure. All patients provided informed consent. The study was conducted under an Investigational Device Exemption (IDE) from the US Food and Drug Administration and was approved by the local institution review board. This study was registered at isrctn.com (Clinical Trial 11165621).

Investigational system

The ultrasound pacing system delivered single ultrasound pulses after each P wave (Figure 1). Surface ECG electrodes were placed on the patient in the Lewis lead configuration to maximize P-wave amplitude (Figure 1A).[15] The ECG signal was amplified and passed to a Bloom cardiac stimulator (model DTU 215B; Fischer Medical, Wheat Ridge, CO) for detection of P waves, followed by addition of an adjustable atrioventricular (AV) delay to create a trigger signal. The trigger signal was then conditioned and amplified by a custom module before triggering a waveform generator (Keysight model 33500, Santa Rosa, CA). The waveform generator produced an electrical burst waveform (frequency 0.5 MHz; pulse width 5 ms), which subsequently was amplified (E&I radiofrequency amplifier model A150, Rochester, NY) and impedance-matched before arriving at a single-element, 500-kHz immersion transducer (Olympus® model I8-0018-P-SU, Webster, TX) (Figure 1B). The transducer drive voltage was preprogrammed into the waveform generator so that the mechanical index (MI) did not exceed the recommended limit of 0.8 for Lumason microspheres (Bracco Diagnostics),[16] and the derated spatial peak temporal average intensity (ISPTA.3) did not exceed the track 1 exposure limits for cardiac imaging of 430 mW/cm^2.[17] This corresponded to a derated peak rarefactional acoustic pressure (pr.3) of approximately 0.6 MPa.

Procedure

For patients in the ultrasound pacing cohort, standard 2-dimensional echocardiography was used to identify suitable acoustic windows for ultrasound stimulation of the LV free wall. The patient was then fitted with a CardioInsight mapping vest (Medtronic plc) according to the standard instructions. Access to the acoustic windows was made possible by cutting into the spandex of the vest while avoiding the electrical circuitry to create temporary flaps (Figure 1A). The patient then underwent chest computed tomographic

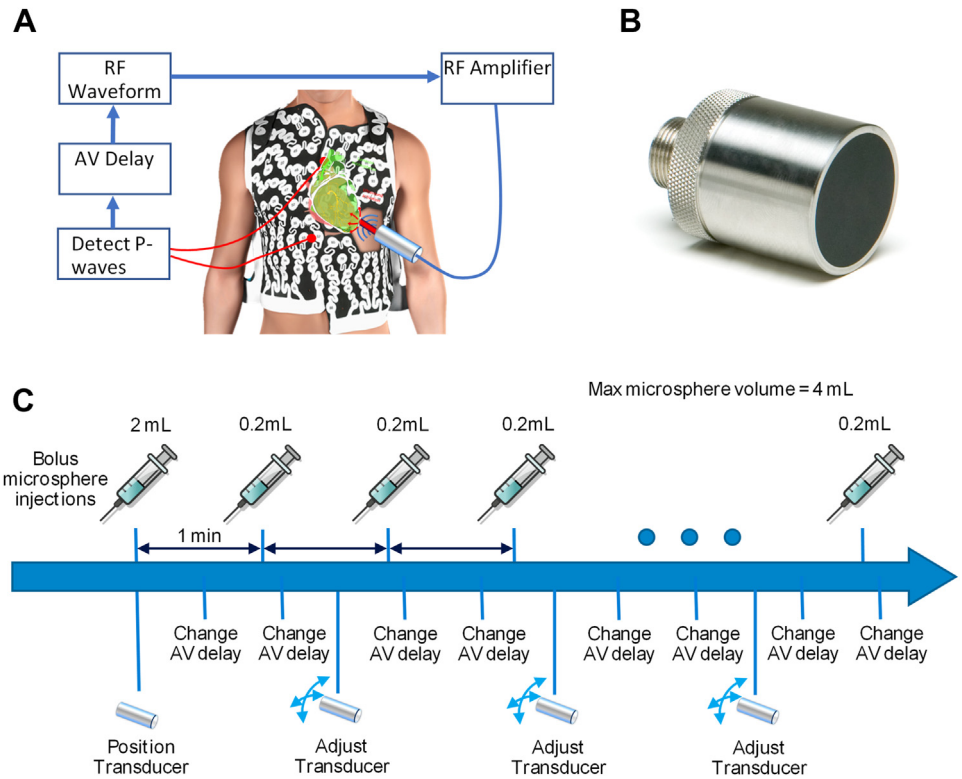

Figure 1 First noninvasive ultrasonic resynchronization pacing system. **A:** The investigational system included electroanatomic mapping with the CardioInsight vest, detection of P waves from a Lewis ECG lead, application of a programmable atrioventricular (AV) delay, triggered production and amplification of 500-kHz, 5-ms radiofrequency (RF) waveform pulses, and ultrasound transduction via an Olympus (I8-0018-P-SU) 1.125-inch-diameter, single-element piezoelectric transducer. **B:** The transducer was placed in contact with the skin after removal of a flap in the CardioInsight vest. **C:** Timeline of the ultrasound stimulation procedure.

scan to register the location of each CardioInsight electrode with respect to the epicardial surface of the heart.

The Lewis lead ECG electrodes and defibrillation patches were placed on the thorax. A range of AV delays was selected so that ectopic ventricular activation generated by the ultrasound pulse fused with intrinsic ventricular activation while avoiding pacing during the vulnerable period of the cardiac cycle if triggering occurred inappropriately on a QRS complex. The range of AV delays was therefore chosen to be less than the PR and RT intervals. The typical initial AV delay was 70% of the patient's PR interval.

Before enabling ultrasound stimulation, appropriate P-wave triggering was confirmed in every patient, and the ultrasound transducer was placed in contact with the patient's skin at the acoustic window. With the patient in a supine position, a series of bolus doses of Lumason microspheres (2-mL first dose + 0.2 mL each subsequent minute) was injected intravenously, and ultrasound stimulation was enabled (Figure 1C). Ultrasound capture beats were counted by monitoring the ECG on the EP recording system, and CardioInsight signals were collected to assess electrical activation during postprocessing. The position and/or angle of the ultrasound transducer were frequently changed to attempt capture at different pacing locations. For each successfully captured location, the AV delay was swept through a range to attempt resynchronization. For patients with complete AV block, the goal of ultrasound pacing was fusion with right ventricular (RV) pacing at a fixed sensed AV interval. Acute ultrasound stimulation ended when a maximum of 150 ultrasound capture beats was achieved, when the total injected Lumason volume reached 4 mL, or per investigator's discretion, whichever occurred first.

After acute ultrasound stimulation, the patient underwent standard CRT implantation. CardioInsight activation maps were shared with the implanting physician and considered during the CRT implant procedures. Although implantation of coronary venous leads in the latest-activated American Heart Association segment or neighboring segment was found to be feasible in nearly all patients, the study was not designed to evaluate the effectiveness of lead placement guided by CardioInsight maps, and further analysis of the effect of CardioInsight-guided LV lead placement on LV function after CRT was not performed. After CRT implant, CardioInsight signals were recorded during a variety of CRT pacing configurations for comparison with the CardioInsight maps obtained during ultrasonic pacing.

To assess the safety of ultrasound pacing, patients in both cohorts provided 3 blood draws for cardiac troponin I (cTnI) measurement: a baseline measurement before the procedure; and 2 follow-up measurements at 4–8 hours and 24–48 hours after the baseline blood draw, before being exited from the study. Therefore, patients in the control cohort provided control measurements of cTnI, influenced only by the CRT implant procedure.

Data analysis

During postprocessing, ultrasound capture beats were annotated by comparing the ECG leads and unipolar CardioInsight ECGs to the patient's native rhythm. From the CardioInsight data, activation maps and QRS widths were obtained for intrinsic beats, ultrasound capture beats, and CRT paced beats. A subset of CardioInsight electrodes (Supplemental Figure S1) was selected to simulate the ECG Belt configuration.[11] The corresponding waveforms were used to calculate the standard deviation of activation times (SDAT) (Supplemental Figure S2), a measure of global electrical heterogeneity.

Statistical analysis

Two-sided *t* tests were used for comparisons: specifically, troponin values between ultrasound paced and control cohorts; and metrics of electrical synchrony between intrinsic and ultrasound paced beats, between intrinsic and CRT beats, and between ultrasound paced and CRT beats. For troponin results, the significance of the interaction between time and pacing method was evaluated using a mixed linear model with an unstructured correlation. In the baseline table, 2-sided *t* tests were used to compare differences in continuous variables between groups, and the Fisher exact test was used to compare differences in count variables between groups. The Pearson correlation coefficient was used to quantify linear relationships. $P \leq .05$ was considered significant.

Results

The ultrasound pacing cohort and the control cohort each included 10 patients. Table 1 summarizes patient demographics. The cohorts were well matched for the goal of comparing changes in troponin after the procedure. Most patients (85%) received a CRT-D device. Ultrasound pacing was achieved in all 10 patients in the ultrasound pacing cohort, with a mean of 81.2 ± 50.8 ultrasound paced beats per patient. Of the 10 patients in the ultrasound pacing cohort, 2 had complete heart block and RV pacing during ultrasound pacing. The duration of attempted ultrasound stimulation was 11.3 ± 2.4 minutes. Between 3 and 9 different AV delays were tested per patient, sweeping through a range of 40 to 100 ms of AV delays. Ultrasound pacing typically was intermittent. Examples of ultrasound pacing from 1 patient are shown in Figure 2. The dashed vertical bars indicate the timing of ultrasound pulses after sensing of the P wave. Shaded regions designate ultrasound paced beats with different paced morphologies.

Although achieving consecutive ultrasound paced beats was not a goal of the study, the longest run of ultrasound

Table 1 Patient demographics

	Control cohort (n = 10)	Ultrasound pacing cohort (n = 10)	*P* value
Sex (male/female)	6/4	8/2	
Weight (lb)	222.0 ± 65.8	191.4 ± 52.3	.26
Height (inch)	67.6 ± 3.2	67.2 ± 3.8	.80
LVEF (%)	27.6 ± 6.7	28.7 ± 9.6	.79
Cardiovascular history			
Cardiac arrest	0 (0)	1 (10)	1
Cardiomyopathy, ischemic	4 (40)	3 (30)	1
Cardiomyopathy, dilated	1 (10)	1 (10)	1
Cardiomyopathy, other	4 (40)	4 (40)	1
Coronary artery disease	7 (70)	5 (50)	.65
Myocardial infarction	3 (30)	3 (30)	1
Congenital heart disease, other	0 (0)	1 (10)	1
Cardiovascular surgical history			
CABG	2 (20)	3 (30)	1
Coronary artery intervention, stent	4 (40)	1 (10)	.30
Aortic valve surgery	2 (20)	0 (0)	.47
VT ablation	1 (10)	1 (10)	1
Previous ICD implant	2 (20)	2 (20)	1
Previous pacemaker implant	2 (20)	2 (20)	1
Arrhythmia history			
AF	4 (40)	0 (0)	.87
AV block, third-degree, pacemaker dependence	1 (10)	2 (20)	1
Right bundle branch block	3 (30)	0 (0)	.21
Left bundle branch block	5 (50)	5 (50)	1
VT	1 (10)	1 (10)	1
Ventricular fibrillation	0 (0)	1 (10)	1
CRT-D	9 (90)	8 (80)	1
CRT-P	1 (10)	2 (20)	1

Values are given as mean ± SD or n (%) unless otherwise indicated.

AF = atrial fibrillation; AV = atrioventricular; CABG = coronary artery bypass graft; CRT-D = cardiac resynchronization therapy–defibrillator; CRT-P = cardiac resynchronization therapy–pacemaker; ICD = implantable cardioverter-defibrillator; LVEF = left ventricular ejection fraction; VT = ventricular tachycardia.

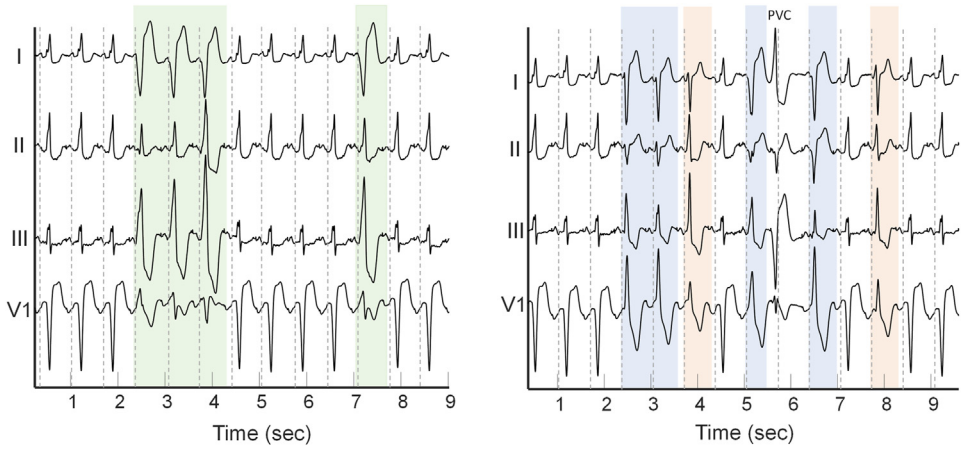

Figure 2 Ultrasound capture beats. Example electrocardiographic strips from a patient demonstrating intermittent ultrasound pacing from 3 different cardiac locations *(colored shaded regions). Vertical dashed lines* indicate the timing of ultrasound pulses. One premature ventricular contraction is identified. PVC = premature ventricular contraction.

pacing was 20 consecutive beats (Figure 3), in a different patient than that shown in Figure 2.

There was a moderate negative relationship between a patient's body mass index (BMI) and the total number of ultrasound paced beats per patient (r = –0.645; P = .044) (Supplemental Figure S3). The 3 patients with the lowest number of paced beats all had BMI >30.

Resynchronization

The CardioInsight system was used to compare the activation maps for intrinsic rhythm, ultrasound pacing, and the subsequent implanted CRT pacing. Figure 4 compares activation maps for 3 of the 10 ultrasound pacing patients, showing examples of the close resemblance of ultrasound paced and CRT paced beats.

Metrics of synchronization

We next compared the electrical resynchronization achieved by ultrasound pacing and by the implanted CRT system by measuring QRS width (according to the unipolar recordings of the CardioInsight system) and SDAT in the 9 patients with complete datasets. The best ultrasound paced beats and the best CRT paced beats showed significant improvements in synchrony over the baseline (intrinsic) beat (Figure 5 and Supplemental Table S1). Average QRS width at baseline (168.2 ± 17.8 ms) decreased significantly to 117.3 ± 21.5 ms (P <.001) in the best ultrasound paced beat and to 125.8 ± 13.3 ms (P <.001) in the best CRT beat. Similarly, average SDAT at baseline (40.4 ± 7.6 ms) decreased significantly to 6.6 ± 6.4 ms (P <.001) in the best ultrasound paced beat and to 13.6 ± 10.9 ms (P <.001) in the best CRT beat. In contrast, there was no significant difference in QRS width between the best ultrasound paced beat and the best CRT beat (P = .19), and there was no significant difference in SDAT between the best ultrasound paced beat and the best CRT beat (P = .15). Therefore, ultrasound pacing and CRT significantly and similarly improved QRS width and SDAT compared to baseline. In 7 of the 9 complete datasets,

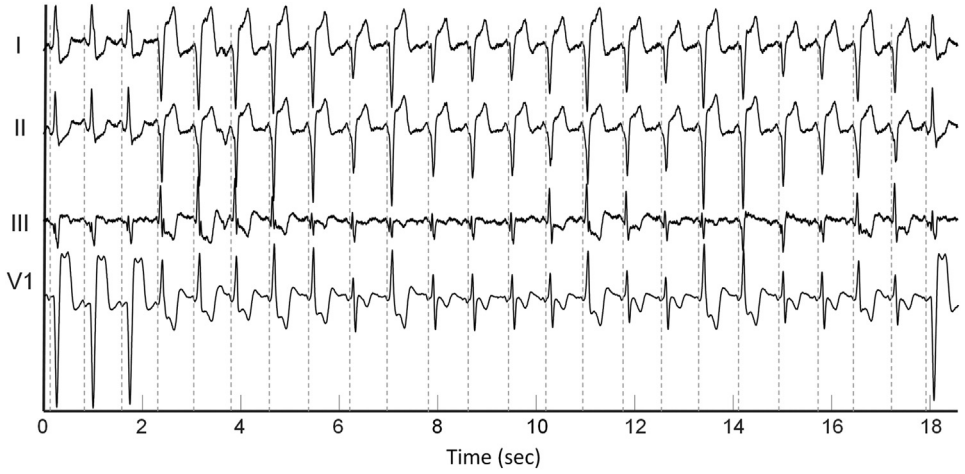

Figure 3 Long run of ultrasound capture beats. The longest consistent run of ultrasound pacing (20 beats) is shown. *Vertical dashed lines* indicate the timing of ultrasound pulses. Three noncapture beats occur at the start and 1 noncapture beat occurs at the end.

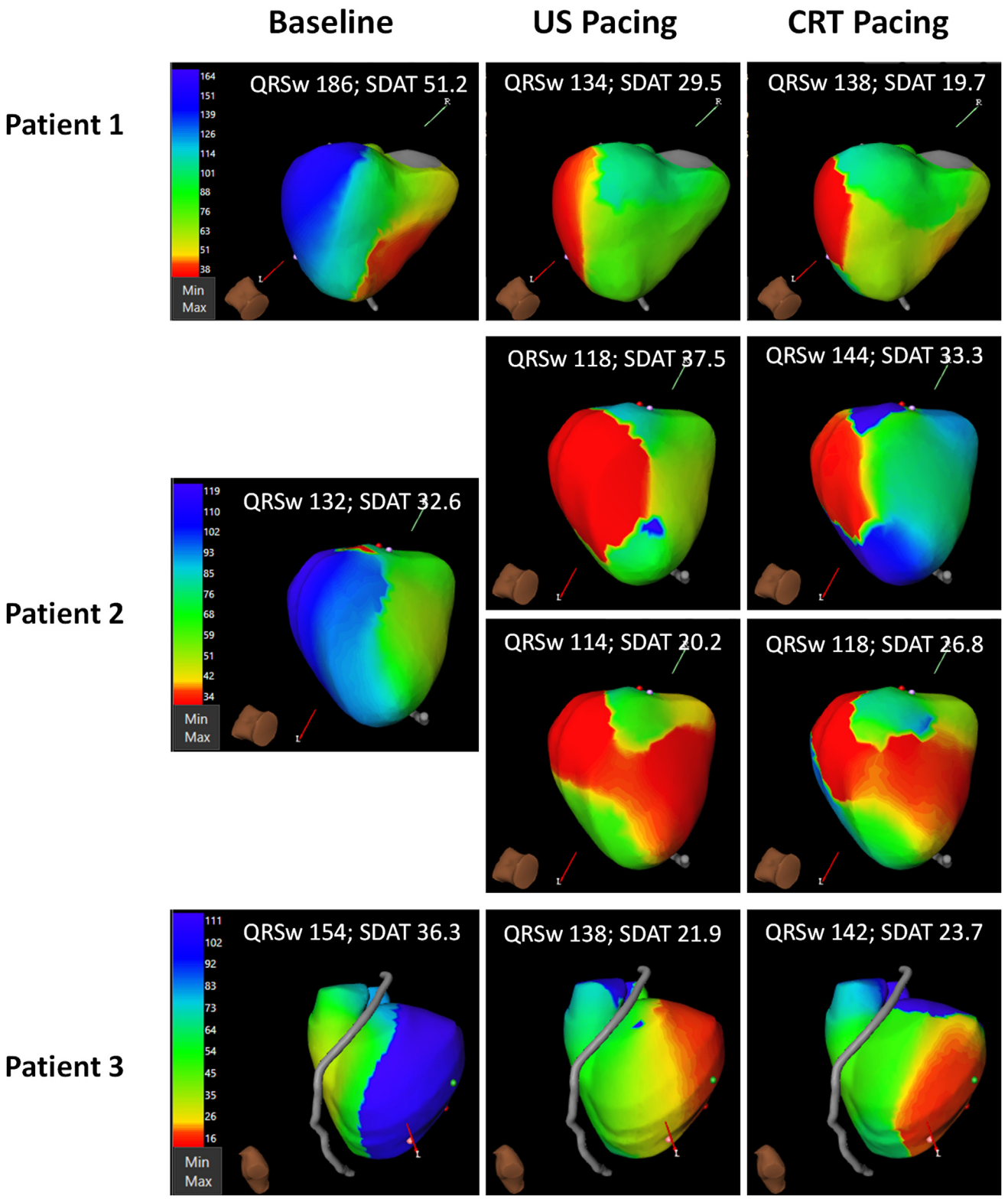

Figure 4 CardioInsight maps for cardiac resynchronization therapy (CRT) pacing and ultrasound (US) pacing. CardioInsight activation maps for 3 patients are shown. **Left:** Intrinsic depolarization. **Middle:** Ultrasound paced beat. **Right:** CRT pacing. For each patient, the activation time scales are equivalent. QRSw = QRS width; SDAT = standard deviation of activation time.

the maximum reduction in QRS width during ultrasound pacing equaled or exceeded the maximum reduction in QRS width during CRT. The 2 outlier patients had the smallest number of ultrasound paced beats (13 each). Similarly, the maximum SDAT reduction during ultrasound pacing equaled or exceeded the maximum SDAT reduction during CRT in 7

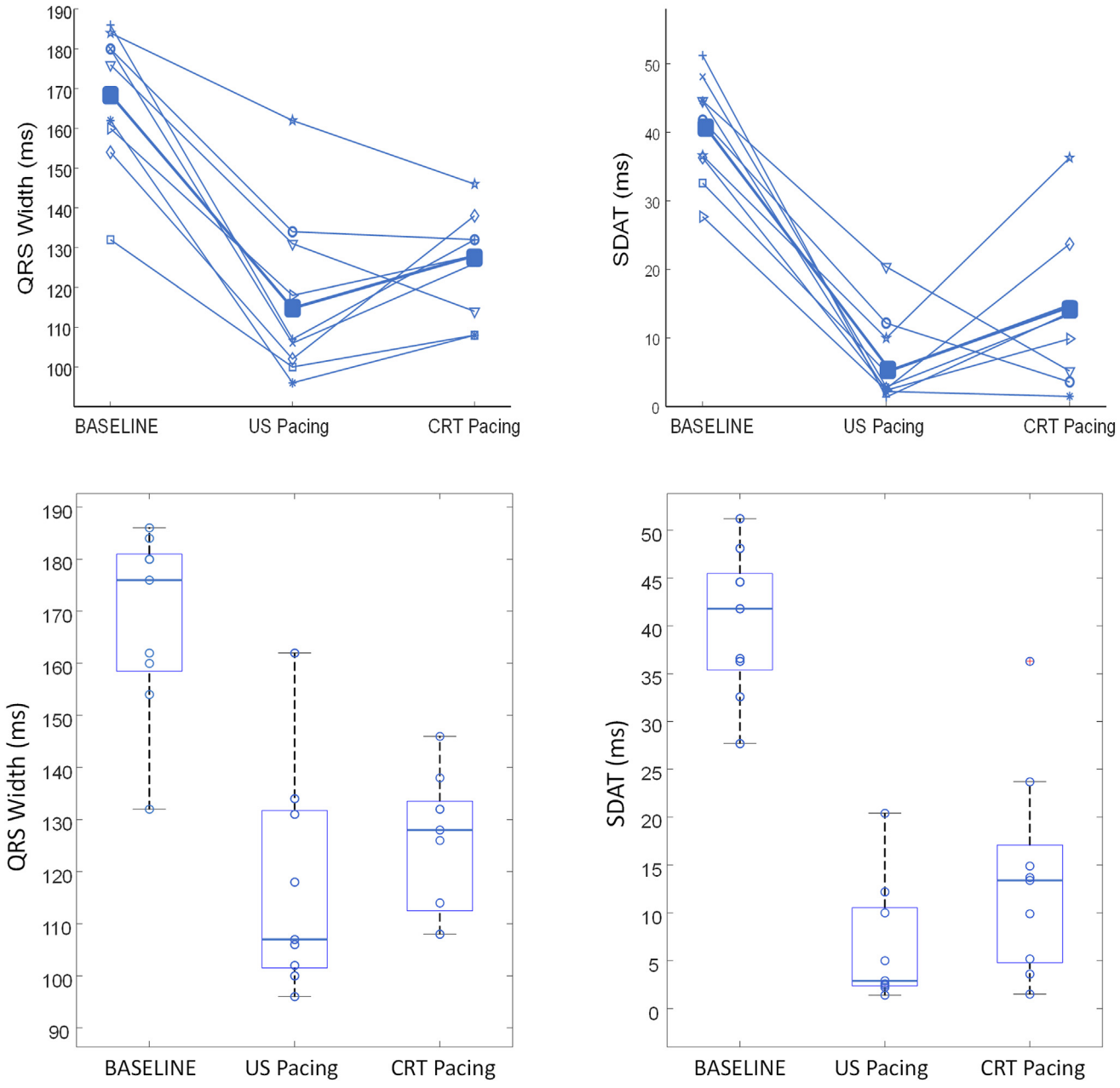

Figure 5 Changes in synchrony for CRT pacing and US pacing. Improvements in synchrony metrics QRS width **(left)** and SDAT **(right)** resulting from US pacing and CRT pacing are shown. The best ultrasound paced beat and CRT beat showed narrowing of the QRS and SDAT compared with the corresponding values in the intrinsic rhythm ($P < .0001$). **Top:** Individual patients have consistent symbols. Mean values are superimposed in *bold.* **Bottom:** Box plots showing median values and interquartile ranges, along with individual datapoints. Abbreviations as in Figure 4.

of 9 datasets. This suggests that ultrasound pacing can be used to approximate the upper limit of possible electrical resynchronization with CRT.

Safety

No patient reported any perception of the ultrasound pacing, and no adverse events (including arrhythmias) occurred. The safety of ultrasound pacing was assessed by comparing cTnI assays between the ultrasound pacing and control cohorts (Figure 6). Although the ultrasound pacing and control cohorts both showed an increase in troponin, there were no statistical differences in the change in troponin between the 2 cohorts ($P = .373$, .843, and .509 for 4–8 hours – baseline, 24–48 hours – baseline, and peak value – baseline, respectively). Troponin results also showed similar levels between the ultrasound pacing and the control groups from the interaction term of (time × group) in a linear model accounting for repeated measures in each patient ($P = .96$). Also, there was no correlation between troponin I and the number of ultrasound paced beats or the duration of the CRT implant procedure.

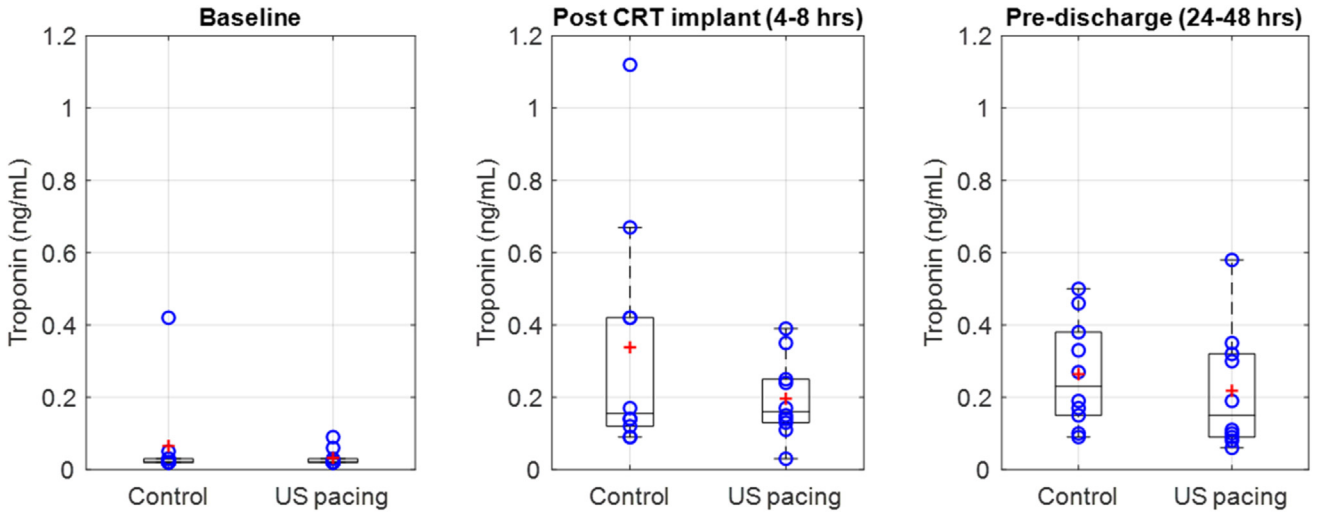

Figure 6 Troponin levels for control and US pacing. Box plots of troponin results for the US pacing and control groups are shown at baseline **(left),** post-CRT implant **(middle),** and pre-discharge **(right).** Compared with baseline, there were no significant differences at 4–8 hours ($P = .373$) or 24–28 hours ($P = .843$). Abbreviations as in Figure 4.

Discussion

The PACE-US (Feasibility of Ultrasound as a Temporary Pacing or Resynchronization Technique—An Acute Clinical Evaluation) study succeeded in demonstrating (1) temporary, noninvasive ultrasound pacing facilitated by ultrasound microspheres is feasible in humans; (2) ultrasound pacing can simulate CRT when delivered with appropriate timing and pacing location; (3) ultrasound pacing and CRT resulted in similarly significant improvements in QRS width and SDAT; and (4) temporary ultrasound pacing seems to be safe in moderation.

Ultrasound pacing seems to indicate the upper limit of electrical synchronization achievable with CRT, with the caveat that ultrasound pacing should include a sufficient variety of LV locations and pace timing. Therefore, our methodology could provide a novel CRT screening procedure that is noninvasive but estimates the potential benefits of CRT through simulation of cardiac activation patterns resulting from CRT pacing before the actual CRT procedure. In our study, the variance in the number of ultrasound paced beats seemed to be influenced by BMI, as higher BMI may lead to reduced quality and size of acoustic windows, greater ultrasound attenuation because of tissue thickness, and a lower concentration of microspheres. Lumason microspheres have a half-life of approximately 10 minutes,[16] but the local microsphere concentration can vary widely spatially and temporarily.

If ultrasound pacing can provide an upper limit of potential electrical synchronization, it could contribute significantly to procedure planning. For example, ultrasound pacing could influence the decision to implant an implantable cardioverter-defibrillator or CRT-D in a patient with intraventricular conduction delay, right bundle branch block, or left bundle branch block with QRS width 120–149 ms. Ultrasound pacing also may be helpful for shared decision-making with candidates for CRT upgrades. In particular, the degree of RV pacing–induced LV dysfunction and infection risk with reoperation may lead to substantial uncertainty regarding the decision to upgrade a patient's pacemaker or implantable cardioverter-defibrillator to the corresponding CRT device.

In a patient for whom the potential electrical resynchronization suggested by ultrasound pacing is not achieved with traditional CRT, likely because of limitations in coronary venous anatomy, alternative approaches to resynchronization such as LV endocardial pacing with a leadless electrode[18] or left bundle branch area pacing[19] may be considered. This represents an exciting opportunity to use of ultrasound pacing and CardioInsight to provide a personalized approach to CRT.

There are several opportunities to improve upon the ultrasound pacing system. A transducer with simultaneous imaging and pacing capabilities would facilitate targeted pacing at desired locations and possible anatomic guidance for the subsequent coronary venous pacing location. Another possibility is image integration with cardiac magnetic resonance[20-22] and cardiac computed tomography[23] to identify the coronary venous branch likely to replicate the ultrasound pacing result or identify scar locations to avoid. Future studies could use such an enhanced system to guide patient selection and implant procedures, and to compare outcomes to a matched cohort without ultrasound screening.

Other possible applications for ultrasound pacing include use as an adjunct tool for noninvasive ablation of ventricular tachycardia (VT) and possible extension to electrophysiological studies, painless cardioversion, antitachycardia pacing, or defibrillation. Stereotactic body radiation therapy using high-dose radiation from a linear accelerator is an increasingly recognized option for noninvasive ablation of refractory VT,[24] and the addition of noninvasive pacing to this

procedure would allow for totally noninvasive VT inductions and VT mapping studies to aid in locating the correct ablation site. Noninvasive antitachycardia pacing could be applied in emergency rooms for patients in VT. If an appropriate acoustic window were available, a wide-beam transducer might be capable of painless cardioversion or defibrillation (atrial or ventricular). These potential applications require further clinical evaluation.

Study limitations

Although the study was not well powered to detect differences in troponin between the ultrasound pacing and control cohorts, the *P* value of 0.96 and the lower point estimates for troponin in the ultrasound pacing cohort are reassuring. Of note, some level of troponin elevation is expected to result from lead implantation. For example, pacemaker implantation has been shown to increase cTnI to 0.39 ng/mL on average, a value that is very similar to our post-CRT results.[25] Similarly, typical cTnI elevations after CRT implantation have been studied.[26] Also, defibrillation testing did not occur during our study in order to avoid the confounding release of troponin due to shocks.

Conclusion

This *first-in-human* demonstration of LV pacing with ultrasound provides evidence that CRT can be simulated noninvasively. This promising approach to simulate CRT may identify the potential degree of electrical resynchronization achievable with LV free-wall pacing, offer important guidance for LV lead implantation, and deliver personalized medicine by helping to match the best approach to CRT to the individual patient.

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Authorship: All authors attest they meet the current ICMJE criteria for authorship.

Patient Consent: All patients provided informed consent.

Ethics Statement: The study was conducted under an Investigational Device Exemption (IDE) from the US Food and Drug Administration and was approved by the local institution review board. This study was registered at isrctn.com (Clinical Trial 11165621). The study was conducted according to the principles of the Declaration of Helsinki.

Appendix

Supplementary data

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.hroo.2022.10.008.

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