Ultrasound contrast and real-time perfusion in conjunction with supine bicycle stress echocardiography for comprehensive evaluation of surgically corrected congenital heart disease

Shelby Kutty1*, Joan Olson2, Christopher J. Danford1, Erin K. Sandene1, Feng Xie2, Scott E. Fletcher1, Christopher C. Erickson1, John D. Kugler1, David A. Danford1, and Thomas R. Porter2

1Joint Division of Pediatric Cardiology, University of Nebraska College of Medicine/Creighton University, Children’s Hospital and Medical Center, Omaha, NE, USA; and 2Department of Internal Medicine, Section of Cardiology, University of Nebraska Medical Center, Omaha, NE, USA

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Aims

We sought to evaluate the efficacy of ultrasound contrast (UC) and low mechanical index real-time perfusion (RTP) in the haemodynamic and anatomic assessment of repaired congenital heart disease (CHD) at rest and during supine bicycle stress echocardiography (BSE).

Methods and results

Patients with CHD (n = 51, median age 21.5 years) were prospectively studied. All had compromised image quality, 20 (39%) had arrhythmias, and 10 (20%) had pacemakers. RTP was performed at rest and during BSE using Definity and Contrast Pulse Sequencing, with assessment of Doppler pressure gradients. Diagnoses included tetralogy of Fallot (n = 27), transposition of the great arteries (TGA) atrial switch (n = 10), TGA arterial switch (n = 2), aortic valve disease (n = 4), Fontan (n = 4), and Kawasaki disease (n = 4). UC with RTP improved endocardial border definition, with increased number of left ventricular (LV) and right ventricular (RV) segments visualized at rest (P < 0.0001) and during stress. LV ejection fraction (EF) and RV fractional area change (FAC) were measurable at rest and peak stress, RV FAC correlating closely with same-day magnetic resonance EFs (r = 0.72; P < 0.001). UC enhanced Doppler signals, enabling subpulmonary ventricular systolic pressure measurements at rest and stress. In six patients, marked elevations of subpulmonary ventricular systolic pressure were detected with UC during BSE, and quantifiable ventricular dysfunction. No adverse events occurred, other than transient low back pain in one patient.

Conclusion

UC at rest and with supine BSE enables safe and comprehensive assessment of anatomy, haemodynamics, and biventricular functional and perfusion reserve in adolescents and young adults with surgically modified CHD.

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Keywords

Ultrasound contrast • Adult congenital heart disease • Paediatric cardiology • Real-time perfusion • Wall motion • Stress testing

Introduction

Transthoracic echocardiography (TTE) is the most widely used non-invasive tool for the assessment and serial follow-up of ventricular size and function. Suboptimal image quality due to the restricted acoustic windows is associated with post-operative changes in paediatric and adult congenital heart disease (CHD) and commonly poses significant challenges to TTE. There is limited experience with ultrasound contrast (UC) in children and young adults with CHD, despite multiple studies demonstrating significantly enhanced TTE image quality in adults with acquired heart disease.1–3
Stress protocols utilizing UC and real-time perfusion (RTP) imaging have proven very helpful and safe in adults for the detection of coronary artery disease. In the same way, theoretically, stress TTE with UC could disclose clinically important changes in ventricular function and transvalvular pressure gradients in CHD that are not evident with conventional TTE. Data demonstrating this in CHD are very limited. Because bicycle stress echocardiography (BSE) can assess haemodynamics, myocardial function, and myocardial perfusion (MP) in real time during physiological exercise, it could potentially identify subclinical pathology in CHD. Supine BSE with UC has the potential to quantify exercise endurance and haemodynamic responses to exercise, yielding a comprehensive functional assessment. We sought to evaluate the efficacy of UC stress TTE with RTP imaging in the assessment of anatomy, haemodynamics, and biventricular function in difficult-to-image adolescents and young adults with repaired CHD. Our primary goal was to evaluate the incremental value of the assessment of wall motion (WM) and MP with RTP during BSE to determine whether there is additional diagnostic benefit of UC imaging compared with non-contrast imaging in this population. The secondary aims were to (i) examine the correlation of right ventricular (RV) fractional area change (FAC) measurements on UC images with cardiac magnetic resonance (CMR)-derived RV ejection fractions (EFs) and (ii) quantify the incidence and types of adverse events associated with the use of UC for rest and stress imaging in patients with CHD.

Methods

This was a single-centre prospective clinical trial. The Institutional Review Board at the University of Nebraska Medical Centre approved the study protocol. Informed, written consent was obtained from all patients or legal guardians. All patients were instructed to discontinue β-blockers at least 24 h prior to the study. Inclusion criteria consisted of residual haemodynamic abnormalities after CHD repair with (i) poor image quality on previous TTE, (ii) absence of any intracardiac shunt on previous imaging studies, and (iii) cardiac diagnosis of repaired tetralogy of Fallot (TOF), d-loop transposition of the great arteries (TGA), Kawasaki disease with coronary artery sequelae, aortic stenosis, or single ventricle after Fontan procedure. Specific exclusion criteria were (i) age <13 years, (ii) contraindications to UC, and (iii) lack of consent to participate in the study protocol.

Patients

The following information was abstracted from medical records: date of birth; gender; type of CHD; date and type of surgical correction; and results of the most recent clinical evaluation and TTE. Any history of cardiac arrhythmias and prior placement of permanent pacemakers or defibrillators were also noted.

Ultrasound contrast protocol

Prior to UC imaging, all patients underwent complete diagnostic TTE including spectral and colour Doppler evaluation of the ventricular inflow, outflow, atrioventricular, and semilunar valves according to the standard institutional practice for CHD evaluation. For UC echocardiography, the lipid encapsulated microbubble, Definity (Lanthus, North Billerica, MA, USA), was infused as a 3% dilution (4–6 mL/min). RTP imaging was performed using Sequoia 512 system (Siemens Medical Solutions, Mountain View, CA, USA), equipped with low mechanical index (MI) real-time pulse sequence schemes (1.7 MI; Contrast Pulse Sequencing). Rest images were acquired for complete anatomic, functional, and perfusion assessments. Intermittent high MI impulses (4–40 frames) were administered in the apical views to clear microbubbles from the microcirculation and allow visual assessment of myocardial contrast replenishment. The high MI impulse duration was adjusted to optimize clearance of UC from the myocardium without visually affecting ventricular cavity contrast. The MI was set at ≤0.2 and frame rate at 20–25 Hz.

Stress echocardiography protocol

The supine BSE protocol was performed using a symptom-limited protocol. Patients pedalled at constant speed beginning at a workload of 25 W, with an increment of 25 W every 3 min until exhaustion on a variable load bicycle ergometer (Medical Positioning, Kansas City, MO, USA). Blood pressures were monitored every minute and 12-lead electrocardiograms continuously. To improve image quality during stress, subjects were rotated ~30° in the left lateral decubitus position via a motorized table. All TTE measurements were repeated at peak stress with UC infusion continued throughout image acquisition. The stress tests were considered diagnostically adequate if the target heart rate (85% predicted maximum for patients with dual-chambered circulation) or an ischaemic endpoint was achieved, defined as an abnormal electrocardiographic response of ≥2 mm horizontal or downsloping ST depression in any lead, or a new or worsening WM abnormality.

Cardiac magnetic resonance protocol

CMR imaging was performed within 2 h of the TTE BSE using a 1.5 T scanner (Intera R 12.6.1.3, Philips, Best, The Netherlands) with a five-channel cardiac coil (Philips). Cardiac synchronization was performed with vector electrocardiography. Left ventricular (LV) and RV dimensions and function were assessed using steady-state free-precession cine (repetition time 2.8–3.2 ms, echo time 1.4–1.6 ms, field of view 380 × 380 mm, matrix sizes ranging from 160 × 130 to 228 × 216) during brief periods of breath-holding in the following planes: ventricular two-chamber, four-chamber, LV and RV outflow tract, and short-axis with 12–14 equidistant slices (slice thickness, 6–8 mm, interslice spacing 0–2 mm). The main pulmonary artery and aortic flows were acquired by use of a retrospective two-dimensional phase contrast sequence during free breathing. Myocardial late enhancement was performed 10–15 min after a magnetic resonance angiogram using 0.2 mmol/kg of gadopentetate dimeglumine (Magnevist, Bayer Healthcare, Wayne, NJ, USA). The late enhancement protocol consisted of electrocardiogram-triggered, fast-gradient echo pulse sequence acquisitions with inversion times selected using the Look–Locke sequence. Measurements of LV and RV end-diastolic and end-systolic volumes were obtained from short-axis cine stack by manual tracing of endocardial contours. A single observer (S.K.) performed all measurements using commercially available software packages (Extended MR work space version 2.6.3.2, Philips).

Ultrasound contrast-enhanced image analysis

Left ventricle

MP and WM were interpreted using the American Heart Association recommended 17-segment model for the LV. Segmental MP and WM were analysed at rest and during peak stress. In the setting of RTP, a brief high MI impulse (MI = 1.9) was given for a sufficient duration to clear the myocardial capillaries of microbubbles in each of the apical views. The subsequent rate of replenishment and the plateau intensity were analysed separately by comparing rest with stress.
images. The time period of myocardial UC replenishment to reach a plateau intensity after the high MI impulse was considered abnormal if the subendocardium or transmural portion of any two contiguous segments required >2 s to replenish with UC at peak stress or required >4 s to replenish under resting conditions.9

Right ventricle
Non-contrast and contrast images at rest and contrast images at peak stress in the apical and parasternal views were evaluated with specific focus on endocardial boundary recognition. Quantitative assessment was performed in the apical four-chamber view by dividing the RV into three parts (basal, mid-cavity, and apical), each part as one-third of the axial length of the cavity from the plane of the tricuspid valve annulus to the apex. The resulting six RV segments were basal free wall, mid-cavity free wall, apical free wall, apical septum, mid-cavity septum, and basal septum. Anterior RV free wall and outflow tract were assessed from parasternal images. All studies were simultaneously supervised, reviewed, and interpreted by an adult cardiologist with expertise in myocardial contrast echocardiography (T.R.P.) and a paediatric echocardiographer cardiologist (S.K.).

Each WM segment was scored at rest and at peak stress using the following scoring system: 1, normal; 2, mild-to-moderate hypokinesis; 3, severe hypokinesis; 4, akinesis; and 5, dyskinesis. A blinded observer assessed the adequacy of endocardial border detection for the LV and RV utilizing a scoring system. The scoring system compared UC-enhanced vs. non-contrast images at rest in each patient using ‘+’ for better boundary detection with UC and ‘0’ for no appreciable improvement.

Assessment of ventricular contractile reserve
Systemic ventricular end-diastolic and end-systolic volumes were computed by planimetry in the apical four-chamber view. Normal LV contractile response was defined as an absolute increase in an LVEF of >6% at peak stress compared with baseline.10 LVEF reserve was calculated as the absolute difference in EF (%) between stress and rest (stress LVEF−rest LVEF). RV FAC was measured in the apical four-chamber view. End-diastole was identified by the onset of the R-wave on the electrocardiogram and end-systole was identified as the smallest RV cavity size just before tricuspid valve opening. The average of three end-diastolic (EDA) and three end-systolic area measurements (ESA) was taken. RV FAC was calculated as (RVEDa – RVEsa)/RVEDa × 100%. Change in FAC between rest and stress (FAC reserve) was used as an index of RV contractile response.

Statistics
Mean, standard deviation (SD), median, and ranges were determined for continuous variables. A comparison of continuous variables was accomplished with linear regression analysis. Differences in the mean number of segments visualized before and after UC per patient were tested using the Wilcoxon signed-rank test. The proportion of patients in whom improved visualization was noted with UC for each myocardial segment for the LV and RV was determined. A P–value of <0.05 was considered significant. Statistical analyses were performed using Minitab 16.1 (Minitab Inc., State College, PA, USA).

Results
Between August 2009 and March 2011, 51 patients were enrolled in the study. Patient demographics are shown in Table 1. All except one patient completed the study protocol without any adverse event. The protocol was incomplete in one 42-year-old patient with repaired TOF who experienced lower back pain. This patient had global left LV hypokinesis and biventricular dysfunction at baseline.

Enhancement of Doppler signals
UC enhanced the Doppler signals used for evaluation of valvular function and estimation of RV systolic pressure at rest and at peak stress in all but one patient (who did not complete the stress testing due to low back pain). These values were not obtainable without UC in eight patients (16%). Semilunar valve velocities suitable for pressure gradient estimation at rest and stress were also quantifiable in all patients with the aid of UC. Representative examples of enhancement of Doppler spectral envelopes using UC in repaired TOF and atrial switch TGA are shown in Figure 1.

Endocardial border definition
Endocardial border definition was improved in all patients, with an increased number of wall segments visualized at rest and during stress. Examples of two-dimensional TTE still frame panels showing non-UC- and UC-enhanced images recorded in TOF are shown in Figure 2. Overall, the mean ± SD of LV myocardial segments per patient with improved visualization using UC was 6 ± 3; and the mean number of RV segments with improved visualization per patient was 2.5 ± 1. Of 23 possible segments for LV

<table>
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<tr>
<th>Parameter (mean ± SD)</th>
<th>All patients</th>
<th>TOF</th>
<th>TGA atrial switch</th>
<th>TGA-ASO</th>
<th>Aortic stenosis</th>
<th>Kawasaki disease</th>
<th>Fontan</th>
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<tr>
<td>n</td>
<td>51</td>
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<td>10</td>
<td>2</td>
<td>4</td>
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<tr>
<td>Gender (male/female)</td>
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<td>16/11</td>
<td>6/4</td>
<td>1/1</td>
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<td>Age</td>
<td>24.1 ± 9.9</td>
<td>22.5 ± 8.9</td>
<td>35.2 ± 7.4</td>
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<td>Weight (kg)</td>
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<td>1.94 ± 0.3</td>
<td>1.75 ± 0.1</td>
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</table>

TOF, tetralogy of Fallot; TGA, transposition of the great arteries; ASO, arterial switch operation.
and RV combined, the mean ± SD of segments with improved visualization per patient using UC was 9 ± 4. The proportion ± SD of patients in whom improved visualization was noted for each segment for the LV and RV is shown in Figure 3. In those patients with a biventricular circulation (n = 47), the number of LV segments visualized improved from 11 ± 2 per patient without UC at rest to 16 ± 1 per patient with UC (P < 0.0001). Similarly, the number of RV segments visualized at rest increased from 3.7 ± 1.0 without UC to 5.5 ± 0.6 segments with UC (P < 0.0001). The LV mid-lateral, apical lateral, and apical septal segments; and RV apical free wall, apical septal, and mid-septal segments were most often better detected with UC. There was improved definition of the RV and RV outflow tract with UC in TOF (in 10 of 27 patients) and atrial baffles in TGA (in 3 of 10 patients).

MP abnormalities were detected in six patients (12%) at peak stress. Of these, three had repaired TOF, one had atrial switch TGA, one had moderate aortic stenosis, and one had coronary arterial sequelae of Kawasaki disease. MP abnormalities were in the mid-septal and apical segments of the LV (TOF; Figure 4), apical septal segment of the RV (atrial switch TGA), inferoapical and anteroseptal LV segments (aortic stenosis), and inferoseptal segments (Kawasaki disease). Five of the six patients had WM abnormalities (WM score 2–4) demonstrated in the same segments at peak stress.

**Ventricular contractile reserve**

Rest and BSE results are summarized in Table 2. LVEF and RV FAC were measurable at rest and at peak stress in all patients when using UC. In six patients, marked elevation of subpulmonary systolic pressure (defined as an increase in atrioventricular valve regurgitation Doppler-estimated subpulmonary systolic pressure of 40 mmHg above baseline) and reductions in systemic/pulmonary ventricular function manifested at peak stress. Four of these had
atrial switch repair of TGA and two had TOF repair. In those with atrial switch TGA, the subpulmonary LV pressures increased to suprasystemic at submaximal stress along with a decrease in RV and LV systolic function. These four patients experienced fatigue early in the study with fall in systemic oxygen saturations and demonstrated reduced biventricular contractile reserve. Of

**Figure 2** Two-dimensional echocardiographic still frame panels showing non-contrast- and contrast-enhanced images recorded in the apical four-chamber, parasternal long-axis, and parasternal short-axis views in a patient with repaired tetralogy of Fallot (A–C). Note improved visualization of the right ventricular endocardial border including the anterior wall and apical segments, especially in the contrast-enhanced apical four-chamber view.
these, two underwent cardiac transplant evaluation and a third was listed for transplantation within a year of the UC stress testing because of limited success with medical management of heart failure. In the fourth patient, diminished biventricular contractile reserve on UC stress was identified to be due to cardiac output limitations from inferior limb systemic venous baffle obstruction. The patient underwent stent placement for relief of inferior limb systemic venous baffle obstruction. The patient underwent stent placement for relief of inferior limb systemic venous baffle obstruction.

**Right ventricular fractional area change and right ventricular ejection fraction correlation**

In patients with TOF and atrial switch TGA who had UC stress echocardiography and CMR performed contiguously on the same day (n = 23), the RV FAC measured on UC-enhanced TTE images at rest and RV EF measured by CMR correlated well (r = 0.72, P < 0.001; Figure 5). Demographic and CMR data from these patients are shown in Table 3.

**Discussion**

The growing population of adolescents and adults with CHD has led to markedly increased use of non-invasive cardiac imaging in their care. These patients often have residual structural and haemodynamic abnormalities, which necessitate serial comprehensive assessment, but TTE is often challenging due to acoustic window limitations secondary to previous cardiac operations, chest wall problems, implanted pacemaker leads, and alterations in cardiac geometry due to shunts and baffles.

This study represents the largest study to date on the efficacy of UC in young CHD patients suspected of physiologically relevant changes in biventricular systolic function. This is also the first study that used UC and RTP in conjunction with supine BSE for the evaluation of structural heart disease. UC added three critical pieces of information in these patients: (i) improved visualization of segmental WM in the LV and RV leading to better quantification of ventricular function at rest and during physiological stress; (ii) enhanced Doppler signals which permitted detection of subpulmonary ventricular systolic pressure and transvalvular pressure gradient changes during exercise; and (iii) RV and LV MP information. All three pieces provided important information with potential impact on their medical and surgical management.

The present study also highlights the potential advantages of RTP over other imaging techniques in this setting. Although CMR provides similar information, physiological stress imaging is nearly impossible with CMR, and nearly 20% of our patients had pacemakers or defibrillators, which precluded the use of CMR. Several reports have shown that radionuclide perfusion imaging techniques may allow evaluation of MP and the effects of myocardial hypoperfusion on contractility. Feasibility studies with positron emission tomography (PET) have been done in patients with TGA after arterial or atrial switch, and in cases of suspected coronary abnormalities. However, clinical use of PET in CHD has been limited because of general unavailability of the test and concerns for radiation exposure. Furthermore, the spatial resolution obtained with radionuclide techniques is suboptimal. The advantages of UC with RTP are that it provides immediate information with better spatial resolution, all without the need for radiation exposure. It also has superior temporal resolution, allowing WM and MP to be analysed simultaneously.

WM analysis on TTE is an effective screening tool for identification of suspected myocardial ischaemia after repair of CHD involving coronary manipulation. In the present study, MP defects were observed in three patients (ages 28, 43, and 45) with repaired TOF. Stress-induced perfusion abnormalities have been reported in TOF in the absence of coronary pathology. These defects are presumed to be due to RV hypertrophy (RVH) and resultant myocardial supply–demand mismatch. Others have shown reduced MP reserve in TOF with RVH, suggesting reduced myocardial microvascular density of the septal wall.

The utilization of UC in our patient population improved LV endocardial visualization, resulting in better quantification of...
Lateral displacement of the LV due to RV dilatation and/or hypertrophy makes visualization of lateral borders more difficult without UC. With UC, both lateral and apical LV segments were better visualized. For the RV, there was improved endocardial border detection, allowing simultaneous RV FAC measurements and MP analysis. There are several potential explanations for why UC has not been utilized more in this clinical setting. Although there have been safety concerns raised by the Food and Drug Administration, several studies have confirmed the clinical safety of UC. Furthermore, the Box Warning in the USA has recently been completely removed for Definity. Currently, the only approved indication for UC remains the enhancement of ventricular borders in adults. It has not been approved for any adolescent applications like the ones used in this study. Although the use of UC may add time and cost to TTE, it has been shown to reduce the need for additional diagnostic studies in over 30% of the patients.

The clinical usefulness of dobutamine or dipyridamole stress TTE and the feasibility of treadmill exercise stress TTE in the evaluation of suspected myocardial ischaemia in Kawasaki disease has been shown. Although limited ultrasound windows and resultant suboptimal image quality have been a hindrance to its acceptance, some studies of stress TTE have been done in CHD, primarily in patients with aortic stenosis, repaired TOF, TGA, and after Fontan palliation. The present study demonstrated the feasibility of RTP with image acquisition during peak stress on the supine bicycle and permitted the simultaneous

Figure 4 Abnormal myocardial perfusion at rest and during supine bicycle stress echocardiography in tetralogy of Fallot (A–F). The left panel shows an image obtained at rest and the right panel shows the same image obtained at peak stress. The apical four- (A and B) and three-chamber (C and D) views of real-time perfusion in a 28-year-old male (Patient 1) with repaired tetralogy of Fallot. Left ventricular myocardial wall thinning and perfusion defects are evident in the septum (arrows) and apical segments (arrows) at rest and peak stress. (E and F) Images are from a 45-year-old female (Patient 2) with repaired tetralogy of Fallot. Note the stress-induced perfusion defect in the basal septum that may be related to the ventricular septal defect patch (arrows).
evaluation of MP and WM. A potential advantage of BSE over treadmill exercise is that during BSE, images can be obtained while the patient is still exercising, thereby improving the detection of any induced ischaemia.

Kaplan et al.24 observed in a mixed population of adult CHD that decreased exercise tolerance was associated with an exaggerated exercise pulmonary artery pressure response, decreased RV and/or LV function with exercise, or both. This matches our observations, especially in patients after atrial switch repair of TGA. Others have shown decreased cardiac index on dobutamine stress TTE after Fontan palliation.26 Most of previously reported stress imaging studies in CHD have been performed with dobutamine, and higher dobutamine infusion rates are often required to achieve peak stroke volumes in some patients with decreased inotropic reserve.26 However, even submaximal doses of dobutamine may precipitate ventricular arrhythmias,27 making it difficult to fully stress a patient with this technique, or clinically assess the haemodynamic significance of any finding.

Of several two-dimensional echocardiographic methods available to assess RV function, RV FAC has been shown to best correlate with CMR-derived RVEF28 and is a predictor of mortality and cardiovascular outcomes.29 We found that RV FAC correlated well with CMR-derived RVEF in the subset of patients who had CMR performed on the same day. This finding is relevant to the CHD population because superior RV endocardial border definition with UC, particularly among patients with significant chamber dilatation, would enhance the feasibility and potentially the accuracy of RV FAC measurements, and thus become a method of choice for assessing RV function in patients with contraindications to CMR.

**Study limitations**

No gold standard reference was used to evaluate the accuracy of any induced perfusion defects in this study. Quantitative
assessments of myocardial blood flow were not performed. In this particular patient population, no reference standard exists, as the possible aetiology of induced perfusion defects is not only coronary artery disease, but also demand–supply imbalances that may exist due to pressure overload or myocardial hypertrophy. The small sample size is an important limitation, and varied CHD types included in the study preclude meaningful subgroup analyses. Finally, simultaneous CMR measurements could not be obtained in all patients, due to contraindications in performing CMR. Nonetheless, the 23 patients in whom CMR could be performed represented both TOF and TGA patients, and thus most likely, our correlations would be similar if all patients were compared.

Conclusions

UC stress echocardiography with RTP enables the safe and comprehensive assessment of anatomy, haemodynamics, and ventricular contractile and perfusion reserve in repaired CHD. This was particularly beneficial in adolescents and adults with compromised image quality from multiple causes including previous surgeries and implanted pacemaker leads.

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