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Fetal Cardiac MRI

A Review of Technical Advancements

Christopher W. Roy, PhD,[*] Joshua F.P. van Amerom, PhD,[†‡] Davide Marini, MD, PhD,[‡] Mike Seed, MD,[‡§] and Christopher K. Macgowan, PhD[||¶]

Abstract: Magnetic resonance imaging (MRI) is an appealing technology for fetal cardiovascular assessment. It can be used to visualize fetal cardiac and vascular anatomy, to quantify fetal blood flow, and to quantify fetal blood oxygen saturation and hematocrit. However, there are practical limitations to the use of conventional MRI for fetal cardiovascular assessment, including the small size and high heart rate of the human fetus, the lack of conventional cardiac gating methods to synchronize data acquisition, and the potential corruption of MRI data due to maternal respiration and unpredictable fetal movements. In this review, we discuss recent technical advances in accelerated imaging, image reconstruction, cardiac gating, and motion compensation that have enabled dynamic MRI of the fetal heart.

Key Words: accelerated imaging, congenital heart disease, fetal heart, magnetic resonance imaging, motion correction

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Imaging plays a vital role in the diagnosis and treatment planning for fetal cardiac abnormalities discovered in utero. Ultrasound is the primary modality for evaluating the fetus due to its spatial and temporal resolutions, widespread availability, and ease-of-use. Nevertheless, there is a growing interest in the use of magnetic resonance imaging (MRI) as an adjunct diagnostic tool for the fetal heart, brain, lungs, liver, and other organs when ultrasound is limited by maternal obesity, oligohydramnios, multiple gestations, fetal diaphragmatic hernia, or fetal bone in late gestation.[1] Several studies have investigated the safety of fetal MRI with respect to peripheral nerve stimulation, acoustic noise, and energy deposition.[2] Overall, it has been concluded that MRI is a safe modality for the fetus when operated within standard limits (normal mode) and scan durations.[2] Moreover, studies have not demonstrate any adverse outcomes in children previously exposed to MRI during fetal development.[3]

From the [*]Department of Diagnostic and Interventional Radiology, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland; [†]School of Biomedical Engineering & Imaging Sciences, King's College London, London, UK; [‡]Division of Pediatric Cardiology, The Hospital for Sick Children, Toronto, Ontario, Canada; [§]Departments of Pediatrics and Diagnostic Imaging, University of Toronto, Toronto, Ontario, Canada; [||]Department of Medical Biophysics, University of Toronto, Toronto, Ontario, Canada; and [¶]Division of Translational Medicine, The Hospital for Sick Children, Toronto, Ontario, Canada.

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Address correspondence to Christopher K. Macgowan, PhD, Division of Translational Medicine, Room 08.9714, 686 Bay Street, Peter Gilgan Centre for Research & Learning, Hospital for Sick Children, Toronto, ON M5G 0A4, Canada (e-mail: christopher.macgowan@sickkids.ca).

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In the context of fetal cardiac imaging, several studies have focused on the development of methods for evaluating fetal cardiac anatomy, function, blood flow, and oximetry.

The purpose of this review is to describe technical developments that have led to the current state-of-the-art MRI methods for assessing the structure and function of the fetal heart. We outline the major challenges facing fetal cardiac MRI and describe advancements ranging from static 2-dimensional (2D) images using readily available sequences to time-resolved volumetric images of the fetal heart using advanced acquisition and reconstruction methods. We conclude with a discussion of the clinical impact of these techniques, although still investigational, and comparisons to the current gold standard of ultrasound.

CHALLENGES OF FETAL CARDIAC MRI

Several practical challenges exist when imaging the fetal heart with MRI. The size of major fetal vessels at full gestation is in the range of 5 to 10 mm in diameter, the width of the fetal ventricles is in the range of 10 to 30 mm,[4] the duration of the fetal cardiac cycle is between 330 and 540 ms with a systolic period between 20 and 50 ms,[5–7] and a relatively large field-of-view (260 to 480 mm) is required to avoid wrap-around artifact from maternal anatomy. Consequently, achieving clinically useful spatial and temporal resolution while maintaining a reasonable scan time is difficult with the conventional sequences available on most scanners. Managing the length of fetal MRI acquisitions is particularly important given the periodic motions (fetal respiratory movements, fetal cardiac motion, maternal respiration) and stochastic motions (gross fetal movement) that can degrade image quality.

In pediatric and adult patients, a combination of cardiac gating and breath-holding or respiratory navigation is used to maintain diagnostically useful image quality. Unfortunately, a fetal electrocardiogram (ECG) signal is not readily available in the MRI environment and maternal breath-holds are brief and ideally avoided to optimize maternal comfort. As a result, standard methods for dynamic imaging of the heart are not directly translatable to fetal subjects. Considering these limitations, early feasibility of fetal cardiac MRI was demonstrated in animals,[8–12] while human studies focused on fast 2D acquisitions as described in the following section.

STATIC IMAGING

Several groups have reported the use of single-shot balanced steady-state free precession (bSSFP) and fast spin echo sequences (HASTE, SS-FSE) to evaluate fetal cardiovascular anatomy and identify abnormalities.[13–20] These sequences are attractive because they provide relatively high resolution (~1.0 to 1.5 mm in-plane) static 2D images in short acquisition times ($\gtrsim$500 ms), allowing for multislice (ie, multiplanar) protocols. Although the temporal resolution of these early methods was too low to resolve fetal cardiac motion, resulting in anatomical blur of dynamic structures, static MRI remains useful for identifying gross anatomy and unusual extracardiac abnormalities that may affect the diagnosis of

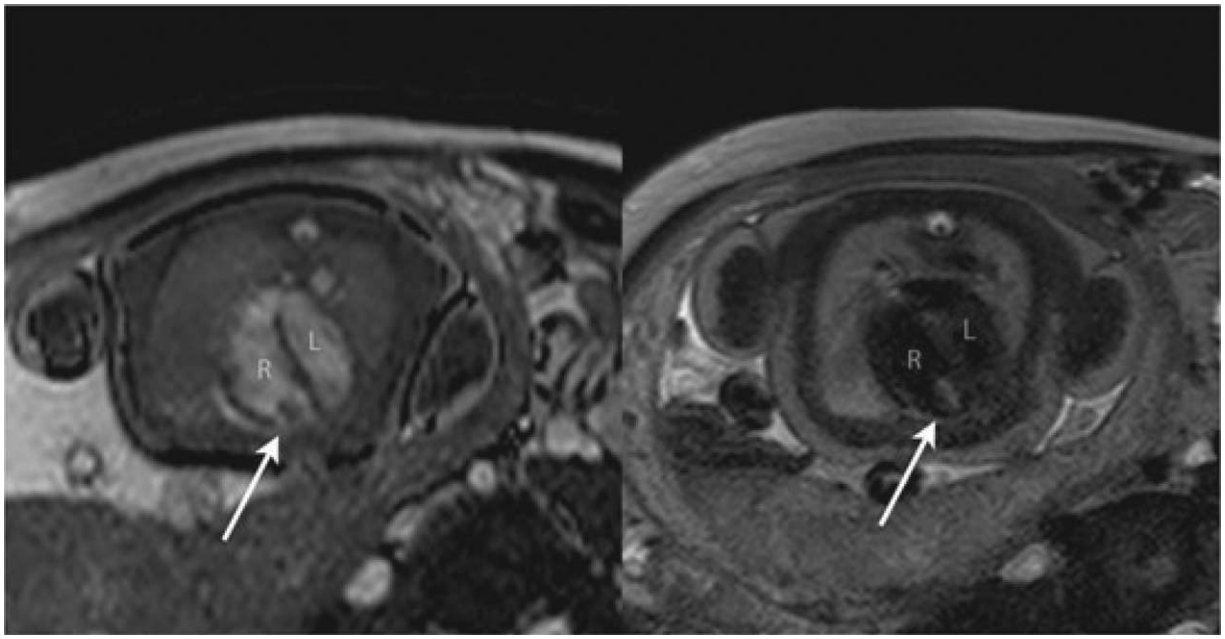

FIGURE 1. Static balanced steady-state free precession (bSSFP) bright-blood image (left) and single-shot fast spin-echo (ss-FSE) black-blood image (right) in a 38-week fetus with a right ventricular mass (arrowed). Reprinted with permission from Prenat Diagn 2016; 36:916–925 used under CC BY. Caption adapted from the original. Caption adapted from the original. Right (R) and left (L) heart sides are labelled.

cardiovascular malformations, such as persistent left superior vena cava or inferior vena caval interruption.[21] These strengths become more apparent in late gestation when greater fetal size facilitates static MRI, and when echocardiography is more challenging. For reference, Fig. 1 shows example SSFP and SS-FSE images of the fetal heart highlighting both bright-blood and black-blood strategies, respectively, which can be used to assess the fetal cardiac anatomy. In addition to the structural information provided by these sequences, the repeated acquisition of bSSFP images in the same anatomical location over time has been used to provide a dynamic ''real-time'' assessment of the fetal heart including measurements of cardiac function.[13,15,17,22–24] However, the spatiotemporal resolution of such real-time methods has historically been inadequate to resolve valvular functionality and to visualize the end-systolic phases of the fetal cardiac cycle, leading groups to focus instead on methods for CINE imaging.

CINE IMAGING

Time-resolved (CINE) bSSFP acquisitions are an integral facet of postnatal cardiac MRI examinations providing assessment of both cardiac structure and function. Using readily available sequences, high spatial and high temporal resolution images ($\sim 1 \times 1\,mm^2$, <50 ms) may be acquired by synchronizing the sequence to the patient's heart rate using an ECG signal (cardiac gating). Unfortunately, a fetal ECG signal is not available in the MRI environment precluding conventional CINE imaging of the fetal heart. Nevertheless, much work has been done to develop fetal CINE imaging using novel post-processing methods and external hardware devices for retrospective fetal cardiac gating.

FETAL CARDIAC GATING

Metric Optimized Gating

Metric optimized gating (MOG) extracts the fetal heart rate by iteratively reconstructing CINE images using a parameterized model of the cardiac cycle and then outputs the optimum image quality according to the minimized image entropy through time,[25] space,[26,27] or both.[28] While this method was first developed for time-resolved phase-contrast measurements of fetal blood flow,[25] it has since been applied to both Cartesian and radial bSSFP acquisitions and was the first method to demonstrate dynamic CINE MRI of the human fetal heart.[26] By independently parameterizing each fetal cardiac trigger, this model accounts for beat-to-beat fluctuations in fetal heart rate for subsequent CINE reconstruction. For Cartesian data without acceleration, the computational time needed for MOG is minor (eg, <5 minutes per slice using conventional desktop computing); however, for acquisitions with more complex reconstructions (ie, compressed sensing), the increased computational demand has led groups to explore alternative fetal gating methods based on intermediate real-time reconstructions, including an alternative formulation of MOG as described by the next section.

Self-gating

Self-gating refers to strategies that extract periodic gating signals from the MRI data itself. These signals can then be used to retrospectively sort the data into high-quality gated images.[29] Implementations of self-gating have used various k-space trajectories for data acquisition, including Cartesian, radial, and spiral trajectories, and also various metrics to detect the cardiac or respiratory cycles, including signal intensity modulation, center-of-mass tracking, and image correlation.[30] In the context of fetal MRI, self-gating has been used to extract the heart-rate from radial data using a principal component-based filtering of the repeatedly sampled k-space center.[31] Alternatively, self-gating signals have been extracted from intermediate real-time reconstructions of radial data by measuring the correlation between frames[32] or applying MOG to the real-time images, with compressed sensing reconstruction of each real-time image series requiring approximately 120 minutes per slice using conventional desktop computing.[33] Potential challenges of non-Cartesian sampling include nonuniform clustering of data after

temporal sorting, k-space trajectory errors, and off-resonance artifact (these latter issues being fairly benign for in utero radial imaging at 1.5T).[34,35] In addition, fetal heart rates have been estimated directly from the temporal frequency spectrum of Cartesian real-time images, that is, the temporal Fourier transform of the image series, as the periodicity of the beating fetal heart appears as a local maximum in the spectrum within the range of expected heart rates.[36]

Hardware

Dramatic advances in fetal cardiovascular MRI have been demonstrated using the tailored acquisition and reconstruction methods described above. These methods, however, have limitations including relatively long reconstruction times that currently prevent evaluation of images during the MRI examination.

To address these limitations, researchers are developing novel external hardware to monitor the fetal cardiac cycle during MRI data acquisition. The most mature device for this purpose uses an MR-compatible Doppler Ultrasound Gating (DUS) probe placed over the maternal abdomen.[37,38] This nonimaging device monitors motions associated with the fetal cardiac cycle, such as blood flow and cardiac contraction, based on a Doppler waveform. Triggers derived from this waveform are supplied to the MRI scanner to synchronize data acquisition. A practical benefit of this approach is the ability to use established cardiovascular protocols for fetal imaging, which provide immediate in-line image reconstructions to support clinical workflow.[39] Such devices may also facilitate studies that require prospective triggering, for example, in applications such as triggered T1 or T2 mapping.[40] Drawbacks to this approach, as with any external device, include patient preparation time and equipment procurement. Furthermore, monitoring the fetal position to ensure it lays within the detection range will likely require pairing such devices with appropriate acquisition schemes, resulting in more elaborate and slower reconstructions.

ACCELERATED CINE IMAGING

With the advent of methods for fetal cardiac gating, CINE imaging of the fetal heart is possible. However, the increased scan time of CINE acquisitions relative to their static 2D counterparts, and the various sources of motion that can occur during the scan, necessitates methods for accelerating fetal acquisitions. Conventional parallel imaging methods are available on most scanners and have been used for fetal cardiac imaging, albeit with modest acceleration factors due to the often poor coil coverage of the fetus within the large maternal abdomen.[26] Conversely, multiple studies have investigated the use of compressed sensing to achieve highly accelerated fetal acquisitions using either Cartesian[27,41] or radial sequences.[31–33] Both compressed sensing and k-t SENSE[36] have been used to reconstruct real-time images with greater spatial and temporal resolution than those described in the static imaging section; however, these were primarily used for motion estimation and correction, before CINE reconstruction. Table 1 summarizes different implementations of fetal CINE MRI from the literature, recognizing that exact comparisons between methods are difficult because actual spatial and temporal resolutions depend on factors such as regularization, motion correction, volumetric reconstruction approach, and gating accuracy, while some publications may also quote effective (interpolated) resolutions.

MOTION COMPENSATION

To prevent artifact from maternal respiration, studies have acquired 2D fetal MRI data under maternal breathhold, but this can be challenging for pregnant subjects and limits the number of slices that can be acquired consecutively.[31,32] Alternatively, free-breathing methods have been developed using motion correction to suppress artifact from both maternal respiration and gross fetal movement, thereby enabling multislice acquisitions covering the whole fetal heart in multiple orientations.[33,42]

Such motion compensation is achieved using real-time 2D imaging to estimate motion parameters that inform higher resolution CINE reconstructions from the same data. Examples of real-time fetal imaging, with increasing levels of motion, are shown in Fig. 2. From such real-time image series, in-plane motion ($D_{x,y}$ in Fig. 2) may be tracked and corrected. Conversely, through-plane motion results in mixing of anatomical information from adjacent structures, producing image degradation if combined blindly. It is thus important to identify periods of through-plane motion and discard data acquired during those periods. As shown in Fig. 2I, real-time images can also be used for manual or semi-automatic detection and rejection of data acquired during periods of through-plane motion associated with fetal motion or maternal respiration.[32,33] Figure 3 provides an example of multislice CINE imaging of the fetal heart using such a motion-robust acquisition and reconstruction.

More recently, fully automated methods have been implemented to identify periods of motion during fetal cardiac MRI,[36,42] leveraging statistical outlier-rejection methods previously established for fetal brain volumetric reconstruction.[43,44] Outlier rejection reduces the impact of inconsistent data during reconstruction, resulting in reduced artifact and sharper images. This automated

TABLE 1. Comparison of CINE MRI Methods Applied to the Human Fetal Heart

Reference	GA Range, wks	Field, T	Trajectory	Spatial Res, mm	Temporal Res, ms	Gating Method	Motion Correction	Outlier Rejection
Roy et al[26]	[35–37] (N = 2)	1.5	Cartesian	1.5 × 1.5 × 4.0	50	MOG	None	None
Roy et al[33]	[34–38] (N = 7)	1.5	Radial	1.0 × 1.0 × 4.0	12–15	MOG	2D rigid (k-space)	Semi-automatic
Haris et al[31]	[29–37] (N = 5)	1.5	Radial	1.4 × 1.4 × 4.0	56	SG k-t	None	None
Kording et al[37]	[30–37] (N = 15)	1.5 and 3.0	Cartesian	1.0 × 1.0 × 5.0	30	DUS	None	None
Chaptinel et al[32]	[26–32] (N = 6)	1.5	Radial	1.0 × 1.0 × 4.0	25	SG x-t	None	None
van Amerom et al[36]	[25–35] (N = 30)	1.5	Cartesian	2.0 × 2.0 × 2.0	72-83	SG x-f	2D rigid (image-space)	Automatic
van Amerom et al[42]	[25–33] (N = 20)	1.5	Cartesian	2.0 × 2.0 × 2.0	64-76	SG x-f (2D) SG x-t (3D)	3D rigid (image space)	Automatic

Note: All studies performed using a balance steady-state free precession (bSSFP) sequence.

DUS indicates Doppler ultrasound gating; GA, gestation age; MOG, metric optimized gating; SG, self-gating based on k-space versus time (k-t), images versus time (x-t), or image temporal frequency (x-f).

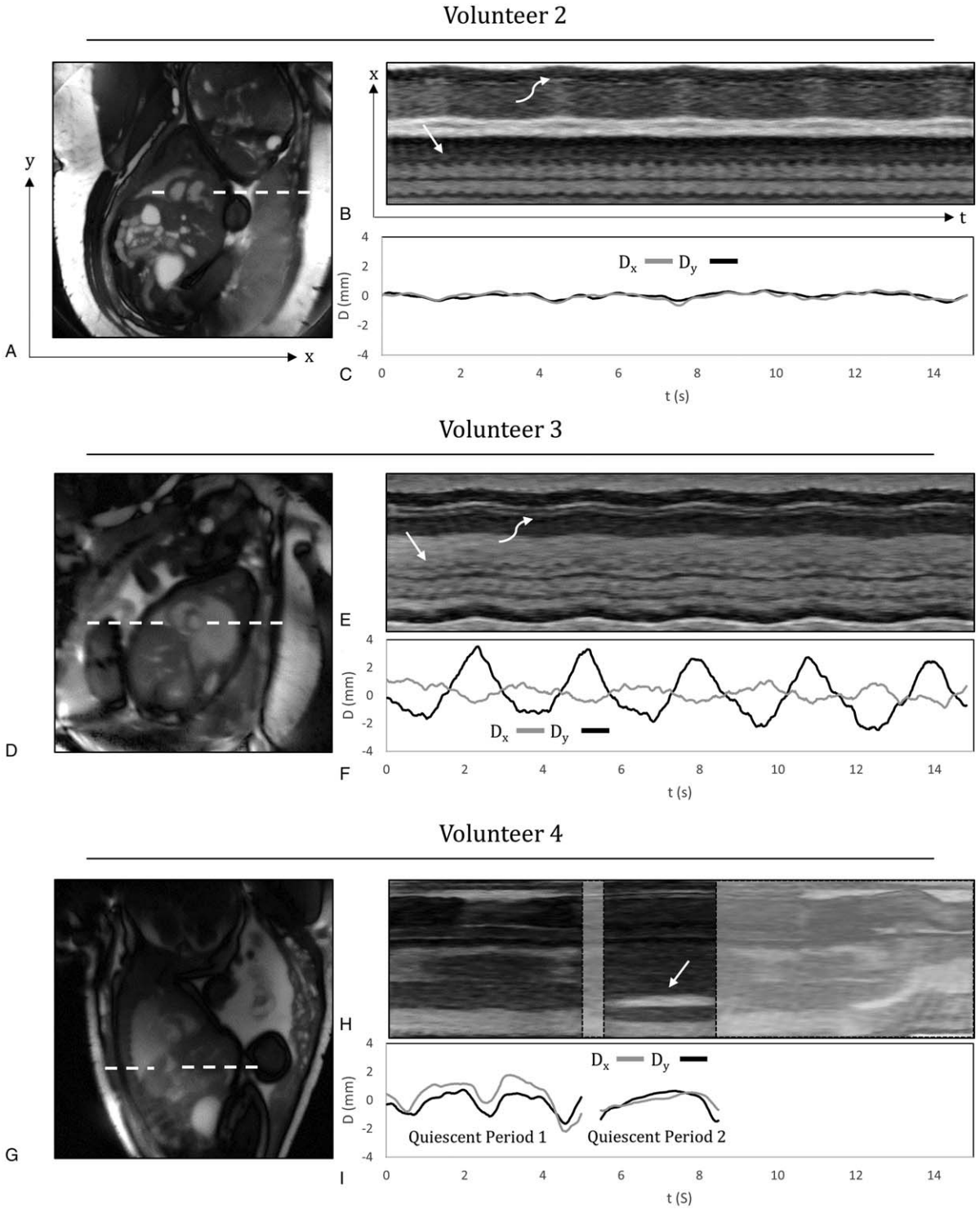

FIGURE 2. Real-time reconstructions of the fetal heart for 3 volunteers with increasing levels of motion. Time-averaged images of the heart and surrounding anatomy (A, D, G), M-mode displays of signal along the white dashed lines (B, E, H), and plots of displacement ($D_{x,y}$) versus time (C, F, I), calculated from the real-time reconstructions over a region of interest containing the heart. D_x and D_y represent the horizontal and vertical components of displacement, respectively. For volunteers 2 and 3, the M-modes show fetal cardiac motion (straight arrow) and maternal respiratory motion (curved arrow). For volunteer 4, the M-mode display shows the fetal stomach (straight arrow), which is used to identify through-plane motion. Reprinted with permission from J Cardiovasc Magn Reson 2017; 19:29 used under CC BY. Caption adapted from the original.

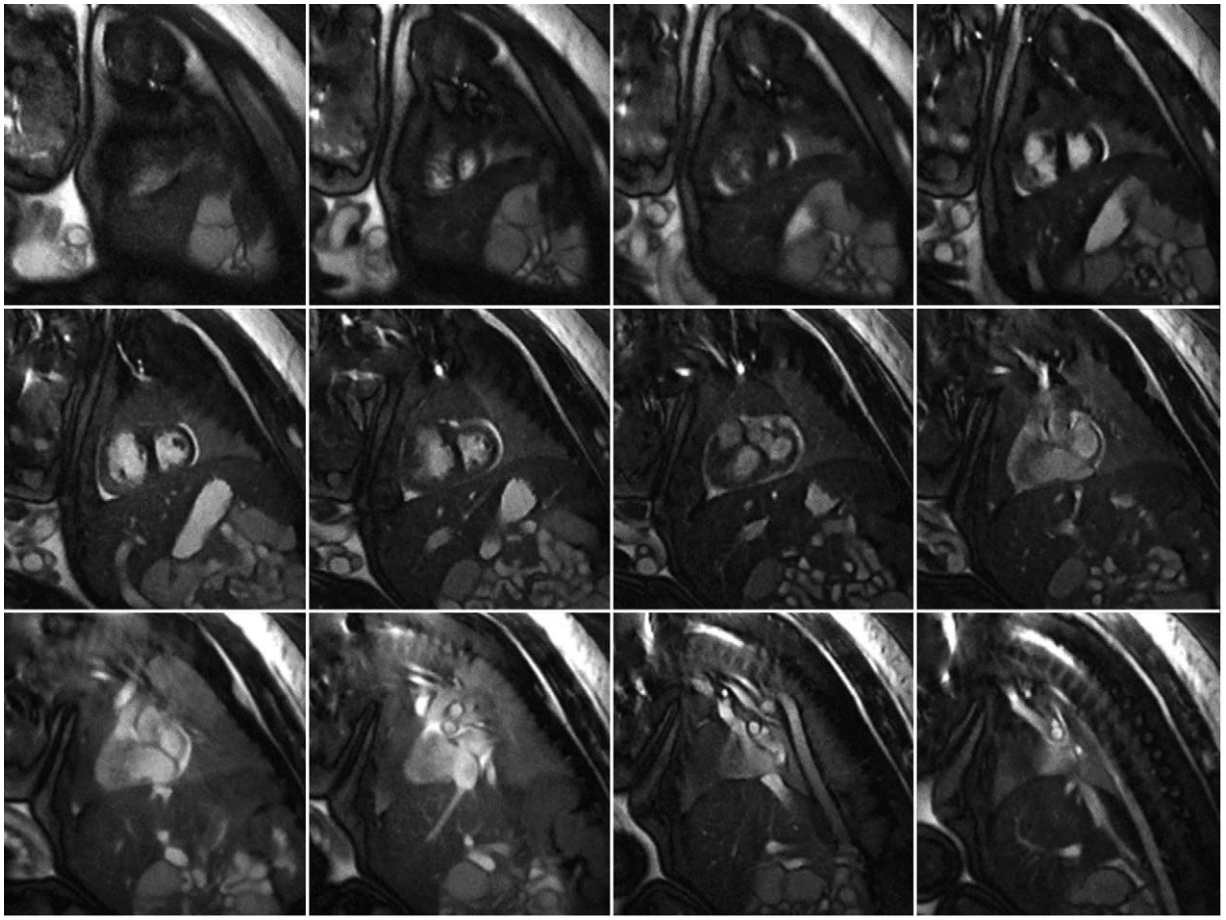

FIGURE 3. Motion-corrected CINE short axis images of the fetal heart using the radial acquisition and reconstruction framework described in J Cardiovasc Magn Reson 2017; 19:29 by Roy et al.[33]

approach estimates the probability of each voxel and real-time image frame being classified as either an inlier or an outlier, and then the probabilities are used to downweight or completely reject outlier voxels and frames from the final CINE reconstruction. As mentioned, these approaches have previously enabled volumetric reconstruction of the fetal brain from multiple 2D static images, and recently, these approaches have been adapted to dynamic, volumetric MRI of the fetal heart.

VOLUMETRIC RECONSTRUCTION

The majority of fetal cardiac MRI is done using fast 2D acquisitions to minimize the impact of fetal and maternal motion. However, the underlying fetal anatomy is 3-dimensional and would be best represented as volumetric data to aid interpretation and assessment. Unfortunately, 3D MR data sets require several seconds to acquire and, consequently, are likely to be corrupted by motion and cardiac pulsation. An inventive solution to this problem is to use a multiplanar acquisition and combine the 2D images using volumetric reconstruction methods.

Volumetric reconstruction of 2D fetal MRI was first demonstrated for fetal brain imaging[43–46] and subsequently applied to the fetal body[47] as well as the placenta.[48] These techniques use scattered data interpolation to achieve volumetric reconstructions from multiplanar 2D SS-FSE MR images. Initial implementations interleaved interpolation with motion correction to generate 3D data, using either cubic B-spline[45] or Gaussian kernel-based[46] interpolation. Subsequently, an error minimization (super-resolution) approach was introduced to reduce the blurring effect from thick-slice MR images when using Gaussian kernel-based interpolation[43] and outlier rejection was employed to reduce the impact of voxels corrupted by motion and images misaligned to the volume,[43,44] removing the need for manual exclusion of inconsistent data. Signal intensity-matching was also added to increase data consistency leading to improved volumetric reconstructions.[44,49]

Methods for volumetric reconstruction of the fetal heart have now been developed for both static (3D) visualization of the fetal heart and extracardiac vasculature[50] as well as CINE (4D) whole-heart visualization.[42] Volumetric reconstruction from 2D MRI has several characteristics that are advantageous for fetal cardiac imaging. First, the acquisition of multiplanar 2D MRI for volumetric reconstruction is robust to motion and does not require highly specific scan plane prescriptions to capture the desired anatomical features, which can be a challenge in 2D single-slice MRI. Second, both in-plane and through-plane motion can be corrected. Lastly, the reconstructed data can provide full coverage of the entire fetal heart, allowing for comprehensive assessment of fetal cardiovascular anatomy.

Figure 4 shows an example of the motion-corrected 3D volumetric reconstruction framework, originally used for fetal brain MRI,[44] adapted to T2-weighted SS-FSE MR images of the fetal heart. Blood flowing through the cardiovascular system has a

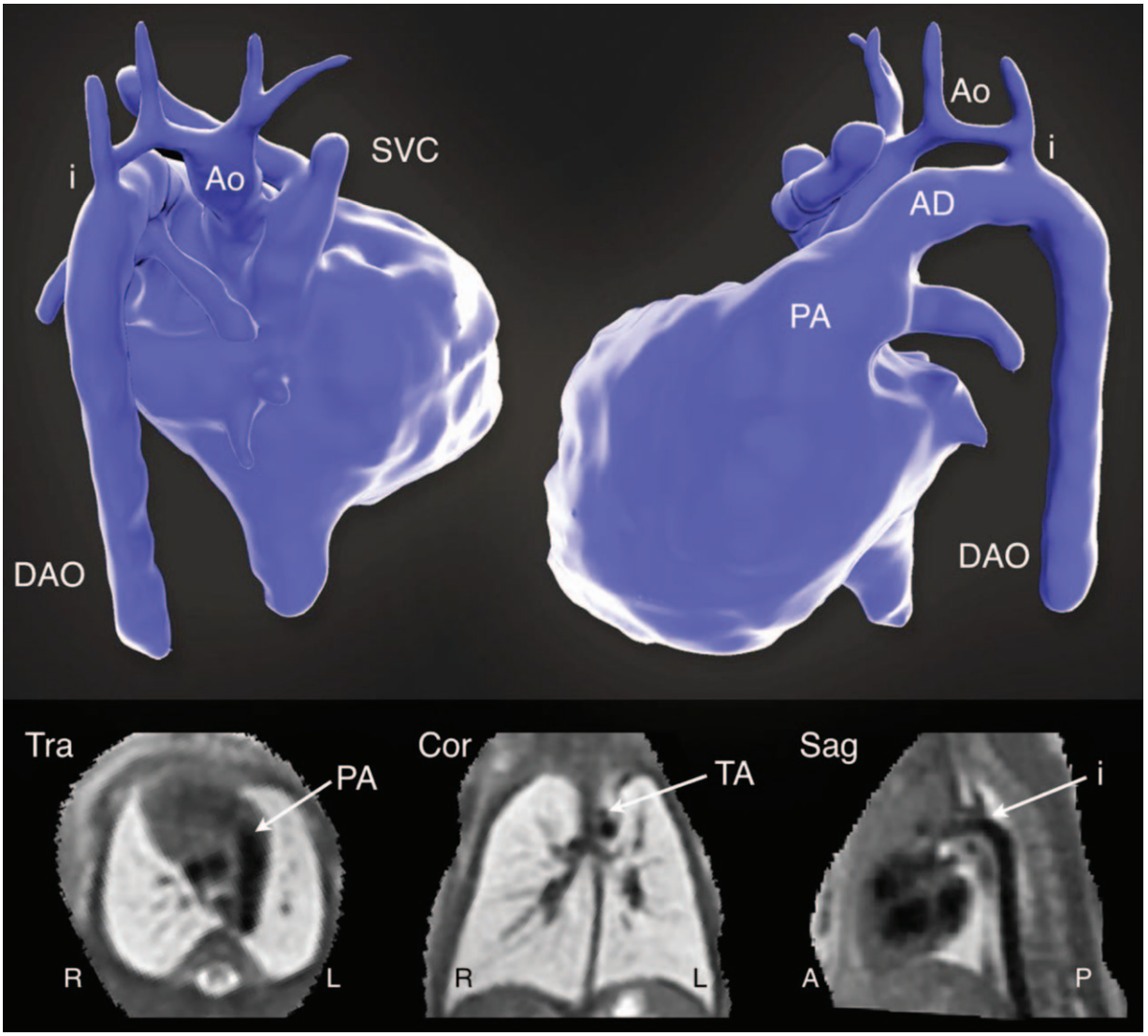

FIGURE 4. Volumetric reconstruction of T2-weighted multiplanar single shot fast spin echo (ss-FSE) MRI in a 33-week gestational age fetus with coarctation of the aorta. A volume rendering of the blood pool is shown in posterior projection (top left) and left lateral projection (top right). The bottom panel shows planes from the volumetric reconstructed data in transverse (Tra), coronal (Cor), and sagittal (Sag) orientations. The aorta (Ao), arterial duct (AD), descending aorta (DAo), aortic isthmus (i), pulmonary artery (PA), transverse arch (TA), and superior vena cava (SVC) are labeled. Reprinted with permission from Lancet 2019; 393:1619–1627 used under CC BY.

hypointense signal in the SS-FSE images and the extracardiac vasculature is well defined. Such 3D reconstructions allow for detailed depiction of cardiovascular anatomy, particularly the aortic arch and pulmonary vessels, with improved diagnostic quality compared with uncorrected 2D SS-FSE.[50] However, due to the signal characteristics of SS-FSE and the long acquisition time relative to the cardiac cycle (~500 to 1000 ms), the heart and the roots of the great vessels appear as a nearly homogeneous signal region with little definition of intracardiac features in both the acquired 2D images and, consequently, the static 3D reconstruction.

Figure 5 shows an example 4D reconstruction of a healthy fetal heart, acquired using real-time bSSFP instead of SS-FSE, showing the great vessels as well as intracardiac anatomy. These data could be resliced in any 2D plane or cardiac phase, allowing for optimal anatomical views and facilitating understanding of the spatial relationships of cardiovascular structures. This 4D reconstruction framework[42] combines the motion-tolerant, image-domain 2D fetal cardiac CINE technique[36] with a 3D volumetric reconstruction technique,[44] and adds a temporal component to the volumetric reconstruction to generate dynamic volumes.

CLINICAL UTILITY AND COMPARISON TO ULTRASOUND

The technical advancements in fetal cardiac MRI described in this review provide new opportunities for evaluating high-risk pregnancies. Recent studies have explored the clinical utility of

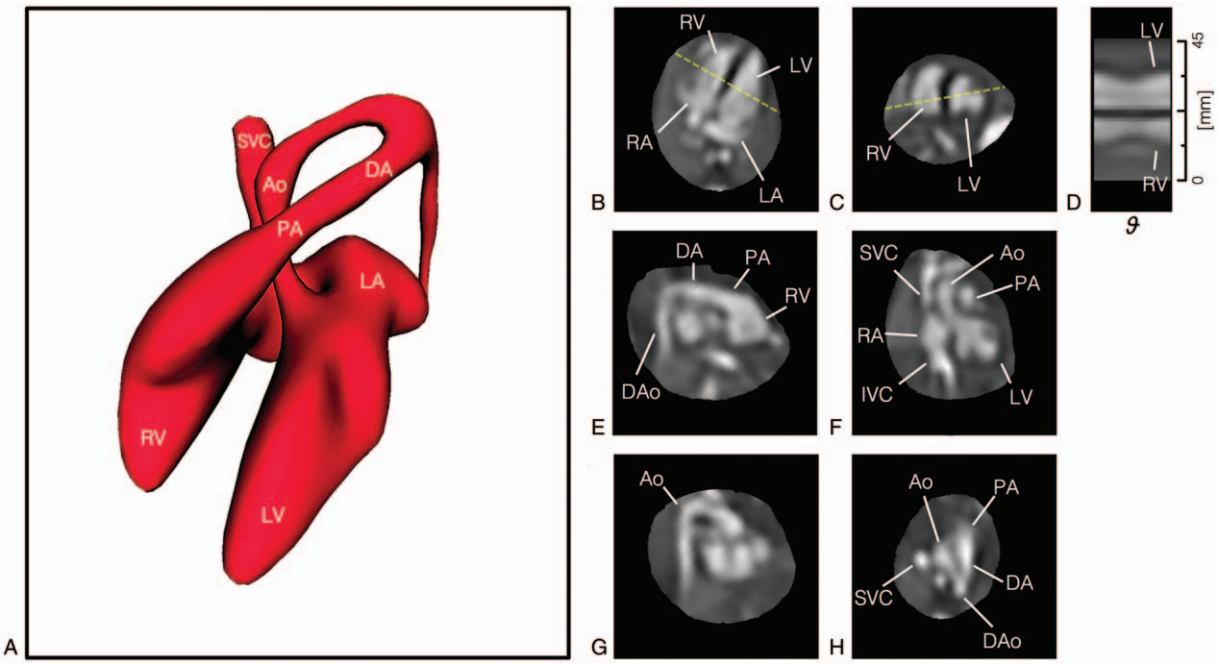

FIGURE 5. 4D CINE volumetric reconstruction of the heart of a healthy 28-week gestational age fetus from multi-planar real-time balanced steady-state free precession (bSSFP) MRI. (A) Volume rendering of blood pool in diastole showing arrangement and connections of chambers and vessels, for reference. The reconstructed 4D data are shown resliced in (B) 4-chamber, (C) mid-short axis, (E) right ventricular outflow tract, (F) left ventricular outflow tract, (G) aortic arch, and (H) 3-vessel views. (D) A line profile at the intersection of the 4-chamber and mid-short axis views (dashed yellow lines) shows the contraction and dilation of the ventricles with cardiac phase (ϑ). Ventriculoarterial connections can be seen in outflow tract views with the pulmonary artery (PA) from the right ventricle (RV) in (E) and the aorta (Ao) arising from the left ventricle (LV) in (F). Systemic venous connections of the superior (SVC) and inferior (IVC) vena cava with the right atrium (RA) can also be seen in (F). The ductal arch (DA) can be seen in both (E) and (H), connecting the PA to the descending aorta (DAo), while the Ao arch can be seen in (G) and (H). All boxes bounding the resliced views measure 65 × 65 mm. The fetal heart is shown in radiological orientation, that is, image axes up and right relative to the page correspond to left, anterior, and/or superior anatomical directions. Views are shown using spatial B-spline interpolation to avoid voxel distortion. Reprinted with permission from Magn Reson Med 2019; 82:1055–1072 used under CC BY.

these methods for detecting and characterizing fetal cardiac abnormalities, and compared their performance against ultrasound, the primary fetal imaging modality.[32,42,50,51] For example, a recent MRI study of fetal CHD investigated motion-corrected volumetric reconstructions (see Fig. 4) of fetal cardiovascular anatomy and found good spatial agreement between these static reconstructions and ultrasound (intraclass correlation coefficient 0.78).[50] Moreover, volumetric visualizations were of significantly higher diagnostic quality than the individual 2D MRI data used to generate the volumes. Dynamic fetal cardiac MRI studies have shown similarly good agreement[32,39,42,51] (Fig. 6) and have proved useful for evaluating specific abnormalities as evidenced by case studies of a cardiac mass[42,52] and an unbalanced common atrioventricular canal.[53] In an evaluation of the utility of 4D volumetric reconstruction,[42] readers had high confidence in their comprehensive assessment of fetal cardiovascular anatomy using reconstructed 4D cine MRI (Fig. 5) and there was good agreement between ventricular dimensions at systole and diastole on 2D M-mode ultrasound and 4D MRI.

In parallel with these MRI studies of fetal cardiovascular anatomy, groups have also demonstrated and validated MRI techniques for quantifying fetal blood flow,[28,54,55] oxygenation,[56–58] and hematocrit[59] noninvasively. These techniques have subsequently been combined to study the impact of pathology on fetal development including the effect of CHD[60] and intrauterine growth restriction[61] on fetal brain development. Specific CHD cohorts that have been investigated using these techniques include fetal left-sided heart disease[62] and transposition of the great arteries.[63,64]

CONCLUSION

Over the last 15 years, fetal cardiac MRI has transformed from static, single-shot imaging into multi-dimensional, motion-tolerant, and high-resolution dynamic imaging of the fetal heart and surrounding vasculature. This information, combined with MRI measurements of fetal physiology, promises to improve our understanding of fetal development and the impact of disease. As such, these methods are a promising adjunct to fetal echocardiography, but challenges remain—especially when imaging small and mobile fetuses at earlier gestation, which require even higher spatial and temporal resolutions with improved motion compensation. Nevertheless, the field of fetal cardiovascular MRI is advancing quickly, and it will be exciting to witness its capabilities grow over the next 15 years.

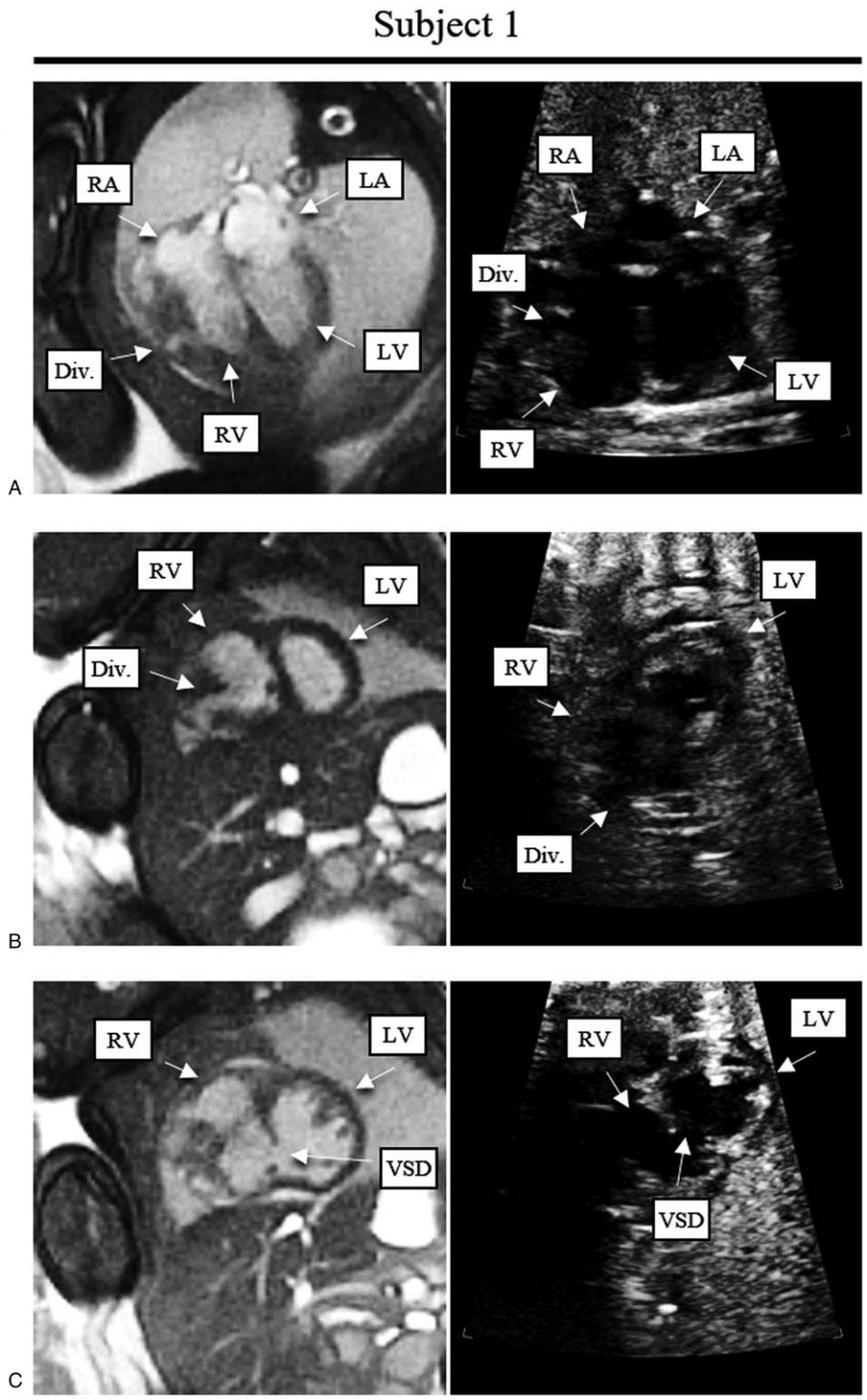

FIGURE 6. A 36-week fetus with a septal defect and diverticulum. Fetal cardiac MRI (left) and echocardiography (right) images demonstrate a diverticulum (Div.) attached to the right ventricle (RV) in long-axis (A) and short-axis views (B), and an interruption of the myocardium indicates a ventricular septal defect (VSD) in a short-axis view (C). Reprinted with permission from Circ Cardiovasc Imaging 2018; 11:e007745 used under CC BY.

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