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Appendix E1. Reconstruction

For this study, $\lambda_c = 0.0075$, $\lambda_r = 0.005$, and $\lambda_\sigma = 0.0015$ were used for all reconstructions. Reconstructions were performed offline in MatLab R2016b (The MathWorks, Natick Mass) (25,26). These weights were empirically determined on the basis of previous studies in compressed sensing-accelerated four-dimensional (4D) flow MRI and five-dimensional (5D) MRI (27,13,21). Workstation specifications were as follows: Tesla Xeon E5–2600 V2 256 gigabyte memory (Intel, Santa Clara, Calif) equipped with Matlab (R2016b, The MathWorks) running on Windows 7 (Microsoft, Redmond, Wash).

Appendix E2. Adult Cohort

Fourteen participants had bicuspid aortic valve disease, three had ascending aortic aneurysm without bicuspid aortic valve disease, two had a mechanical aortic valve, and two had a history of a cerebrovascular accident. All 21 participants received 0.2 mmol/kg of Gadobutrol (Gadavist, Bayer) or Gadoterate Meglumine (Dotarem, Guerbet) contrast material as part of their imaging protocol. Of 21 enrolled adult participants, one participant with bicuspid aortic valve disease was fully excluded because they were unable to finish the imaging protocol. In addition, part of the clinical 4D flow of the posterior ascending aorta (AAo) was cut off for one participant and two participants with mechanical valves had signal loss in the AAo. For respiratory analysis, the distal inferior vena cava (IVC) was partially cut off in two participants, because of its location at the edge of the field of view, and peak velocity in one participant could not be accurately determined because of noisy data and streaking. Thus, 18 participant datasets were used in the Root, AAo1, and AAo2 planar analysis, and 18 datasets were used for IVC peak velocity and IVC1 and IVC2 planar analyses, and 19 datasets were used for superior vena cava (SVC) peak velocity analyses. Twenty participants' values were used for all the other analysis locations. 5D flow MRI was performed before 4D flow MRI, when possible (18 of 21 examinations). However, perhaps more importantly, these long phase-contrast examinations (4D and 5D) were not performed until the end of the imaging session, 10–30 minutes after initial contrast material injection.

Appendix E3. Extended Discussion

We have demonstrated that (1) fully self-gated free-running 5D flow MRI shows good to excellent agreement with conventional 4D flow in a pulsatile in vitro aortic phantom; (2) 5D flow can capture whole-heart respiratory-motion effects on cardiovascular hemodynamics in less than 8 minutes.

In vitro experiments validated 5D flow imaging gradients and the reconstruction pipeline and demonstrated good agreement of the 5D flow reconstructions (<7% in all planes) with conventional 4D flow in net flow, peak flow, and peak velocity. Larger deviations from conventional 4D flow tended to be concentrated at the edges of the field of view, potentiallybecause of uncorrected background phase effects. Radial techniques are known to have less-predictable eddy currents and background phase, and thus this was extensively investigated prior to analysis of all datasets (Figs E1, E2). While prior 4D flow studies have

primarily used slice-by-slice two-dimensional (2D) background phase correction, background phase correction analyses demonstrated that a first-order fit is inadequate for radial data, and thus a second-order fit was used to correct and minimize overfitting.

In vivo experiments demonstrated the potential of 5D flow to resolve respiration-dependent changes in hemodynamics. While the aortic cohort may not be ideal for respiratory-induced investigations, these participants were the only ones getting standard-of-care 4D flow at our institution, and thus were chosen for clinical workflow evaluation. The in vivo protocol was created to fit within the clinical workflow (approximately 8 minutes), and showed moderate agreement with the standard-of-care aortic 4D flow, which was on average 2 minutes longer, had much less coverage of the heart, had less predictable imaging times, and was more dependent on technologist placement—one participant was excluded because 4D flow data did not cover the majority of the arch and proximal descending aorta (Dao). 5D flow tended to overestimate flows and velocities in the AAo, and significantly underestimated values in the arch and descending aorta compared with conventional 4D flow. Overestimation in the AAo may have been caused by background phase by the radial trajectory that could not be adequately corrected. However, this effect was not observed in vitro, and thus physiologic effects captured by the 3D radial technique, which traverses the center of the k-space with each line, but not by Cartesian imaging, cannot be ruled out. Prior studies of highly accelerated imaging have found that temporal undersampling and regularization often lead to blunted peak velocities and flows, potentially accounting for some 5D flow underestimation (22,27). While this initial study extensively evaluated potential background phase correction using static tissue and 3D polynomial fitting (Fig E3), variations of the radial trajectory have not yet been explored. In addition, 4D and 5D flow demonstrated good agreement with clinically derived stroke volume with moderate variability among participants. Increased variability in 5D flow may be related to inadequate acquisition lengths for patients with bradycardia, as well as variable times after contrast injection. These results suggest the need for further investigation of 4D and 5D flow comparisons to clinical stroke volume.

A number of previous studies have investigated the use of self-gating techniques for respiratory-resolved hemodynamics (6–8,10–12,28–30). Bastkowski et al (10) investigated a stack of spirals technique for assessment of respiratory-resolved hemodynamics in with Fontan circulation (mean age, 19.7 years ± 7.5), and 10 healthy volunteers (mean age, 25.1 years ± 4.4). Bastkowski was able to show increased respiration dependency of caval blood flow in patients who underwent the Fontan procedure compared with volunteers, with an average imaging time of 15:00–16:05 minutes (current study, 7:39 minutes ± 0:21) using a self-gated stack of spirals 5D flow sequence and CG sensitivity-encoding reconstruction (31). However, CG sensitivity encoding is a relatively old reconstruction technique compared with compressed sensing, likely limiting acceleration rates and failing to take full advantage of dimensionality in the reconstruction. Schrauben et al (12) proposed a free-running 3D radial technique for assessment of respiratory-resolved hemodynamics in 20 patients with congenital heart disease. However, this required averaging of the cardiac dimension and reconstruction of only two respiratory bins (current study, four bins) for preservation of undersampled data fidelity. Walheim et al (8) investigated a free-running 5D flow technique with seven-point velocity encoding and local low-rank image reconstruction for cardiac- and respiratory-motion–resolved assessment of velocities and turbulent kinetic energy in the aorta in 4 minutes. Walheim used a pseudo-radial Cartesian sampling pattern, respiratory self-gating, and found that local low-rank compressed sensing reconstruction resulted in fewer artifacts than a reconstruction penalizing tricuspid valve (current

study). Given the improved results using local low-rank compared with tricuspid valve in volunteers, future studies of the proposed technique may benefit from the incorporation of local low-rank into the compressed sensing reconstruction. However, Walheim's study was limited to young, uncomplicated healthy volunteers. Furthermore, his study did not include a description of how a 3D Cartesian sampling pattern was chosen for each patient.

Unlike in 3D radial coordinate systems, Walheim's and Bastkowski's Cartesian and stack-of-spirals sampling, respectively, require a predefined sampling pattern for each slice (kz). Thus, even if the acquisition is "free-running," the sampling trajectory must be predefined and somewhat optimized on the basis of each participant's estimated heartrates and breathing frequency. Of course, other sampling techniques have their inherent benefits as well. Spiral sampling is one of the most efficient ways to sample k-space, especially compared with the somewhat inefficient repetitive sampling of center k-space in 3D radial imaging. However, spiral and cartesian sampling are also more sensitive to motion and flow artifacts, and thus various sampling patterns are worth exploring in different forms of fixed imaging time protocols.

The "cubic" nature of 3D radial imaging, while not ideal for all applications, is well suited to whole-heart imaging. One participant in this study had to have his Cartesian clinical 4D flow data excluded because of insufficient acquisition of the 4D flow volume. This occurred because the experienced technical operator did not cover the right number of slices over the thoracic aorta out of a desire to decrease imaging time, coupled with slight participant movement after the acquisition of the planning localizers. Even when the 5D flow, 3D radial volume was slightly off center, or the participant moved slightly in the scanner, the 5D flow volume was able to effectively cover the entire heart in all participants.

Respiratory-resolved analyses suggested increased peak velocity and net flow in the SVC and decreased peak and net flow in the IVC at end inspiration. While the influence of respiration on cardiopulmonary flow has been investigated for decades, the exact relationship is still unclear (1,23,24). The varying effects of respiration reported in the current study and among previous studies suggest that studies with more respiratory bins are warranted. Future studies may also benefit from 2D real-time phase contrast comparisons, which cannot alone capture 3D hemodynamics, but may provide additional insight in combination with deep breathing maneuvers. In addition, future participant recruitment will focus on individuals with physiologic characteristics that may benefit from further respiratory investigation (patients who underwent the Fontan procedure and those with cardiac shunts) (1,10,32).

A main limitation of this study was the number of participants relative to the variety of diseases. In addition, a contrast-enhanced protocol was used in this study, but the time between contrast material injection could not always be optimized to the same time window on the basis of the clinical speed and work flow. 5D flow examinations were performed immediately before 4D flow examinations in 18 of 21 participants, but 10–30 minutes after contrast material injection because of the unpredictable clinical workflow. Moreover, while the current study investigated aortic valve participants with a wide range of ages and diseases, these also contributed to the wide range of standard deviations and variable data quality. Patients with bicuspid aortic valve diseasein particular, can present with anywhere from normal aortic valve function, where a velocity encoding of 150 cm/sec is sufficient, to severe aortic stenosis requiring a velocity encoding of 400+ cm/s. The same number of radial views were acquired for all participants, but depending on the heartrate, or time between gadolinium contrast injection and 5D flow scanning (which was as long as 30 minutes in some of the more difficult, clinical

participants), longer scan times and a noncontrast flip angle (approximately 7°) likely would have contributed to higher signal-to-noise ratios and data fidelity in some participants. Reconstruction times were also long, at 8–15 hours. However, as hardware and reconstruction techniques rapidly improve, these times should be reduced accordingly. In addition, 5D and 4D comparisons in both aortic and caval or pulmonary systems would have been ideal. However, the Cartesian 4D flow sequence was limited in coverage based on clinical workflow timing.

Future studies should include increased participant recruitment, different radial imaging trajectories, contrast investigation, a deep-breathing phantom and a protocol for emphasis of respiration-driven effects, and potential exploration of additional or reduced dimensionality (30). It also may be worth investigating patients with arrhythmias using this framework for more efficient methods of arrhythmia rejection, although the range of physiologic cardiac frequencies may have to be adjusted, depending the extent of arrhythmia. In addition, analysis times of 4D flow data took approximately 30 minutes, whereas for 5D flow, they took up to 2 hours. In addition, this workflow was nonoptimized but allowed complete control over all processing steps. Moreover, 4D flow data only required a single segmentation, while 5D flow caval veins were segmented for all four respiratory phases (and an end-expiratory aorta). This study did not focus on optimizing data postprocessing, however, future studies can use a streamlined, dedicated 4D flow software that is provided by an increasing number of vendors.

In summary, we have successfully implemented and applied a fully self-gated free-running 5D flow MRI framework for acquisition and evaluation of cardiac and respiratory motion-resolved 3D hemodynamics in less than 8 minutes. While this technique requires further exploration of differences from conventional 4D flow, 5D flow is a promising starting point for a variety of applications and easy-to-operate protocols.

Materials and Methods

Background Phase Information

Although a flow-off subtraction of pulsatile phantom Cartesian data would have provided a closer to “ground truth” background correction, this was unfortunately not performed during the imaging session.

Prior studies have found that higher-order polynomial fitting (above first order) tends to work well for phantoms, but less well for in vivo studies (26).

Thus, for our Cartesian examinations, for in vitro experiments, we used the best possible background correction (higher, second order, 3D), and for in vivo, we used what has been conventionally used more often (2D, slice-by-slice, first order). This was also because the clinical workflow uses a first-order 2D correction for 4D flow preprocessing, and since the majority of our patients were receiving clinically-indicated 4D flow, this was used for their clinical examinations. Moreover, Cartesian 4D flow background correction has been more extensively studied, and the methods used follow most correction guidelines (27). First-order correction is generally used in vivo to prevent overfitting of the polynomial for background phase correction.

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Table E1: In vivo conventional 4D flow and 5D flow imaging parameters

Parameter	Conventional 4D Flow	5D Flow
R	2	40.8–76.9
Scan time (sec)	9:53 ± 3:10 (4:44 to 17:17 min)	7:39 ± 0:21 (7:11 to 8:56 min)
Echo time (msec)	2.1–2.3	2.6–3.11
Repetition time	4.8–5.1	4.3–4.9
Acceleration rate (R)	2	36.0–76.9
Temporal resolution (msec)	38.2–40.6	35.1–48.4 (34.3–39.1)
Bandwidth	455	600
Flip angle (degrees)	15	15
Interpolated voxel size (mm^3)	2.4–2.6 × 2.4–2.6 × 2.4–2.9	2.3–2.4 × 2.3–2.5 × 2.3–2.5
acquired matrix size	160 × 80 × 20–22	96 × 96 × 96
Field of view (mm^3)	380–400 × 285–315 × 72–90	220–240 × 220–240 × 220–240
Venc (cm/sec)	150–400	150–400
Reconstructed cardiac phases	30	15–32
Navigator acceptance window (mm)	8	NA
Slab orientation	Sagittal Oblique	Transverse
Average nominal interval (ms)	951 ± 194 (601–1356)	951 ± 194 (601–1356)

Note.—5D flow nominal acceleration rates are based on Nyquist criteria for 3D radial imaging. Nominal and acquired resolutions differ due to trigger time stamp normalization. Acquired time stamps are thus in parentheses

(repetition time × 8). Acceleration rates were derived on the basis of Nyquist criteria for 3D radial sampling and the number of radial views per binned volume (acquired radial views had to be divided into bins based on the cardiac, respiratory, and the velocity encode dimension) (25). NA = not applicable.