Preclinical 4D flow MRI remains challenging and is restricted for parallel imaging acceleration due to the limited number of available receive channels. A radial acquisition with combined parallel imaging and temporal compressed sensing reconstruction was implemented to achieve accelerated preclinical 4D flow MRI. In order to increase the accuracy of the measured velocities, a quantitative evaluation of different temporal regularization weights for the compressed sensing reconstruction based on velocity instead of magnitude data is performed. A 3D radial retrospectively triggered phase contrast sequence with a combined parallel imaging and compressed sensing reconstruction with temporal regularization was developed. It was validated in a phantom and in vivo (C57BL/6 J mice), against an established fully sampled Cartesian sequence. Different undersampling factors (USFs [12, 15, 20, 30, 60]) were evaluated, and the effect of undersampling was analyzed in detail for magnitude and velocity data. Temporal regularization weights $\lambda$ were evaluated for different USFs. Acceleration factors of up to 20 compared with full Nyquist sampling were achieved. The peak flow differences compared with the Cartesian measurement were the following: USF 12, 3.38%; USF 15, 4.68%; USF 20, 0.95%. The combination of 3D radial center-out trajectories and compressed sensing reconstruction is robust against motion and flow artifacts and can significantly reduce measurement time to 30 min at a resolution of 180 $\mu$m$^3$. Concisely, radial acquisition with combined compressed sensing and parallel imaging proved to be an excellent method for analyzing complex flow patterns in mice.

**KEYWORDS**

4D flow, aorta, cardiovascular MRI, compressed sensing, phase contrast, preclinical MRI
Mouse models of cardiovascular diseases are important in translational cardiovascular research. A variety of knockout models that mimic cardiovascular diseases are available, e.g., mouse models of atherosclerosis, high blood pressure or aortic aneurysms. Preclinical phase contrast MRI (PC-MRI) can measure blood flow or tissue motion in mice at various locations. Commonly, one reference image and three velocity images are acquired, generally requiring long scan times. Therefore, 2D approaches have been preferred in the past in preclinical MRI, with extensions to 3D proposed recently. The 3D approach can assess the velocities of different vessels simultaneously. This allows us to display and analyze complex flow patterns, making 4D flow MRI a viable tool for the assessment of flow in the curved shape of the aorta.

Non-Cartesian methods have been shown in the literature; e.g., Janiczek et al applied a stack of spirals for the analysis of wall shear stress. Winter et al established a 2D radial phase contrast acquisition scheme for local pulse wave velocity measurements. Common coil configurations for preclinical imaging only provide a few receiver coils. This restricts the possible acceleration of the common parallel imaging methods such as GRAPPA (generalized autocalibrating partially parallel acquisitions) or SENSE (sensitivity encoding). Therefore, protocols with either long scan times or low resolution are used. For example, the protocol of Bovenkamp et al requires between 1 and 2 h and those of Braig et al and Janiczek et al around 50 min (assuming heart rates of around 400-500 bpm).

Recently, Krämer et al presented a 3D PC-MRI approach that uses a radial sampling trajectory. This has been achieved by the following means: (i) data sampling is started directly in the k-space center; (ii) no phase-encoding gradient is necessary as 3D encoding is inherent to the radial readout; and (iii) the slice-selection gradient can be omitted under certain limitations as related artifacts are distributed in a streak-like manner over the whole image. The main limitation of the method presented from Krämer et al is an inherent long scan time (in the presented protocol approximately 2 h). In our study, we explore the limits and possibilities to shorten acquisition times by radial undersampling in combination with a combined parallel imaging and temporal compressed sensing reconstruction. We compare our results against an established Cartesian acquisition. Commonly, regularization parameters are empirically obtained from magnitude images. Thorough establishment of the temporal regularization weighting is challenging and mostly disregarded, despite its heavy impact on the resulting velocities. Our study analyses the impact of different temporal regularization weights on the velocity fields for different degrees of undersampling. Additionally, optimized regularization parameters based on both magnitude and velocity image data are provided.

2 | METHODS

2.1 | Data acquisition

PC-MRI was acquired on a 7 T Bruker BioSpec 70/20 USR system with a maximum gradient amplitude of 676 mT/m and a slew rate of 4570 mT/m/ms operated with ParaVision 6.0.1 (Bruker BioSpin, Ettlingen, Germany). A two channel transmit and receive cryogenic (26 K helium cooled, Bruker) mouse head surface coil was used for acquisition. The coil is used in quadrature mode via a splitter. During receive it is used in parallel receive mode with two independent receive channels.

2.2 | Cartesian acquisition

Details of the prospective Cartesian acquisition and data reconstruction can be found in Reference 5. In brief, an established modified prospective Hadamard encoded PC-MRI cine sequence was used (FLOWMAP, Bruker BioSpin). The four velocity encodings are acquired consecutively in different heartbeats and fully sampled; the sequence continues to apply dummy scans when outside the respiratory window to avoid disruption of the steady state. Relevant sequence parameters are listed in Table 1. The sequence was prospectively electrocardiogram (ECG) triggered and respiratory gated by an SA Instruments 1030 (Stony Brook, New York) monitoring device. Only around 80% of the heart cycle can be covered due to prospective gating.

2.2.1 | Radial acquisition

A center-out 3D radial PC-MRI sequence, with velocity encoding along three orthogonal directions, was implemented based on the vendor’s radial imaging sequence as shown in Figure 1A. A reference dataset is acquired followed by velocity encoding in all three spatial directions separately. Figure 1B shows the used Koosh ball trajectory of the radial acquisition sampled from top to bottom as indicated by the red line. Calibration trajectories using the vendor supplied trajectory measurement were acquired, based on phase differences between two slices for each spatial direction. As in Reference 11, the slice selection gradient was omitted in order to achieve a short echo time (0.6 ms). The acquisition is synchronized
TABLE 1  Protocol parameters. Acquisition parameters of the sequences of the phantom and in-vivo acquisitions. The scan time of the Cartesian in-vivo sequence is the average acquisition duration from all measured subjects

| Parameter                          | Cartesian (phantom): constant/pulsatile | Radial (phantom): constant/pulsatile | Cartesian (in vivo) | Radial (in vivo) |
|------------------------------------|----------------------------------------|--------------------------------------|---------------------|-------------------|
| Field of view [mm³]                | 22³                                    | 22³                                  | 20 × 16 × 14        | 22³               |
| Matrix                             | 82 × 120 × 56                          | 120³                                 | 67 × 56 × 50        | 120³              |
| Reconstructed resolution [μm³]     | 90 × 90 × 200                          | 90³                                  | 160³                | 90³               |
| Velocity encoding [cm/s]           | 170                                    | 170                                  | 170                 | 170               |
| Flip angle [°]                     | 12                                     | 8                                    | 12                  | 8                 |
| Tₑ [ms]                            | 2.1                                    | 0.6                                  | 1.9                 | 0.6               |
| Tᵣ [ms]                            | 5.1                                    | 3.6                                  | 5.1                 | 3.6               |
| Temporal resolution                | --5.1                                  | --3                                 | 5.1                 | 3-3.8 (see text)  |
| Bandwidth [Hz]                     | 81 521                                 | 100 000                              | 81 521              | 100 000           |
| Scan time [min]                    | 3~/50                                  | 11/54                                | ~50                 | 54                |
| Echo position                      | 33%                                    | Center out                           | 26%                 | Center out        |

FIGURE 1  Sequence diagram and physiological signals. A, Sequence diagram of the radial sequence. B, The radial center out sampling, with the red line indicating the sampling pattern of the spokes. C, An exemplary ECG and respiration signal derived from one mouse during scanning. The R-peak of the ECG is detected and prominent (blue circle). D, The respiration signal shows periodic movements. These respiratory peaks are detected and a user defined amount of data before and after the peak is removed during reconstruction (blue rectangle)

to the ECG and respiratory recordings, so that each spoke of the acquisition can be assigned to the corresponding time point of the ECG and respiratory cycle. The signals were recorded using an NI-DAQ USB 6251 device synchronized to the MRI acquisition.

Data reconstruction
Data was reconstructed offline in MATLAB 2018b (MathWorks, Natick, MA). The raw data, as well as corresponding trajectories, were loaded into MATLAB and each spoke was assigned to the corresponding ECG timestamp individually for each velocity encoding direction. A peak detection algorithm was used to detect the R-peak of the ECG signal (example shown in Figure 1C). Data containing respiratory movement was discarded.
during reconstruction as shown in Figure 1D. The amount of data to discard can be chosen by the user according to the blue rectangle. A GPU based gridding algorithm (gpuNUFFT\textsuperscript{14}) was used to reconstruct the data. Afterwards, combined compressed sensing parallel imaging reconstruction as described by Feng et al\textsuperscript{12} was used, in order to reduce the artifacts due to undersampling. The reconstruction was formulated as

\[
\hat{d} = \arg\min_{d} \left\{ \| Fsd - m \|^2_2 + \lambda \|Td\|_1 \right\},
\]

with image series \(d\), temporal total variation (TV) operator \(T\), multi-coil radial \(k\)-space data \(m\), NUFFT operator \(F\), \(S\) the coil sensitivity maps and \(\lambda\) the regularization weight that controls the tradeoff between parallel imaging data consistency and sparsity. Coil sensitivity profiles are calculated from time-averaged reconstructed data. Regularization weights \((\lambda = \{0; 0.005; 0.01; 0.02; 0.06; 0.1; 0.2; 0.4\} M_0)\) were analyzed for different USFs, where \(M_0\) is the maximal magnitude value of the image of each velocity encoding. After reconstruction the baseline scan was subtracted from each velocity encoding direction. Velocity values from the lowest USF were used for comparison.

### 2.3 Phantom validation

To verify the developed method, both a flow phantom with constant flow and a flow phantom with pulsatile flow were measured with the radial and the Cartesian sequence. The constant flow phantom is used to validate the developed sequence against non-MRI-based flow measurements. The phantom consisted of a tube connected to a water pump. A phantom with agarose gel was placed next to the tube to correct for phase errors during reconstruction and to measure the correction trajectories. Constant flow was measured for several pump settings for flow velocities up to 170 cm/s, which corresponds to the velocity encoding for the Cartesian and the radial acquisition. For each pump setting one Cartesian and one radial dataset (one fully Nyquist sampled \(k\)-space) were acquired (velocity encoding constant). Simultaneously the amount of water flowing through the tube was measured for 1 min.

Pulsatile flow was realized by a valve outside of the scanner that periodically blocked water flow with a period of 120 ms. The repetition period of 120 ms was chosen to represent a mouse heartbeat period. A trigger signal of this periodic change was sent to the scanner and used as the necessary ECG signal. The pulsatile phantom itself is non-moving; therefore, a previously recorded respiration trigger signal of an in-vivo mouse acquisition was used during reconstruction to simulate respiratory motion and spokes were discarded accordingly. For each velocity encoding 225 110 spokes (one Nyquist dataset of 45 022 spokes sampled five times) were acquired to ensure enough data sampling coverage. The acquired data was binned into 40 frames according to the trigger signal, and data indicated as respiratory movement (artificial) were discarded. This re-binning leads to undersampling factors of 12, 15, 20, 30 and 60 for the different reconstructions compared with a full Nyquist sampled \(k\)-space; e.g., for USF 15, four fully Nyquist sampled datasets were acquired (4 \(\times\) 45 022 spokes = 180 088 spokes). Discarding 33% of respiratory data, this leads to 120 659 spokes, and divided by the number of reconstructed movie frames (120 659 spokes/40) 3016 spokes, which corresponds to a USF of 15 compared with a fully Nyquist sampled \(k\)-space of 45 022 spokes. This allowed validation of the developed radial method itself as well as the compressed sensing reconstruction pipeline and possible effects of the data undersampling ex vivo. The pulsatile phantom was reconstructed with a regularization weight of \(\lambda = 0.005\). Scan times are fixed and given by scan time = \(N_{\text{ spokes}} \cdot N_{\text{ repetition}} \cdot T_{R} \cdot N_{\text{ flow encoding}}\) resulting in the following scan times: USF 12, 54 min; USF 15, 43 min; USF 20, 32 min; USF 30, 22 min; USF 60, 11 min. Scan parameters are given in Table 1.

### 2.4 In vivo

This study was carried out in accordance with international recommendations and guidelines of the local ethics committee (protocol approval Regierungsspräsidium Freiburg AZ:35-9185.81/G-14/91, AZ: 35-9185.81/G-12/01). For sequence development seven C57BL/6 J mice (age = 29 ± 3 weeks; weight = 28.5 ± 2.5 g; values given with standard deviation) were measured with the Cartesian and radial sequences. The C57BL/6 N strain was used for sequence development, as it is a common inbred strain for animal research without any genetic modifications. One apolipoprotein E (ApoE) knockout mouse (age = 15 weeks, weight = 28.6 g) was acquired with the radial sequence to show the application of the method in a mouse model of disease. The ApoE mouse was fed a western diet starting from age 11 weeks, which enhances the development of atherosclerosis. The main components of this diet are 21% raw fat, 33% sugar and 2% cholesterol. The animals were ordered from a commercial breeder (Charles River Laboratories, Freiburg, Germany) and were housed in the local animal facility. MRI examinations were performed under narcosis (1-2% isoflurane in O\textsubscript{2} during spontaneous breathing). Mice were placed head first in supine position to bring the heart close to the surface coil. Temperature was monitored (rectal temperature probe) and maintained around 36.4-37.0 °C throughout the measurement using a water circulation system. The measured heart periods during the scan were 133 ± 10 ms with an average respiration period of 658 ± 110 ms detected with a respiration cushion. The total protocol duration was around 2.5 h including mouse preparation. The same amount of data as for the
pulsatile phantom was acquired (225 110 spokes). The whole ECG cycle was divided into 40 timeframes and the acquired data was assigned to its corresponding timeframe (~5600 spokes for each cardiac phase for every encoding using all five repetitions). The mean period of the heart beats divided by the number of cine frames then defines the temporal resolution. Therefore, temporal resolution is dependent on the heart rate of the animal. The average amount of data for each bin remains the same for each animal if the number of bins is chosen constant as in our case. Five radial reconstructions with different degrees of undersampling (1-5 repetitions) were reconstructed. Respiration was analyzed based on the recorded signal from the respiration cushion, and on average 33% of the respiratory cycle was discarded, based on the visible motion in the respiration signal as seen in Figure 1. The remaining spokes were used for reconstruction; this corresponds to USFs of 12, 15, 20, 30 and 60 (numbers rounded to the next integer) with respect to a full Nyquist sampling. The measurement duration is the same as in the pulsatile phantom case. Acquisition parameters are given in Table 1.

### 2.4.1 Post-processing and data analysis

After data reconstruction, a commonly used phase offset correction based on static tissue of the velocity data was applied. The threshold for static tissue detection was manually defined for each reconstruction so that a minimum of moving blood or moving tissue, e.g. heart muscle, is present. For the phantom analysis evaluation planes were chosen perpendicular to the phantom (tube) and a circle with the diameter (1.59 mm) of the tube was used in the segmentation process. In vivo, evaluation planes were placed perpendicular to a centerline in the aortic arch based on anatomical references derived from an isosurface of the time-averaged speed-sum-of-squares data \( v = \sqrt{v_x^2 + v_y^2 + v_z^2} \). Landmarks for the placement of the evaluation planes include the three aortic branches and the heart. Three analysis planes were defined within the aortic arch: (i) proximal to the brachiocephalic artery; (ii) distal to the left common carotid artery; and (iii) distal to the subclavian artery. The vessel was manually delineated in 2D in the analysis planes for the Cartesian and the radial USF 12 datasets and this segmentation was copied for the other radial reconstructions. This allowed analysis of velocities and flow of the heart cycle within the segmented area. Absolute velocity \( |v| \) is used to visually compare the flow profiles in the analysis planes. Data was cut off for all subjects at the duration corresponding to the shortest heart cycle in order to be able to calculate the mean value for all animals.

Linear regression was used to compare measured flow values with flow values from MRI in the phantom experiments. A pixel-by-pixel Bland-Altman comparison between the Cartesian and radial reconstructions was compromised by the different temporal samplings of the two methods as well as minor spatial displacements between the two methods. Therefore, we performed a Bland-Altman analysis comparing peak mean velocities and peak maximum velocities of the Cartesian method to the radial reconstructions. Peak mean velocity was defined as the average over all pixels in one evaluation plane at the timepoint with the highest mean velocity. The peak maximum velocity values were calculated as the three highest valued pixels in one evaluation plane.

The impact of data undersampling and temporal regularization was assessed by comparing peak mean velocity and peak maximum velocity for different values of the regularization weight \( j \) at different levels of undersampling.

Furthermore, pulse wave velocity was calculated by determining the time shift of the through plane velocity time curves between analysis planes 1 and 3. The time shift was calculated by the cross-correlation method as described by Fielden et al. The distance between the planes was calculated using the prior generated centerline of the aorta. The above parameters are commonly used as recommended by a consensus statement regarding 4D flow MRI for most clinical indications. To perform a streamline analysis an isosurface of the data was generated and streamlines were emitted from the most proximal analysis plane (both directions). 500 emitters were used. This visualization was done with EnSight 10.2 (ANSYS). The streamline quality of each image was graded by five experienced MRI researchers in a blinded survey.

### 3 RESULTS

#### 3.1 Phantom validation

##### 3.1.1 Constant flow

Figure 2A shows the measured flow of both methods measured with MRI plotted against the measured flow volume. Dashed lines represent the linear fit; symbols show the actual values. The fit results were the following. Cartesian: \( y = 1.0098x - 0.0173; R^2 = 0.9996 \); error bars show the standard deviation obtained from the analysis of multiple slices within the 3D volume. Radial: \( y = 0.9910x - 0.0047; R^2 = 0.9994 \). At the bottom of Figure 2A flow profiles for two pump settings of the radial and Cartesian sequence are shown, with visually good agreement of the flow profiles. The segmented tube diameter of the MR images showed excellent agreement with the known tube diameter (1.59 mm) for both methods.
3.1.2 Pulsatile flow

Figure 2B shows the flow profiles for different USFs over time for the pulsatile phantom with a regularization weight of $\lambda = 0.005$. Both methods reach the peak velocity between 60 and 75 ms and show similar velocity over time profiles. The Cartesian method is not able to cover the full cycle as it is prospectively triggered. The radial method reaches its initial value at the end of the cycle as expected for a periodic phantom. The flow-time curve remains stable even for high USF. However, USF 60 shows various deviations from the other USFs. Figure 2B bottom shows flow profiles of one exemplary slice within the phantom for both methods and all reconstructions. The Cartesian flow profile shows minor flow artifacts in the phase-encoding direction (red arrow); these artifacts may distort the flow profile.

3.2 In vivo

In Figure 3A, the mean for all animals of the measured flow values is plotted over time for the three analysis planes. The location of the analysis planes is shown in the middle with an isosurface illustration of the aorta. Each plot contains the result of the Cartesian method as well as the results of the radial reconstructions with USF 12 ($\lambda = 0.005$), USF 15 ($\lambda = 0.01$) and USF 20 ($\lambda = 0.02$). Shaded areas represent the standard error of the mean (SEM) of the measured subjects for the Cartesian measurement and USF 12. USFs above 20 are not shown as they do not provide reasonable results in the in-vivo case. Peak flow occurs around 25 ms (Plane 1), 30 ms (Plane 2) and 35 ms (Plane 3), shifted to later time points within the heart cycle for distal planes. Similarly, peak flow is decreased for distal planes. The peak flow differences compared with the Cartesian measurement were the following: USF 12, 3.38%; USF 15, 4.68%; USF 20, 0.95%. Table 2 summarizes the measured values including the results.
of the pulse wave analysis. Figure 3B compares magnitude images of Evaluation Plane 1 between the Cartesian and different radial reconstructions at peak systole. During peak systole the Cartesian method occasionally showed signal voids in the ascending aorta due to fast flowing blood. The radial images show homogeneous signal intensities for all reconstructions, with increased blurring for higher USF. Corresponding velocity images (bottom) show velocity profiles of similar shape for all methods; maximum velocities are highest for the Cartesian and radial USF 12 reconstructions (Figure 3B) and decrease with higher USF (Figure 3B). Supplementary Video 1 shows an exemplary magnitude movie of one subject (Cartesian and radial USF 12, USF 15, USF 20) and Supplementary Video 2 provides the corresponding absolute velocity for the same measurements and same location.

Figure 4 shows Bland Altman plots of the peak systolic mean (A) and maximum (B) velocities with the result of all mice and all evaluation planes. The results from the Cartesian measurement are compared with the radial USF 12, USF 15 and USF 20 reconstructions. The radial measurements were reconstructed with $\lambda = 0.02$. The mean and maximum peak velocities of both methods agree well. USF 20 shows slightly decreased mean peak velocities. High maximum velocities are underestimated by the radial reconstructions compared with the Cartesian method, especially for USF 20.

Figure 5A shows flow values over time (ascending aorta; mean for all animals) of different temporal weighting factors $\lambda$ for USF 15/USF 20 of Plane 1 (the same as in Figure 3A). The lowest USF, 12 ($\lambda = 0$), is shown as a reference. There is good agreement between all reconstructions. Elevated values around 0-10 ms and reduced peak flow are observed for $\lambda = 0.06$. Figure 5B provides velocity ($|v|$) profiles of the ascending aorta (Plane 1; same as in Figure 3B) during peak systole for different values of $\lambda$ for USF 15/USF 20. These show coherent distribution of the velocities and higher maximum velocities for increased $\lambda$. Magnitude images of an arbitrary slice within the heart exemplary for one mouse for $\lambda = [0.005, 0.01, 0.06]$ show increased image sharpness/less blurring with increasing $\lambda$ (Figure 5C). Line plots of the magnitude images at the position indicated by the dotted blue line are shown on the right of Figure 5C.
In Figure 6, the impact of the regularization weight $\lambda$ on the peak mean and maximum velocities of the radial method is shown. In A, $\lambda$ is plotted against the mean peak velocity. Mean peak velocity decreases for increasing values of $\lambda$ for all USF, except a slight increase at $\lambda = 0.005$ for USF 15. Maximum peak velocity (B) increases for higher values of $\lambda$ until $\lambda = 0.02$. Beyond $\lambda = 0.02$ USF 12 shows a strong decrease, USF 15 remains stable and USF 20 shows a further minimal increase in maximum peak velocity.

### TABLE 2

Analysis results. Peak flow, peak velocity and pulse wave velocity for the Cartesian and radial acquisitions. $n = 7$

|                     | Peak flow (ml/s) | Plane 1     | Plane 2     | Plane 3     | Mean all planes |
|---------------------|-----------------|-------------|-------------|-------------|-----------------|
| Cartesian flow      |                 | 0.94 ± 0.095| 0.68 ± 0.073| 0.68 ± 0.078| 0.76            |
| Radial USF 12       |                 | 0.99 ± 0.039| 0.71 ± 0.04 | 0.66 ± 0.044| 0.79            |
| Radial USF 15       |                 | 0.99 ± 0.042| 0.73 ± 0.038| 0.68 ± 0.05 | 0.80            |
| Radial USF 20       |                 | 0.96 ± 0.036| 0.69 ± 0.053| 0.66 ± 0.06 | 0.77            |

|                     | Peak velocity (m/s) | Plane 1     | Plane 2     | Plane 3     | Mean all planes |
|---------------------|---------------------|-------------|-------------|-------------|-----------------|
| Cartesian flow      |                     | 0.61 ± 0.045| 0.50 ± 0.045| 0.48 ± 0.06 | 0.53            |
| Radial USF 12       |                     | 0.59 ± 0.031| 0.50 ± 0.026| 0.52 ± 0.016| 0.54            |
| Radial USF 15       |                     | 0.59 ± 0.033| 0.50 ± 0.024| 0.53 ± 0.02 | 0.54            |
| Radial USF 20       |                     | 0.57 ± 0.034| 0.48 ± 0.028| 0.51 ± 0.03 | 0.52            |

|                     | Pulse wave velocity (m/s) | PwVf      | PwVr 12    | PwVr 15    | PwVr 20     |
|---------------------|---------------------------|-----------|-----------|-----------|-------------|
| Cartesian flow      |                           | 2.75 ± 0.2| 1.96 ± 0.7| 2.26 ± 0.7| 1.9 ± 0.7   |
| Radial USF 12       |                           |           |           |           |             |
| Radial USF 15       |                           |           |           |           |             |
| Radial USF 20       |                           |           |           |           |             |

**FIGURE 4** Bland-Altman comparison, Cartesian versus radial. Peak mean velocity A, and peak maximum velocity B, of the radial reconstructions are compared with the Cartesian reference values.
Figure 7 shows a qualitative comparison of streamlines emitted during peak systole for one mouse. Streamlines from the other mice can be found in the appendix (supplementary 1). The Cartesian and radial time points shown may differ within a few milliseconds as they have different temporal resolutions. 500 streamlines are emitted from the plane shown. Streamlines are color coded according to the color bar on the right. An isosurface at the current time point created from the magnitude data is provided for anatomical reference. Visually comparable streamlines are observed for all reconstructions. In general, streamlines follow the aortic arch geometry as expected. Streamlines from the Cartesian method disconnect earlier than streamlines from the radial method, which can be followed to the descending aorta. Some erroneous streamlines protrude from the vessel in all four cases, but with a visually increased number in the Cartesian case and clearly attributed to streamlines with low velocity (higher error). Streamline connectivity and density of the streamlines in the descending aorta were rated higher for the radial reconstructions than the Cartesian measurement. The survey revealed that fewer non-physiological streamlines are present in the radial streamline visualizations than in the Cartesian streamline visualizations. The survey results are presented in detail in the appendix (supplementary 2). Maximum velocities are decreased for higher USF. The isosurface vanishes at the descending aorta as there is a high signal intensity gradient for objects located distal to the coil element (surface coil).

3.3 Application to a mouse model of disease

The radial sequence was exemplarily applied to a mouse model of disease. Figure 8A shows flow over time values of the ApoE knockout mouse in the three evaluation planes. Flow values are decreasing for distal planes, as in the C57BL/6 N mice. Figure 8B...
There is good agreement for the different values of $\lambda$. For $\lambda = 0.06$ a drop in peak flow is visible. Magnitude images of the ventricle for $\lambda = 0.005, 0.01$ and 0.06 are provided in C. A line plot is shown for better comparison of the provided magnitude images. In D streamlines during systole of the ApoE knockout mouse are visualized.

4 | DISCUSSION

4.1 | Phantom experiments

Phantom experiments showed highly accurate velocity measurements for the Cartesian and radial method with to the non-MRI-based measurements. By using a pulsatile phantom, we could evaluate the effect of the compressed sensing reconstruction and confirm good agreement with the Cartesian technique. Considering the requirements regarding the fast periodic switching of this rather simple phantom, flow profiles of the Cartesian and radial methods coincide closely. Minor deviations can be explained by the phantom itself, which may exhibit minor changes in its flow profile over time. The pulsatile phantom reached similar velocity values that can be found in mice within the aorta. However, it is limited in the fact that its velocity time profile is smoothly rising and falling whereas in the animal a rather sharp peak during systole is seen, therefore the effect of the temporal component of our compressed sensing reconstruction may be slightly different than in vivo, which is why we decided not to perform a regularization weight analysis on the phantom data. Flow measurements were feasible up to an acceleration factor of 60 compared with Nyquist sampling, but with increased variation on accelerations over 30. The radial method shows fewer artifacts than the Cartesian method whose velocity profile is obscured by flow artifacts.
4.2 | In vivo

4.2.1 | Comparison of the radial method with the Cartesian method

Flow over time and peak mean and peak maximum velocities showed good agreement for both the Cartesian and radial reconstructions (Figures 3A and 4). Overall, there is no significant difference between the Cartesian and radial peak mean and peak maximum velocities for all USFs (Figure 4). The velocity distribution is visually similar as exemplarily shown for one mouse in the flow profiles and streamline visualization (Figures 3B and 7). The asymmetric distribution in the Bland-Altman analysis in Figure 4B shows that the measured peak maximum velocities for the Cartesian method tend to be increased for high peak maximum velocities. This means that peak maximum velocity is slightly underestimated by the radial method in the ascending aorta. The retrospective sampling in the radial method may decrease fast peak maximum velocities compared with the prospective sampling at discrete time points as for the Cartesian method. A quantitative pixel-by-pixel comparison of the Cartesian method with the radial method was not feasible due to spatial-temporal differences of the two acquisitions.

There is a higher stability in the magnitude images at high velocities (Figure 3B), due to the shorter echo time (reduced intra-voxel dephasing) and therefore higher accuracy in depicting the vessel lumen. Signal inhomogeneities due to fast flowing blood (systole) can be observed in the Cartesian method as exemplarily shown in Figure 3B. These inhomogeneities may comprise segmentation of the systolic time points in the Cartesian method, which is a crucial point because wrong segmentation substantially impacts segmentation dependent parameters. The homogenous depiction of blood within the vessel facilitates potential automatic segmentations of the blood vessels. In cases of stenotic jets, as occurring in mouse models of disease (e.g. transverse aortic constriction), short echo times and therefore the radial method have been shown to be superior to the Cartesian approach.18–20

FIGURE 7 | Streamline comparison of the Cartesian and radial reconstructions. Streamline visualizations of the aortic arch of one mouse are shown for the Cartesian and the radial reconstructions (USF 12, USF 15, USF 20). 500 streamlines are emitted from the emitter plane shown. Streamlines are color coded according to their velocity. Maximum velocity is reduced for higher USF.
4.2.2 Undersampling and regularization analysis

Higher acceleration factors in $k\cdot t$ GRAPPA or in temporal compressed sensing reconstructions have been shown to lead to a reduction of peak flow, peak velocity\textsuperscript{21,22} and reduced maximum velocities during peak systole. This is an effect of the temporal component of the $k\cdot t$ GRAPPA or temporal compressed sensing reconstruction and/or data inconsistency due to undersampling. Determination of the temporal weighting parameter $\lambda$ is often performed on magnitude images.\textsuperscript{12,21}

In our approach, $\lambda$ is determined by magnitude image quality and velocity data. Magnitude image quality decreases for higher undersampling, as seen in the heart images in Figure 5C. For the analyzed regularization weights, general image quality visibly improves for higher regularization weight, as data consistency is improved. Figure 5C shows that increased $\lambda$ provides improved image sharpness and less blurring. This is also seen in the line plots, where $\lambda = 0.01$ and $\lambda = 0.06$ show a generally improved sharpness compared with $\lambda = 0.005$. The difference between $\lambda = 0.01$ and $\lambda = 0.06$ is challenging to assess, as static and moving tissue are affected differently.

The flow over time analysis of Plane 1 shows good agreement for all analyzed regularization weights. A minor decrease in peak flow is observed for $\lambda = 0.06$. The analysis of peak mean and maximum velocities (Figure 6A and 6B) shows a relatively stable peak mean velocity up to $\lambda = 0.02$ and higher decrease for $\lambda = 0.06$. Peak mean flow is similar for all USF but slightly reduced for USF 20.

Peak maximum velocities increase with $\lambda$ up to $\lambda = 0.02$ (USF 12, USF 15) and $\lambda = 0.06$ for USF 20. Peak maximum velocities are decreased for USF 20, except for higher regularization. Our results suggest that the decrease in maximum velocity in undersampled data is due to blurring, which can be reduced by optimizing $\lambda$. Increasing the temporal weighting factor provides better data consistency and therefore less blurring and better maximum velocities. On the other hand, it increases the temporal filtering of the data and may lead to reduction of peak flow and reduced maximum velocities if chosen too high.
Reduction of peak velocity, maximum velocity and flow by compressed sensing reconstructions has been reported previously in humans, but we are not aware of a comparable analysis of the temporal regularization parameter \( \lambda \) in that case. Our study suggests that an inadequate choice of \( \lambda \) may lead to a substantial underestimation of peak flow and maximum velocities. Theoretically, higher data undersampling necessitates stronger regularization. This can be seen in the peak maximum analysis, as USF 20 benefits from higher regularization whereas USF 12 already shows a strong decrease in peak maximum velocity for \( \lambda = 0.06 \).

From the analyzed regularization weights, \( \lambda = 0.02 \) is the best choice as it provides stable peak mean velocity and accurate peak maximum velocities. The analysis in Figure 6B suggests that for USF 20 a regularization weight between \( \lambda = 0.02 \) and \( \lambda = 0.06 \) may provide additional benefit, as peak maximum velocities continue to increase \( \lambda = 0.06 \). The use of \( \lambda = 0.06 \) is discouraged, as it visibly reduces the peak mean velocities.

The proposed combined parallel imaging and compressed sensing approach shows that it is feasible to achieve USFs of up to 20 without major compromises in image quality and velocity accuracy if \( \lambda \) is chosen appropriately.

Calculated pulse wave velocities (Table 2) are slightly lower for the radial acquisition compared with the Cartesian acquisition and with results reported in literature for C57BL/6 J (32 week old) mice. Herold et al.\(^{23} \) quote 2.6 ± 0.2 m/s compared with our results of 2.7 ± 0.2 m/s (Cartesian) and 1.96 ± 0.7 m/s (radial USF 12). Both of our methods are likely limited in measuring pulse wave velocity, as the temporal resolution is inherently low compared with temporal resolutions of 1 ms used by Herold et al. Our measured time differences between the planes range around 2 ms, which is lower than the actual reconstructed temporal resolution of 3.3 ms.

For USF 20 with an acquisition matrix of 120 isotropic and \( T_\text{R} \) of 3.6 ms the total scan time is 32 min. In comparison, Krämer et al.\(^{11} \) require measurement times of more than 2 h for an isotropic resolution of 230 \( \mu \text{m}^2 \). There, a \( k \)-space coverage of 85.1% is quoted, in our terms corresponding to a USF of 1.18. In addition, the shown reference Cartesian sequence with the same matrix size as our radial acquisition would need more than 4 h.

For USF above 20 the resulting velocity over time curves showed high variations, and their results were distinctly different from the Cartesian reference and unphysiological. Therefore, USF 30 and higher have been considered not feasible in this study. Flow curves of USF 30 and USF 60 can be found in the supplementary files. Ex vivo, accelerations above USF 20 could be achieved, as there was a high signal to noise ratio and no physiological motion or gating imperfections.

Two major approaches are often used for binning the acquired data in retrospective cardiac gated reconstructions: (i) keeping the number of spokes per bin constant (resulting in different temporal resolution for each subject); and (ii) keeping the temporal resolution constant (resulting in unequal numbers of spokes per bin). The former (our case) may result in inaccurate velocities in cases where subjects with very different heart rates are compared and the number of reconstructed heart frames is too low to cover the temporal changes in the velocity-time curve. This will likely result in underestimation of peak velocities for low heart rates as the temporal resolution is reduced. Therefore, enough heart frames should be considered to cover cases with low heart rates, which is why we decided on 40 frames in our study. In the latter case (iii), different heart rates lead to different numbers of spokes for subjects with different heart rates, as the number of acquired spokes must be distributed between the higher number of bins. Considering a group comparison (diseases versus control) where the diseased group shows bradycardia (slow heart rate), this would result in different results for the two groups just from the effects of increased data undersampling.

In our approach, the retrospective spoke assignment intrinsically leads to an efficient spoke distribution in \( k \)-space. For high USF (e.g. 30 or 60), the overall distribution of the spokes could be suboptimal as only one or two sets of spokes are acquired and assigned to the different time frames. Spokes removed by respiration may lead to a non-uniform \( k \)-space coverage, which is normally accounted for when using multiple repetitions. This potentially limits our approach in vivo to a USF of 20. A golden angle approach (e.g. References 24 and 25) could potentially allow further acceleration and improvement. Furthermore, approaches such as XD-GRASP,\(^{26} \) which apply compressed sensing in the respiration dimension, may be beneficial. In our reconstruction, we use combined compressed sensing and parallel imaging; however, the cryogenic coil used in this study has only two receive channels. Further improvements may be possible by using a different coil with more receivers. To our knowledge, only up to four receivers are commercially available for the cryogenic coil. Room temperature coils may be an alternative but have the drawback of a reduced signal to noise ratio.

As a proof of concept, the radial method was applied to a mouse model of disease. Excellent quality in the magnitude images is achieved, with a homogeneous blood signal in the ventricle. Flow over time curves show results similar to those obtained in the C57BL/6 J mice. As expected, peak flow decreases in the distal evaluation planes towards the descending aorta. Regularization analysis confirms the observations from the C57BL/6 J mice. Systolic streamlines are similar to those of the measured C57BL/6 J mice.

5 | CONCLUSION

The presented method allows us to measure complex flow at high resolution, covering the whole heart including the aortic arch over the whole heart cycle with substantially reduced measurement times. The compressed sensing reconstruction used enables an acceleration of radial 4D flow imaging up to a factor of 20 compared with full Nyquist sampling. Due to its stability against motion and flow turbulences, it may be the ideal choice to analyze flow in mouse models of disease. A quantitative evaluation of the temporal weighting factor \( \lambda \) in the compressed sensing...
reconstruction was shown to be essential to obtain accurate peak flow and maximum velocities. Determination of $\lambda$ for phase contrast imaging solely based on magnitude data is not recommended.

**ETHICS APPROVAL**
This study was carried out in strict accordance with international recommendations and the guidelines of the local ethics committee. The protocol was approved by the responsible committee (reference Regierungspräsidium Freiburg AZ:35-9185.81/G-14/91). All examinations were performed under isoflurane narcosis; animal physiology was continuously monitored.

**AVAILABILITY OF DATA AND MATERIALS**
All data is available from the corresponding author upon request.

**ACKNOWLEDGEMENTS**
The authors would like to acknowledge the funding from the DFG grant no. EL 534/6-1 and MOST grant no. MOST-106-2221-E-110-024. We would like to acknowledge the support of Annette Merkle and Michaela Schäper in animal handling during the measurements. Also, we would like to thank the employees of Wissenschaftliche Werkstätten Neurozentrum for their helpful discussions on the ECG signal recording. Open access funding enabled and organized by Projekt DEAL.

**CONFLICTS OF INTEREST**
The authors declare that they have no competing interests.

**AUTHOR CONTRIBUTIONS**
All authors read and approved the final manuscript. Individual contributions: MB—conceptualization, data curation, formal analysis, investigation, methodology, project administration, software, validation, visualization, writing (original draft), writing (review and editing). MM—methodology, software, supervision, review and editing. JL—methodology, software, review and editing. PL—software, statistical guidance, review and editing. LF—software, review and editing. CK—project administration, supervision, funding acquisition, review and editing. DE—conceptualization, data curation, funding acquisition, project administration, resources, supervision, validation, writing (review and editing).

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**REFERENCES**
1. Guo Y, Zhang C, Du X, Nair U, Yoo T-J. Morphological and functional alterations of the cochlea in apolipoprotein E gene deficient mice. Hear Res. 2005;208(1/2):54-67. https://doi.org/10.1016/j.heares.2005.05.010
2. Shesely EG, Maeda N, Kim H5, et al. Elevated blood pressures in mice lacking endothelial nitric oxide synthase. Proc Natl Acad Sci U S A. 1996;93(23):13176-13181.
3. Judge DP, Biery NJ, Keene DR, et al. Evidence for a critical contribution of haploinsufficiency in the complex pathogenesis of Marfan syndrome. J Clin Invest. 2004;114(2):172-181. https://doi.org/10.1172/JCI20641
4. Pelc NJ, Bernstein MA, Shimakawa A, Glover GH. Encoding strategies for three-direction phase-contrast MR imaging of flow. J Magn Reson Imaging. 1991;1(4):405-413. https://doi.org/10.1002/jmri.1880010404
5. Braig M, Leupold J, Menza M, et al. Preclinical 4D-flow magnetic resonance phase contrast imaging of the murine aortic arch. PLoS ONE. 2017;12(11):e0187596. https://doi.org/10.1371/journal.pone.0187596
6. Bovenkamp PR, Brix T, Lindemann F, et al. Velocity mapping of the aortic flow at 9.4 T in healthy mice and mice with induced heart failure using time-resolved three-dimensional phase-contrast MRI (4D PC MRI). Magn Reson Mater Phys Biol Med. 2015;28:315-327. https://doi.org/10.1007/s10334-014-0466-z
7. Janiczek RL, Blackman BR, Roy RJ, Meyer CH, Acton ST, Epstein FH. Three-dimensional phase contrast angiography of the mouse aortic arch using spiral MRI. Magn Reson Med. 2011;66(5):1382-1390. https://doi.org/10.1002/mrm.22937
8. Winter P, Kampf T, Helluy X, et al. Fast retrospectively triggered local pulse-wave velocity measurements in mice with CMR-microscopy using a radial trajectory. J Cardiovasc Magn Reson. 2013;15(1):88–89. https://doi.org/10.1186/1532-429X-15-88
9. Grollhold MA, Jakob PM, Heidemann RM, et al. Generalized autocalibrating partially parallel acquisitions (GRAPPA). Magn Reson Med. 2002;47(6):1202–1210. https://doi.org/10.1002/mrm.10171
10. Pruessmann KP, Weiger M, Scheidegger MB, Boesiger P. SENSE: sensitivity encoding for fast MRI. Magn Reson Med. 1999;42(5):952-962.
11. Krämer M, Motaal AG, Herrmann KH, et al. Cardiac 4D phase-contrast CMR at 9.4 T using self-gated ultra-short echo time (UTE) imaging. J Cardiovasc Magn Reson. 2017;19:39. https://doi.org/10.1186/s12968-017-0351-9
12. Feng L, Grimm R, Block KT, et al. Golden-angle radial sparse parallel MRI: combination of compressed sensing, parallel imaging, and golden-angle radial sampling for fast and flexible dynamic volumetric MRI. Magn Reson Med. 2014;72(3):707-717. https://doi.org/10.1002/mrm.24980
13. Zhang Y, Hetherington HP, Stokely EM, Mason GF, Twieg DB. A novel k-space trajectory measurement technique. Magn Reson Med. 1998;39(6):999-1004. https://doi.org/10.1002/mrm.1910390618
14. Knoll F, Schwarzl A, Diwoky C, Lodickson D. gnuUFFT—an open-source GPU library for 3D gridding with direct Matlab interface. Proc Int Soc Magn Reson Med. 2014;22:4297.
15. Bock J, Kreher B, Hennig J, Markl M. Optimized pre-processing of time-resolved 2D and 3D phase contrast MRI data. Proc Int Soc Magn Reson Med. 2007:604.
16. Fielden SW, Fornwalt BK, Jerosch M, Stillman AE, Oshinski JN. A new method for the determination of aortic pulse wave velocity using cross-correlation on 2D PCMR velocity data. J Magn Reson Imaging. 2008;27(6):1382-1387. https://doi.org/10.1002/jmri.21387
17. Dyverfeldt P, Bissell M, Barker AJ, et al. 4D flow cardiovascular magnetic resonance consensus statement. J Cardiovasc Magn Reson. 2015;17. https://doi.org/10.1186/s12968-015-0174-5
18. Ståhlberg F, Thomsen C, Söndergaard L, Henriksen O. Pulse sequence design for MR velocity mapping of complex flow: notes on the necessity of low echo times. Magn Reson Imaging. 1994;12(8):1255-1262. https://doi.org/10.1016/0730-725X(94)90090-E
19. Schnallbrock P, Yuan C, Chakeres DW, Kohli J, Pelc NJ. Volume MR angiography: methods to achieve very short echo times. Radiology. 1990;175(3):861-865. https://doi.org/10.1148/radiology.175.3.2343137
20. O’Brien KR, Myerson SG, Cowan BR, Young AA, Robson MD. Phase contrast ultrashort TE: a more reliable technique for measurement of high-velocity turbulent stenotic jets. Magn Reson Med. 2009;62(3):626-636. https://doi.org/10.1002/mrm.22051
21. Ma LE, Markl M, Chow K, et al. Aortic 4D flow MRI in 2 minutes using compressed sensing, respiratory controlled adaptive k-space reordering, and inline reconstruction. Magn Reson Med. 2019;81(6):3675-3690. https://doi.org/10.1002/mrm.25684
22. Schnell S, Markl M, Entezari P, et al. k-t GRAPPA accelerated four-dimensional flow MRI in the aorta: effect on scan time, image quality, and quantification of flow and wall shear stress. Magn Reson Med. 2014;72(2):522-533. https://doi.org/10.1002/mrm.24925
23. Herold V, Parczyk M, Mörchel P, et al. In vivo measurement of local aortic pulse-wave velocity in mice with MR microscopy at 17.6 Tesla. Magn Reson Med. 2009;61(6):1293-1299. https://doi.org/10.1002/mrm.21957
24. Chan RW, Ramsay EA, Cunningham CH, Plewes DB. Temporal stability of adaptive 3D radial MRI using multidimensional golden means. Magn Reson Med. 2009;62(3):354-363. https://doi.org/10.1002/mrm.21837
25. Park J, Shin T, Yoon SH, Goo JM, Park J-Y. A radial sampling strategy for uniform k-space coverage with retrospective respiratory gating in 3D ultrashort-echo-time lung imaging. NMR Biomed. 2016;29(5):576-587. https://doi.org/10.1002/nb.3494
26. Feng L, Axel L, Chandarana H, Block KT, Sodickson DK, Otazo R. XD-GRASP: golden-angle radial MRI with reconstruction of extra motion-state dimensions using compressed sensing. Magn Reson Med. 2016;75(2):775-788. https://doi.org/10.1002/mrm.25665

**SUPPORTING INFORMATION**

Additional supporting information may be found online in the Supporting Information section at the end of this article.

**How to cite this article:** Braig M, Menza M, Leupold J, et al. Analysis of accelerated 4D flow MRI in the murine aorta by radial acquisition and compressed sensing reconstruction. NMR in Biomedicine. 2020;33:e4394. [https://doi.org/10.1002/nbm.e4394](https://doi.org/10.1002/nbm.e4394)