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Quantitative 4D flow MRI-derived thoracic aortic normal values of 2D flow MRI parameters in healthy volunteers

Quantitative 4D-Fluss-MRT-generierte Normwerte für die thorakale Aorta von 2D-Fluss-MRT-Parametern in gesunden Probanden

Authors

Sebastian Ebel[1], Alexander Kühn[2], Benjamin Köhler[3], Benjamin Behrendt[3], Boris Riekena[2], Bernhard Preim[3], Timm Denecke[1], Matthias Grothoff[2], Matthias Gutberlet[2]

Affiliations

1 Diagnostic and Interventional Radiology, Leipzig University, Leipzig, Germany

2 Diagnostic and Interventional Radiology, Leipzig Heart Centre University Hospital, Leipzig, Germany

3 Simulation and Graphics, Otto von Guericke Universität Magdeburg, Germany

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Correspondence

Dr. Sebastian Ebel
Diagnostic and interventional radiology, University Hospital Leipzig, Liebigstr. 20, 04103 Leipzig, Germany
Tel.: +49/34/19 71 74 24
sebastian.ebel@icloud.com

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ABSTRACT

Purpose To utilize 4 D flow MRI to acquire normal values of "conventional 2 D flow MRI parameters" in healthy volunteers in order to replace multiple single 2 D flow measurements with a single 4 D flow acquisition.

Materials and Methods A kt-GRAPPA accelerated 4 D flow sequence was used. Flow volumes were assessed by forward (FFV), backward (BFV), and net flow volumes (NFV) [ml/heartbeat] and flow velocities by axial (VAX) and absolute velocity (VABS) [m/s] in 116 volunteers (58 females, 43 ± 13 years). The aortic regurgitant fraction (RF) was calculated.

Results The sex-neutral mean FFV, BFV, NFV, and RF in the ascending aorta were 93.5 ± 14.8, 3.6 ± 2.8, 89.9 ± 0.6 ml/heartbeat, and 3.9 ± 2.9 %, respectively. Significantly higher values were seen in males regarding FFV, BFV, NFV and RF, but there was no sex dependency regarding VAX and VABS. The mean maximum VAX was lower (1.01 ± 0.31 m/s) than VABS (1.23 ± 0.35 m/s). We were able to determine normal ranges for all intended parameters.

Conclusion This study provides quantitative 4 D flow-derived thoracic aortic normal values of 2 D flow parameters in healthy volunteers. FFV, BFV, NFV, and VAX did not differ significantly from single 2 D flow acquisitions and could therefore replace time-consuming multiple single 2 D flow acquisitions. VABS should not be used interchangeably.

Key points:

- 4 D flow MRI can be used to replace 2 D flow MRI measurements.
- The parameter absolute velocities can be assessed by 4 D flow MRI.
- There are sex-dependent differences regarding forward, backward, net aortic blood flow and the aortic valve regurgitant fraction.

ZUSAMMENFASSUNG

Ziel Nutzung des 4 D Flusses zur Normwertgenerierung „konventioneller" 2D-Flussparameter in gesunden Probanden, um multiple 2D-Flussmessungen durch eine einzige 4D-Flussmessung zu ersetzen.

Materialien und Methoden Es wurde eine kt-GRAPPA-beschleunigte 4D-Fluss-Sequenz verwendet. Bei 116 Probanden (58 Frauen, 43 ± 13 Jahre) wurden die Flussvolumina als Vorwärts- (FFV), Rückwärts- (BFV) und Nettoflussvolumina (NFV) [ml/Herzschlag] und die Flussgeschwindigkeiten als axiale (VAX) und absolute Geschwindigkeiten (VABS) [m/s] erfasst. Die aortale Regurgitationsfraktion (RF) wurde berechnet.

Ergebnisse Die geschlechtsneutralen mittleren FFV, BFV, NFV und RF in der Aorta ascendens betrugen 93,5 ± 14,8, 3,6 ± 2,8, 89,9 ± 0,6 ml/Herzschlag bzw. 3,9 ± 2,9 %. Die Werte für FFV, BFV, NFV und RF waren bei Männern signifikant höher, während bei VAX und VABS keine Geschlecht-

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sabhängigkeit bestand. Die mittlere VAX war niedriger (1,01 ± 0,31 m/s) als VABS (1,23 ± 0,35 m/s). Für alle vorgesehenen Parameter konnten Normwerte berechnet werden.

Schlussfolgerung Diese Studie liefert quantitative, aus dem 4D-Fluss abgeleitete Normwerte für 2D-Flussparameter in der thorakalen Aorta bei gesunden Probanden. FFV, BFV, NFV und VAX unterschieden sich nicht signifikant von 2D-Flussmessungen und könnten daher zeitaufwändige einzelne 2D-Flussmessungen ersetzen. VABS kann nicht austauschbar verwendet werden.

Kernaussagen:
- 4D-MRT-Flussmesssungen können genutzt werden, um 2D-MRT-Flussmessungen zu ersetzen.
- Der Parameter Absolute Flussgeschwindigkeit kann mittels 4D-Fluss-MRT erhoben werden.
- Es gibt geschlechtsspezifische Unterschiede in Bezug auf Vorwärts-, Rückwärts- und Nettofluss der Aorta sowie die Aortenregurgitationsfraktion.

Zitierweise
- Ebel S, Kühn A, Köhler B et al. Quantitative 4D flow MRI-derived thoracic aortic normal values of 2D flow MRI parameters in healthy volunteers . Fortschr Röntgenstr 2024; 196: 273–282

ABBREVIATIONS

2 D flow MRI	time-resolved 2-dimensional phase contrast flow
MRI	magnetic resonance imaging
4 D flow MRI	time-resolved 3-dimensional phase contrast flow
kt-GRAPPA	GeneRalized Autocalibrating Partially Parallel Acquisition with linear interpolation of missing data in the k-space
FFV	forward flow volume
BFV	backward flow volume
NVF	net flow volume
VAX	axial velocity
VABS	absolute velocity

Introduction

Time resolved 2-dimensional phase contrast flow measurements (2 D flow MRI) play a major role in the assessment of cardiovascular pathologies in magnetic resonance imaging (MRI) [1]. Although singular 2 D flow MRI measurements can be performed rather fast, it is necessary to perform an individual measurement of each vessel of interest. Furthermore, it is mandatory to acquire each 2 D flow MRI measurement exactly perpendicular to the main flow vector. In the setting of congenital heart disease, e. g., in aortic isthmic stenosis (coarctation) with a possible elongation of the aorta or otherwise altered anatomic conditions, it can be a quite time-consuming process, if you need one in-plane and maybe three through-plane measurements pre-, intra- and post-stenotic. Misaligned measurements lead to inaccurate results and might need to be repeated [2].

Similar to conventional 2 D flow MRI sequences, time-resolved 3-dimensional phase contrast flow measurements (4 D flow MRI) enable absolute quantification of flow parameters, such as forward and backward flow volumes, flow velocities, and shunt volumes [3, 4]. In addition, 4 D flow MRI enables quantification of advanced flow parameters, such as helical flow, wall shear stress, and analysis of flow displacement with full coverage of the complete vascular systems, such as the great mediastinal vessels [5]. In contrast to 2 D flow MRI, isotropic data in all spatial directions can be obtained in 4 D flow MRI, making it possible to create 3 D reconstructions of every vessel within a given field of view after data acquisition. This enables off-line placement of measuring planes during post-processing for retrospective evaluation of blood flow-like flow volumes and velocities in multiple vessels [6]. With these reconstructions from 4 D flow MRI data sets, results are independent of plane angulation or flow directions, enabling fast forward planning during image acquisition. Numerous studies demonstrated good agreement between 2 D and 4 D flow MRI measurements in healthy volunteers and patients so that 4 D flow MRI could replace conventional 2 D flow MRI [7–9]. However, 4 D flow MRI is still neither an established part of the evaluation of patients, nor part of the decision-making process. To overcome this issue and to achieve a broader use of 4 D flow MRI in daily practice, it could be helpful to define normal values of “2 D flow MRI parameters” derived from 4 D flow MRI, like forward and backward flow volumes and flow velocities. These normal ranges may differ substantially, because not only one flow direction as in 2 D flow MRI is incorporated but rather flow components in all spatial directions are used. This study is an extension of previous work, in which we evaluated the used 4 D flow MRI sequence against a flow phantom using pulsatile and non-pulsatile flow and the standard of care 2 D flow MRI and found no significant differences between 2 D and 4 D flow MRI measurements [8]. The aim of this study was to utilize 4 D flow MRI in the thoracic aorta of healthy volunteers to generate normal values of the “2 D flow MRI parameters” derived from 4 D flow MRI in order to possibly replace multiple 2 D flow MRI measurements (e. g., in the setting of aortic isthmic stenosis (coarctation)) by one 4 D flow MRI measurement.

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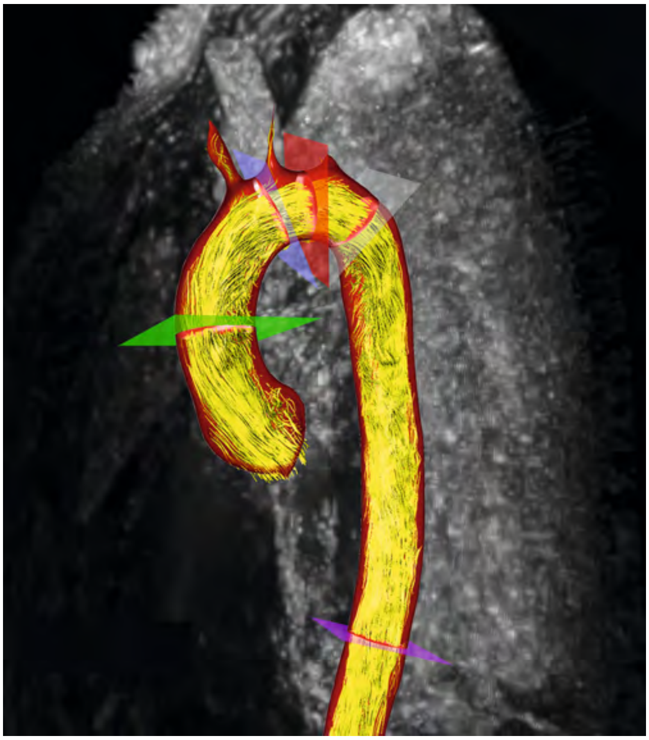

▶ **Fig. 1** Visualization of intraaortic blood flow with time-resolved 3 D pathlines. Measuring planes in the mid-ascending aorta (green, Plane **A**), in the aortic arch behind the origin of the brachiocephalic trunk (blue, Plane **B**), behind the origin of the left carotid artery (red, Plane **C**), behind the origin of the left subclavian artery (white, Plane **D**), and in the descending aorta on the level of the diaphragm (purple, Plane **E**).

▶ **Abb. 1** Visualisierung des intraaortalen Blutflusses mit zeitlich aufgelösten 3 D pathlines. Messebenen in der mittleren Aorta ascendens (grün, Ebene **A**), im Aortenbogen hinter dem Ursprung des Truncus brachiocephalicus (blau, Ebene **B**), hinter dem Ursprung der linken Arteria carotis communis (rot, Ebene **C**), hinter dem Ursprung der linken Arteria subclavia (weiß, Ebene **D**) und in der Aorta descendens auf Höhe des Zwerchfells (lila, Ebene **E**).

Materials and methods

Study cohort

116 healthy volunteers with no history of cardiovascular disease (58 females, mean age 43 ± 13 years) were included. To investigate the influence of age, we included participants in various age groups: 19–30 (n = 24); 31–40 (n = 28); 41–50 (n = 26); 51–60 (n = 22), and ≥ 61 years (n = 16). The local ethics board approved the study and written informed consent was obtained from all participants.

Magnetic resonance image acquisition

The 4 D flow MRI datasets were acquired at 3 Tesla using a 16-channel surface coil in combination with a 12-element spine coil (Magnetom Verio Dot, Siemens Healthcare GmbH, Erlangen, Germany). The used 4 D flow MRI kt-GRAPPA5 (**G**ene**R**alized **A**uto-calibrating **P**artially **P**arallel **A**cquisition) sequence is commercially available and was validated before *ex vivo* using a flow phantom with pulsatile and non-pulsatile flows and *in vivo* in healthy volunteers against the standard of care (2 D flow MRI) [8, 9]. The imaging parameters were: TR = 4.6 ms, TE = 2.8 ms, flip angle 10°, FOV 320x240 mm with a mean temporal resolution of 39.2 ms (35.3–39.9 ms), and a spatial resolution of 2.5 × 2.5 × 2.5 mm^3, VENC 150 cm/s, phase encoding direction anterior to posterior, slice number 24. Respiratory gating was performed using a navigator on the diaphragm/liver interface. As standard of care, 2 D flow MRI measurements were performed: TR = 8.5 ms, TE = 2.9 ms, flip angle 15°, with a mean temporal resolution of 20.5 ms, spatial resolution of 1.9 × 1.9 mm^2, slice thickness 5 mm, VENC 150 cm/s.

Data analysis

Vessel segmentation, blood flow visualization, and pre-processing

All processing and measurement steps were carried out using the software Bloodline (University of Magdeburg, Germany) [10]. The segmentation of the aorta and the placement of the centerline were performed automatically as described by Köhler et al. [10]. The ascending aorta was defined as the volume of the aorta between the aortic valve and the origin of the brachiocephalic trunk, the aortic arch was defined as the volume between the origin of the brachiocephalic trunk and the left subclavian artery, and the thoracic descending aorta was defined as the volume between the origin of the left subclavian artery and the diaphragm. A centerline was semi-automatically drawn through the whole thoracic aorta. Aortic blood flow was visualized using time-resolved pathlines. We corrected for eddy currents and background noise as described previously [11, 12].

Measurements and flow quantifications

The software tool "Bloodline" enables positioning of multiple measuring planes for the assessment of flow volumes and flow velocities as mentioned elsewhere [10]. Measuring planes were positioned at specific landmarks (▶ **Fig. 1**) as follows: In the middle of the ascending aorta (plane A), behind the origin of the brachiocephalic artery (plane B), behind the origin of the left common carotid artery (plane C), behind the origin of the left subclavian artery (plane D), and at the level of the diaphragm (plane E). All measuring planes were oriented perpendicular to the centerline of the thoracic aorta (▶ **Fig. 1**). 2 D flow MRI measurements were performed on planes A and D. Planes A and D in 2 D and 4 D flow MRI were matched manually by the investigator.

Flow volumes were assessed by measuring the forward flow volume (**FFV**), the backward flow volume (**BFV**), and the net flow volume (**NFV**) in [ml/heartbeat] that passes through the above-mentioned measuring planes. Net flow was calculated by subtracting BFV from FFV. The regurgitant fraction (**RF**) was calculated by dividing BFV by FFV in [%]. As quality control, comparisons of NFV in the main pulmonary artery and the ascending aorta has been performed in 10 datasets (Qp/Qs) as suggested in a consensus statement by Dyverfeldt et al. [12].

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Flow velocities were assessed with different parameters:

The parameter maximum axial velocity ($\mathbf{V_{AX}}$) describes the maximum velocity in [m/s] of blood flow that passes strictly perpendicularly (axial) through a measuring plane, corresponding to the "classic" 2 D flow MRI velocity acquired from 2 D flow MRI sequences. This parameter describes the through-plane component of the velocity vector. The maximum velocity was defined as the local velocity maximum on a measurement plane at the timepoint of maximum blood flow.

The 4 D flow MRI parameter maximum absolute velocity ($\mathbf{V_{ABS}}$) is defined as the maximum velocity in [m/s] of blood flow through a measuring plane independent of the flow orientation. This parameter also contains the radial and the circumferential component of the blood flow (**Supplemental Fig. 1**).

Intra- and interobserver variability

For the assessment of the inter-observer variability, a second investigator with > 9 years of cardiac MRI experience analyzed a subgroup of 10 randomly selected datasets, according to the above-described methodology (including all import and segmentation steps). For the assessment of the intra-observer variability, this investigator repeated all measurements 10 days after the first assessment. These assessments have been performed without further differentiation regarding age or sex.

Statistical analysis

All results were given as their mean values and standard deviation (SD). Statistical analysis was performed using the statistical software package SAS 9.4 (SAS Institute Inc., Cary, NC, USA). In a first step, normal distribution was confirmed using the Shapiro-Wilk test. Differences between male and female volunteers and between 2 D and 4 D flow MRI were assessed using a paired t-test. A p-value < 0.05 was considered statistically significant. Dependencies between variables and age or sex were assessed using Pearson's correlations. Since all measured values were distributed normally, normal ranges were given as mean ± 2SD. Intra- and interobserver variability was assessed using interclass correlation (ICC) and were given as correlation coefficient R.

Results

Volunteer characteristics:

116 volunteers were included: 58 females, mean age 43 ± 13 years. The mean body mass index was 24.6 ± 5.2 kg/m^2. The mean resting heart rate during the examination was 69 ± 12/ min., the mean cardiac output was 6.45 ± 1.59 l/min as measured by 4 D flow MRI.

Data acquisition

The mean scan time was 8.4 ± 4.2 minutes for the 4 D flow MRI sequence. All datasets were completely assessable.

Flow volumes

The female and male normal ranges of all measuring planes are given in ▶ **Table 1, 2**, respectively. At the level of the ascending aorta (plane A), the overall mean FFV, BFV, and NFV were generally slightly, but not significantly higher with 93.5 ± 14.8, 3.6 ± 2.8, and 89.9 ± 15.8 ml/heartbeat using the 4 D flow MRI sequence as compared to 90.1 ± 13.4, 3.2 ± 3.1, and 85.7 ± 16.2 ml/heartbeat using the 2 D flow MRI sequence. The overall mean regurgitant fraction (RF) was 3.9 ± 2.9 % (4 D flow MRI) and 3.6 ± 3.4 % (2 D flow MRI). The mean Qp/Qs in a subset of 10 datasets was 1.2 ± 0.1.

These values were significantly higher in males compared to female volunteers ($p < 0.05$). The FFV, BFV, and NFV were 102.2 ± 16.4, 4.2 ± 1.9, and 98.1 ± 16.9 ml/heartbeat in males and 84.8 ± 13.1, 2.8 ± 1.1, and 82.1 ± 14.6 ml/heartbeat in females using 4 D flow MRI and 100.9 ± 15.9, 3.8 ± 1.6, and 97.1 ± 14.3 ml/heartbeat in males and 82.0 ± 14.5, 2.2 ± 1.6, and 78.8 ± 13.3 ml/heartbeat in females using 2 D flow MRI. The RF in 4 D and 2 D flow MRI was 4.1 ± 1.9 and 3.8 ± 1.6 % in males and 3.3 ± 1.3 and 2.7 ± 2.0 % in females (▶ **Table 3**). There were no relevant correlations between age and FFV, BFV, or NFV.

Flow velocities

The female and male normal ranges of all measuring planes are given in ▶ **Table 4, 5**, respectively. At the level of the ascending aorta (plane A), the overall $\mathbf{V_{AX}}$ and $\mathbf{V_{ABS}}$ were 1.01 ± 0.31 and 1.23 ± 0.35 m/s using the 4 D flow MRI sequence and the overall $\mathbf{V_{AX}}$ using the 2 D sequence was 1.11 ± 0.38 m/s. There were no significant differences regarding sex and age ($p < 0.05$, respectively) and no significant differences between 4 D flow MRI and 2 D flow MRI ($p < 0.05$). There were no datasets with phase wraps. Therefore, no aliasing correction had to be performed.

Inter- and intraobserver variability

The interobserver variabilities ranged from R = 0.91 to 0.99 ($p < 0.05$) for the forward and backward flow volumes and from R = 0.89 to 0.99 ($p < 0.05$) for the flow velocities. The intraobserver variabilities ranged from R = 0.94 to 0.99 ($p < 0.05$) for the forward and backward flow volumes and from R = 0.93 to 0.99 ($p < 0.05$) for the flow velocities on the different measuring planes (▶ **Table 6**).

Discussion

The aim of this study was to utilize 4 D flow MRI measurements to acquire normal ranges of "*conventional 2 D flow MRI parameters*" regarding aortic blood flow volumes and velocities in healthy volunteers. The used 4 D flow MRI sequence has been evaluated before in a phantom study at pulsatile and non-pulsatile flow, in healthy volunteers and patients with bicuspid aortic valves including head-to-head comparisons between 4 D and 2 D flow MRI as the current standard of care [8, 9, 13].

However, thorough validations of the MRI sequences being used are required for reporting normal values. Recent studies suggest that there is a relevant variability in 4 D flow MRI-derived

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▶ **Table 1** Mean 2 D flow MRI volumes derived from 4 D flow MRI including normal ranges of female healthy volunteers.

▶ **Tab. 1** Aus der 4D-Fluss MRT abgeleitete 2D-Fluss-MRT-Volumina und Normbereiche von weiblichen gesunden Probanden.

Parameter in female volunteers	Measuring plane	Mean (95 % CI)	SD	Lower limit	Upper limit
Forward flow volume [ml/heartbeat]	Plane A	84.8 (80.1–89.6)	13.1	58.6	111.1
	Plane B	68.9 (64.4–73.4)	12.4	44.2	93.7
	Plane C	64.4 (62.1–76.7)	13.1	38.2	84.6
	Plane D	56.8 (51.9–61.7)	11	34.9	78.7
	Plane E	55.1 (49.9–60.3)	10.7	33.7	76.6
Backward flow volume [ml/heartbeat]	Plane A	2.8 (2.3–3.3)	1.1	0.6	5.0
	Plane B	2.2 (1.8–2.6)	1.0	0.1	4.3
	Plane C	3.6 (3.2–4.0)	0.9	1.9	5.3
	Plane D	3.8 (3.6–4.0)	1.8	0.5	7.1
	Plane E	3.6 (3.2–4.0)	0.9	1.8	5.4
Regurgitant fraction [%]	Plane A	3.3 (2.9–3.7)	1.3	0.7	5.9
	Plane B	3.2 (2.8–3.6)	1.5	0.2	3.2
	Plane C	5.6 (4.6–6.7)	1.6	2	8.8
	Plane D	6.7 (5.9–7.5)	3.2	0.3	13.1
	Plane E	6.6 (5.8–7.3)	1.8	3.0	10.2
Net flow volume [ml / heartbeat]	Plane A	82.1 (78.4–85.8)	14.6	53.0	111.2
	Plane B	66.7 (63.9–70.5)	13	40.8	92.6
	Plane C	60.8 (57.2–64.4)	14.5	31.9	89.8
	Plane D	55.1 (53.2–57.0)	11.9	31.3	77.9
	Plane E	53.5 (50.4–56.6)	12.6	28.3	75.7

stroke volume and flow velocity using different sequences and different scanners [14, 15]. There are numerous studies regarding the validation of 4 D flow MRI sequences against 2 D flow MRI *in vivo* showing no significant differences between 2 D flow MRI and 4 D flow MRI, and excellent correlation between both techniques with a correlation coefficient of up to R = 0.98 has been found [13, 16, 17]. Contrary to those results, other groups reported that 4 D flow MRI significantly underestimates systolic peak flow velocities, while 2 D flow MRI gives accurate results [18, 19]. Other groups found significant underestimation of aortic or pulmonary regurgitation and intracardiac flow when using 4 D flow MRI measurements [20–22]. It is not clear if those differences occur when using sequences and scanners from different vendors or if there are other explanations. However, those results underline that thorough validation and quality control of the MRI sequences being used are mandatory. In this current study 2 D flow MRI measurements have been performed at 2 specific landmarks (plane A and D) for quality control without significant differences between both techniques. As further quality control, Qp/Qs in 10 datasets has been measured and we found no abnormalities. In a previous study, our group validated the used 4 D flow MRI sequence against 2 D flow MRI sequences using a custom-made flow phantom with pulsatile and non-pulsatile flow and found no significant differences between both techniques and an excellent correlation between flow measurements and the reference given by the flow phantom [8]. Therefore, the assumption that flow volumes and velocities derived from 4 D flow MRI might differ substantially from 2 D flow MRI measurements because 4 D flow MRI includes flow volumes and velocities in all spatial directions can be rejected for most parameters. However, we were able to demonstrate an effect on the overall results with a tendency towards generally higher flow volumes in the flow volumes derived from 4 D flow MRI as compared to the conventional 2 D flow MRI volumes, but these differences were not statistically significant and can therefore be neglected, except for the parameter $\mathbf{V_{ABS}}$, which provided approximately 20 % higher velocities than $\mathbf{V_{AX}}$. $\mathbf{V_{ABS}}$ should therefore not be used interchangeably. Since the comparability of commercially available 4 D flow MRI sequences with standard 2 D flow MRI sequences has been demonstrated in many studies before, including by our own group and in this current study, there is sufficient data to justify the use of 4 D flow MRI in the clinical routine and to replace 2 D flow MRI. However, one major drawback of 4 D flow MRI measurements is still the rather long acquisition time. Early 4 D flow MRI sequences took more than 17 minutes for the assessment of the mediastinal vessels [9]. Newer sequences with more sophisticated acceleration techniques take significantly shorter acquisition times and are therefore more suitable for clinical applications. In this current study,

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▶ **Table 2** Mean 2 D flow MRI volumes derived from 4 D flow MRI including normal ranges of male healthy volunteers.

▶ **Tab. 2** Aus der 4D-Fluss MRT abgeleitete 2D-Fluss-MRT-Volumina und Normbereiche von männlichen gesunden Probanden.

Parameter in male volunteers	Measuring plane	Mean (95 % CI)	SD	Lower limit	Upper limit
Forward flow volume [ml/heartbeat]	Plane A	102.2 (100.2–104.3)	16.4	69.4	135.1
	Plane B	91.9 (88.3–94.7)	20.3	51.2	112.4
	Plane C	71.1 (69.6–73.6)	13.9	43.4	98.7
	Plane D	65.8 (63.7–67.3)	13.4	39.0	92.4
	Plane E	63.8 (60.2–67.3)	13.2	37.5	90.2
Backward flow volume [ml/heartbeat]	Plane A	4.2 (4.0–4.4)	1.9	0.4	8.0
	Plane B	5.3 (5.0–5.6)	1.5	2.3	8.3
	Plane C	4.3 (3.9–4.8)	0.8	2.7	5.9
	Plane D	4.2 (3.5–4.9)	1.7	0.8	7.6
	Plane E	3.8 (3.2–4.4)	1.4	1.0	5.6
Regurgitant fraction [%]	Plane A	4.1 (3.9–4.3)	1.9	0.3	7.9
	Plane B	5.8 (5.6–6.0)	1.6	2.2	9.4
	Plane C	6.0 (5.7–6.3)	1.1	3.8	8.2
	Plane D	6.4 (6.0–6.8)	2.6	1.2	11.6
	Plane E	5.9 (5.5–6.3)	2.2	1.5	10.3
Net flow volume [ml/heartbeat]	Plane A	98.1 (96.2–100.1)	16.9	64.4	131.7
	Plane B	86.6 (84.4–88.8)	14.3	58.0	115.2
	Plane C	66.9 (61.5–72.3)	14	38.9	94.9
	Plane D	61.6 (58.2–64.9)	12.1	37.4	85.8
	Plane E	59.9 (56.3–63.5)	12.5	34.9	84.9

▶ **Table 3** Comparison of flow volumes using 2 D flow and 4 D flow at measuring planes A and D.

▶ **Tab. 3** Vergleich der Flussvolumina von 2D-Fluss und 4D-Fluss in den Messebenen A und D.

Parameter	Measuring plane	male			female		
		4 D flow mean ± SD	2 D flow mean ± SD	Comparison 4 D vs. 2 D flow p-value	4 D flow mean ± SD	2 D flow mean ± SD	Comparison 4 D vs. 2 D flow p-value
Forward flow volume [ml/heartbeat]	Plane A	102.2 ± 16.4	100.9 ± 15.9	> 0.05	84.8 ± 13.1	82.0 ± 14.5	> 0.05
	Plane D	65.8 ± 13.4	66.2 ± 15.1	> 0.05	56.8 ± 11.0	52.9 ± 13.3	> 0.05
Backward flow volume [ml/heartbeat]	Plane A	4.2 ± 1.9	3.8 ± 1.6	> 0.05	2.8 ± 1.1	2.2 ± 1.6	> 0.05
	Plane D	4.2 ± 1.7	3.8 ± 1.1	> 0.05	3.8 ± 1.8	3.5 ± 2.1	> 0.05
Regurgitant fraction [%]	Plane A	4.1 ± 1.9	3.8 ± 1.6	> 0.05	3.3 ± 1.3	2.7 ± 2.0	> 0.05
	Plane D	6.4 ± 2.6	5.7 ± 1.7	> 0.05	6.7 ± 3.2	6.6 ± 4.0	> 0.05
Net forward flow volume [ml/heartbeat]	Plane A	98.1 ± 16.9	97.1 ± 14.3	> 0.05	82.1 ± 14.6	78.8 ± 13.3	> 0.05
	Plane D	61.6 ± 12.1	62.4 ± 14.7	> 0.05	55.1 ± 11.9	49.4 ± 14.1	> 0.05

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▶ **Table 4** Flow velocities including normal ranges of male and female healthy volunteers.

▶ **Tab. 4** Flussgeschwindigkeiten und Normbereiche von männlichen und weiblichen gesunden Probanden.

Parameter in male and female volunteers	Measuring plane	Mean (95 % CI)	SD	Lower limit	Upper limit
Maximum axial velocity [m/s]	Plane A	1.01 (0.97–1.05)	0.31	0.39	1.63
	Plane B	1.11 (1.07–1.15)	0.36	0.40	1.70
	Plane C	0.98 (0.93–1.03)	0.14	0.41	1.89
	Plane D	0.95 (0.91–0.99)	0.3	0.35	1.67
	Plane E	0.90 (0.84–0.96)	0.27	0.36	1.68
Maximum absolute velocity [m/s]	Plane A	1.23 (1.17–1.29)	0.35	0.53	1.93
	Plane B	1.19 (1.11–1.27)	0.36	0.48	1.98
	Plane C	1.05 (1.00–1.10)	0.3	0.45	1.97
	Plane D	1.06 (1.00–1.11)	0.26	0.55	1.88
	Plane E	1.05 (1.00–1.10)	0.26	0.54	1.98

▶ **Table 5** Comparison of flow velocities using 2 D flow and 4 D flow at measuring planes A and D.

▶ **Tab. 5** Vergleich der Durchflussgeschwindigkeiten bei 2D- und 4D-Fluss in den Messebenen A und D.

Parameter	Measuring plane	Overall volunteers	
		4 D flow mean ± SD	2 D flow mean ± SD
Maximum axial velocity [m/s]	Plane A	1.01 ± 0.31	1.11 ± 0.38
	Plane D	0.95 ± 0.27	0.97 ± 0.27
Maximum absolute velocity [m/s]	Plane A	1.23 ± 0.35	
	Plane D	1.06 ± 0.26	

the mean scan time was 8.4 minutes using a kt-GRAPPA 5 accelerated sequence. In the clinical routine, for a complete assessment of blood flow of the great mediastinal vessels, this is an acceptable duration. In addition, compared to 2 D flow MRI acquisitions, 4 D flow MRI acquisitions enable planning in a "*straight forward*" manner without the need for exact angulation of the measuring planes, therefore saving time during the examination if multiple measurements have to be performed or if altered anatomic conditions complicate the exact perpendicular planning of 2 D measuring planes. In addition to that, a single 4 D flow MRI measurement includes information about all other vessels within the field of view like, e. g., the pulmonary artery and enables 3 D reconstructions of the vessel of interest (▶ **Fig. 1**).

A recent study by Kroeger et al. elucidated stroke volumes in 44 healthy volunteers using 4 D flow MRI and found a mean value of 72 ± 13.5 ml/heartbeat to be normal [23]. Kroeger did not differentiate between male and female participants, and in our study, we found slightly higher sex-neutral normal values with 93.5 ± 14.8 ml/ heartbeat. Nevertheless, the normal mean value of 72 ± 13.5 ml/heartbeat published by Kroeger's et al. lies within our normal range in both male and female volunteers at the aortic plane level A (58.6–135.1 ml/heartbeat) – ▶ **Table 1, 2**. Another study reports flow volumes normalized to the body surface area of 126 healthy individuals [24]. However, since in most guidelines, like the ACC/AHA Guideline for the Management of Patients With Valvular Heart Disease, cut-off values for the grading of aortic stenosis or regurgitation are given as absolute values in ml and m/s and are not normalized to the body surface area, we waived the normalization [25].

We found a mean backward flow volume of 4.2 ± 1.9 ml/heartbeat and 2.8 ± 1.1 ml/heartbeat to be normal in healthy males and females in the ascending aorta, which is equivalent to a mean regurgitant fraction of 4.1 ± 1.9 % and 3.3 ± 1.3 %, respectively. The overall sex-neutral mean regurgitant fraction was 3.9 ± 2.9 % ranging from 0–9.7 %. This is in line with other studies highlighting that small aortic regurgitation should not be taken as a pathologic finding and that regurgitant volumes of < 30 ml/heartbeat and RF < 30 % should be considered mild [26–28].

Regarding flow velocities, we analyzed the axial flow velocity ($\mathbf{V_{AX}}$), which describes blood flow that moves exactly perpendicular to the measurement plane comparable to a standard 2 D flow MRI acquisition. We found mean values of 1.01 ± 0.31 m/s to be

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▶ **Table 6** Inter- and intraobserver correlations for 4 D flow MRI measurements of flow volumes and flow velocities.

▶ **Tab. 6** Inter- und Intrauntersucher-Varianz der 4D-MRT-Messungen von Flussvolumina und -geschwindigkeiten.

	Measuring plane	**Interobserver correlation, correlation coefficient R, and p-value**	**Intra-observer correlation, correlation coefficient R, and p-value**
Forward flow volume [ml/heartbeat]	Plane A	R = 0.95; p < 0.05	R = 0.98; p < 0.05
	Plane B	R = 0.94, p < 0.05	R = 0.97; p < 0.05
	Plane C	R = 0.91, p < 0.05	R = 0.96; p < 0.05
	Plane D	R = 0.95; p < 0.05	R = 0.96; p < 0.05
	Plane E	R = 0.99; p < 0.05	R = 0.99; p < 0.05
Backward flow volume [ml/heartbeat]	Plane A	R = 0.94; p < 0.05	R = 0.95; p < 0.05
	Plane B	R = 0.95, p < 0.05	R = 0.94; p < 0.05
	Plane C	R = 0.91, p < 0.05	R = 0.97; p < 0.05
	Plane D	R = 0.95; p < 0.05	R = 0.94; p < 0.05
	Plane E	R = 0.99; p < 0.05	R = 0.99; p < 0.05
Maximum axial velocity [m/s]	Plane A	R = 0.92; p < 0.05	R = 0.94; p < 0.05
	Plane B	R = 0.91, p < 0.05	R = 0.97; p < 0.05
	Plane C	R = 0.89, p < 0.05	R = 0.93; p < 0.05
	Plane D	R = 0.97; p < 0.05	R = 0.95; p < 0.05
	Plane E	R = 0.99; p < 0.05	R = 0.99; p < 0.05
Maximum absolute velocity [m/s]	Plane A	R = 0.93; p < 0.05	R = 0.97; p < 0.05
	Plane B	R = 0.90, p < 0.05	R = 0.97; p < 0.05
	Plane C	R = 0.91, p < 0.05	R = 0.94; p < 0.05
	Plane D	R = 0.92; p < 0.05	R = 0.95; p < 0.05
	Plane E	R = 0.98; p < 0.05	R = 0.99; p < 0.05

normal, which is in line with many other sources, reporting comparable values in mostly smaller cohorts [29–34]: Based on the analysis of 16 volunteers, Bollache et al. reported in 2016 0.96 ± 0.24 m/s to be normal and in 2014 Schnell et al. found 1.06 ± 0.2 m/s to be normal [31, 35]. Utilizing 2 D flow MRI, Lotz et al. described that misaligned measuring planes lead to inaccurate findings [2]. Later, in a phantom study it was shown that 4 D flow MRI sequences deliver accurate measurements even with misaligned acquisition planes [8]. Since 4 D flow MRI enables measurements of flow that does not move perpendicular to the measuring plane, we introduced the parameter absolute flow velocity ($\mathbf{V_{ABS}}$), which includes both flow that moves perpendicular to the measuring plane and oblique flow in all spatial directions. Our results indicate slightly higher values for $\mathbf{V_{ABS}}$ compared to $\mathbf{V_{Ax}}$, indicating that flow that moves perpendicular to the measuring plane and oblique flow add up. The authors hypothesize that both kinds of flow exist in vivo, flow that moves perpendicular to the measuring plane and oblique flow and since $\mathbf{V_{ABS}}$ includes any flow, it should depict in vivo flow more precisely compared to $\mathbf{V_{Ax}}$.

One limitation of this study is that it only provides 2 D flow MRI data for planes A and D and not for all measuring planes, but since we found no significant differences on these two planes, it is highly unlikely that the other planes would show any differences. Additionally, head-to-head comparisons between the used kt-GRAPPA 4 D flow MRI sequence and 2 D flow MRI has been published already in a phantom study and in vivo as well, without significant differences between both techniques [8, 9] in pulsatile and non-pulsatile flow. Another limitation is the rather long acquisition time of the used 4 D flow MRI sequence, while there are other sequences with more advanced acceleration techniques that allow for scanning of the whole aorta within < 5 minutes [36]. This is because the aim of this study was to generate normal values using a commercially available and widely accessible 4 D flow MRI sequence.

Conclusion

In conclusion, this current study provides sex-dependent quantitative 4 D flow MRI-derived thoracic aortic normal ranges regarding flow volumes and flow velocities of aortic blood flow in healthy individuals. The acquired normal values of forward, backward, and net flow volumes as well as axial velocities did not differ significantly from normal values of single 2 D flow MRI acquisitions and can therefore be used to replace multiple single 2 D flow MRI acquisitions, which can lead to a broader use of 4 D flow MRI in the

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clinical routine. The parameter $\mathbf{V_{ABS}}$ should not be used interchangeably. This study shows that 4 D flow MRI can be integrated in the clinical routine and due to its “straight forward planning”, it may replace conventional 2 D flow MRI sequences in the future.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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