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DOI:
10.1016/j.ijcard.2017.05.125

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Document Version
Peer reviewed version

Citation for published version (Harvard):
Moody, W, Pickup, L, Plunkett, E, Fryearson, J, Clift, P, Morris, K, Thompson, P, Thorne, S & Hudsmith, L 2017, 'Feasibility of performing non-contrast magnetic resonance angiography in pregnant subjects with familial aortopathies', *International Journal of Cardiology*. https://doi.org/10.1016/j.ijcard.2017.05.125

Link to publication on Research at Birmingham portal

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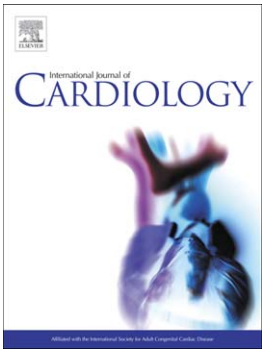

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PII: S0167-5273(17)32141-1
DOI: doi:10.1016/j.ijcard.2017.05.125
Reference: IJCA 25083

To appear in: *International Journal of Cardiology*

Received date: 4 April 2017
Revised date: 11 May 2017
Accepted date: 25 May 2017

Please cite this article as: Moody William E., Pickup Luke, Plunkett Emma, Fryearson John, Clift Paul, Katie Morris R, Thompson Peter J., Thorne Sara, Hudsmith Lucy E., Feasibility of Performing Non-Contrast Magnetic Resonance Angiography in Pregnant Subjects with Familial Aortopathies, *International Journal of Cardiology* (2017), doi:10.1016/j.ijcard.2017.05.125

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Short Communication

Feasibility of Performing Non-Contrast Magnetic Resonance Angiography in Pregnant Subjects with Familial Aortopathies

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1. This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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Revised word count: 1,606 (excluding abstract, references, tables and figures).

Running head: Non-Contrast Magnetic Resonance Angiography in Pregnancy

Conflict of interest: No relationships with industry

ClinicalTrials.gov Identifier: NCT02793570

Keywords: aortopathy, magnetic resonance angiography, pregnancy, variability

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Background: Pregnancy is associated with an increased risk of aortic pathology. We sought to assess the feasibility of performing non-contrast 3D steady-state free-precession (SSFP) magnetic resonance angiography (MRA) in pregnant subjects with inherited aortopathy.

Methods: Fifteen pregnant subjects (age 27 ± 4 yr) with positive genotyping for aortopathy (Marfan, Loeys-Dietz, Ehlers-Danlos) and/or a family history of aortic dissection underwent non-contrast 3D-SSFP MRA at 1.5T (Avanto, Siemens Healthcare, Erlangen, Germany) using a modified ECG-triggered orientated in a sagittal-oblique plane with a respiratory navigator at the diaphragmatic level (mean acquisition time 4.1 ± 1.9 min). Imaging was performed during the mid-trimester (21 ± 5 weeks). Image analysis was performed off-line using Cvi42 software (Circle Cardiovascular Imaging, Calgary, Canada). An assessment of image quality (score 0–3) was made before performing inner edge to inner edge measurements of the thoracic aorta at 7 levels from the multiplanar reconstructions by two independent blinded observers.

Results: Non-contrast 3D-MRA was successfully acquired in all 15 subjects. Image quality was deemed excellent in 87% (13/15) of cases after a mean acquisition time of 4.1 ± 1.9 min. There was a high level of agreement for aortic measurements, with low intra- and inter-observer variability (ICC ranges; 0.95–0.99 and 0.92–0.98, respectively). All pregnancies reached term (≥37/40) with a mean gestation at delivery of 38.0 ± 0.5 weeks. The mode of delivery was vaginal in 9 out of 15 subjects (60%).

Conclusions: Non-contrast SSFP MRA imaging provides a quick and reproducible method of assessing the thoracic aorta in pregnancy.

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Pregnancy is recognized as a high risk period for patients with aortic pathology.[1] Recent data suggest exposure to MRI during pregnancy is not associated with increased risk of harm to the fetus, although use of gadolinium-based contrast agent is associated with a small increase in the risk for stillbirth or neonatal death.[2] These findings support the current published recommendations that non-contrast magnetic resonance angiography (MRA) is used to assess the thoracic aorta in pregnant subjects, avoiding exposure to both ionizing radiation and gadolinium.[3-5] The guidance for this specific indication however, is based on consensus opinion (Level of Evidence C) and to our knowledge is only supported by case reports. We therefore designed a prospective observational study to assess the feasibility of performing non-contrast 3D steady-state free-precession (SSFP) MRA in pregnant subjects with inherited aortopathy.

PATIENTS AND METHODS

Patients

Prospective patients with inherited thoracic aortic disease were identified after referral to a joint cardiology and obstetric clinic based in a University hospital centre 2007-2015. Consecutive subjects (n = 15; mean age 27 ± 4 yr) deemed at high risk for progressive aortic dilatation or dissection were included in this study based on positive genotyping (Marfan, Loeys-Dietz, Ehlers-Danlos and/or a family history of aortic dissection). Exclusion criteria included age <18 years and contraindications to MRI.

MR imaging

Non-Contrast Magnetic Resonance Angiography in Pregnancy

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Patients underwent a non-contrast 3D-SSFP MRA at 1.5T (Avanto, Siemens Healthcare, Erlangen, Germany) in the mid-trimester using a modified ECG-triggered sequence orientated in a sagittal-oblique plane, aligned along the aortic arch, with a respiratory navigator at the diaphragmatic level (gating window ±4 mm). Subjects were imaged during "free breathing" adopting a "left uterine displacement" position; using a wedge under the right buttock, the abdomen and pelvis were tilted at least 15 degrees off the midline, offloading the gravid uterus from the inferior vena cava. Imaging parameters were as follows: FOV 400 × 400 mm^2, matrix size 302 × 302, slice thickness 1.3 mm (no interpolation), leading to a true voxel size of 1.3 × 1.3 × 1.3 mm^3, flip angle (FA) 90°, bandwidth 967 Hz/pixel, TE 1.1 ms, TR 2.3 ms, 50-60 slices, and 60 segments (adjusted according to heart rate), parallel imaging (GRAPPA) with acceleration factor 2, and 24 integrated reference lines, acquisition period: 286 ms per cardiac cycle, mean acquisition time 4.1 ± 1.9 min. A six-element body matrix and a six-element spine matrix coil were used for signal reception and the body coil for transmission. The power of the sequence was limited to "normal" mode (avoiding "1st level") to reduce the risk of increasing the subject's core temperature. An axial HASTE (40-50 slices; 6mm, no gap, TE 44 ms, repetition time (TR) 750 ms, parallel sat bands, images acquired in diastole) was used prior to the non-contrast 3D-MRA. Depending on the clinical scenario, SSFP cine imaging for cardiac chamber quantification, or valvular assessment, and phase-contrast flow measurements were also performed.

Image analysis

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MRA image analysis was performed off-line using Cvi42 software (Circle Cardiovascular Imaging, Calgary, Canada). Multiplanar reconstructions of the thoracic aorta were used to evaluate the aorta qualitatively and quantitatively.[6] Qualitatively, an assessment of image quality was performed (score 0–3: 0 = poor, non-diagnostic, 1 = impaired image quality that may lead to misdiagnosis; 2 = good; and 3 = excellent). The decision was based on border sharpness and image contrast. Quantitatively, aortic dimensions were measured by two independent blinded observers (6 and 12 years' experience, respectively) at 7 predefined levels: (1) aortic annulus; (2) sinus of Valsalva; (3) sinotubular junction; (4) proximal ascending aorta (at the level of the pulmonary artery bifurcation); (5) mid aortic arch (between the common carotid artery and the left subclavian artery); (6) proximal descending aorta (2 cm distal of the left subclavian artery); and (7) distal descending aorta diaphragm (at the level of the diaphragm). A mean of the anterior–posterior and left–right diameter was recorded from the reconstructed multiplanar axial image taking measurements from inner edge to inner edge as suggested by current guidelines (Figure).[7]

Statistics

Data were analysed using SPSS (v. 22, Chicago, IL). Data are expressed as mean ± SD, median (interquartile range) or frequency (%). The normality of distribution was determined using normality plots and the Kolmogorov-Smirnov test. Reliability was assessed using the intra-class correlation coefficient (ICC) with a model of absolute agreement. To assess intraobserver report variability of aortic measurements, ten studies were re-analyzed by one of the observers 4 weeks later, blinded to the original data. The inter- and intra-

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observer differences were compared with a Student's paired t-test. For all statistical comparisons, $P < 0.05$ was considered significant.

RESULTS

Non-contrast 3D-MRA was successfully acquired in all subjects during the mid-trimester (20.6 ± 4.9 weeks) and without any complication. No patients were excluded from this pilot feasibility study. Subject characteristics and pregnancy outcomes are summarised in Table 1. Two thirds of cases (10/15) had a dilated thoracic aorta. Image quality was deemed excellent in 87% (13/15) of cases after a mean acquisition time of 4.1 ± 1.9 min (range 3.4-9.2 min). In 2 out of 15 cases, although still diagnostic, image quality was deemed less than excellent which related to an inefficient navigator due to irregular breathing. Typically, the total scan time was less than 20 minutes. There was a high level of agreement for aortic measurements, with low intra- and inter-observer variability (ICC ranges; 0.95 – 0.99 and 0.92 – 0.98, respectively; Table 2). All pregnancies reached term (≥37/40) with a mean gestation at delivery of 38.0 ± 0.5 weeks. Despite the high risk nature of this cohort, close imaging surveillance in combination with satisfactory haemodynamic and clinical status permitted vaginal delivery in 9 out of 15 subjects (60%). This proportion approaches the UK vaginal delivery rate in 2014-15 for all pregnancies (73.5%).[8]

DISCUSSION

Despite published recommendations from the American College and European Society of Cardiology to use non-contrast magnetic resonance imaging in pregnancy to assess the

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thoracic aorta,[2,3] this is the first study demonstrating the feasibility of this practice in this population. We have shown that non-contrast SSFP MRA imaging provides a quick and reproducible method of assessing aortic dimensions in pregnant subjects. The main advantages of non-contrast 3D SSFP over previous MRI sequences are the higher spatial resolution and the creation of a 3D dataset, which allows the user to create the optimal perpendicular image plane from reformatted images for each segment of the thoracic aorta. These pilot data also suggest that this imaging approach is safe and perhaps more importantly, allows informed decisions regarding the timing and mode of delivery.

The clinical utility of unenhanced MR angiography to assess the thoracic aorta in clinical practice was first described in 2008.[9] Early validation studies suggested non-contrast 3D SSFP MRA provided at least as robust visualization of the aortic root compared with single-phase 3D contrast-enhanced magnetic resonance angiography.[10,11] In a further study which made a comparison with alternative sequences (3D contrast-enhanced MRA, 2D T2 black blood, and 2D cine SSFP), noncontrast 3D MRA provided a high level of interobserver agreement akin to that demonstrated in our study.[12] More recently, in many centers noncontrast 3D MRA has become the first-line imaging technique employed for serial assessment of the thoracic aorta,[6] and in our center is used even in patients in whom contrast material can be safely administered. Before completing this study, in our center subjects would have routinely undergone 2D T2 black blood imaging.

It is worth noting that there are other available imaging modalities, which can provide an assessment of aortic pathology and enable the accurate monitoring of disease.[13] Echocardiography provides the benefit of real time imaging in high resolution and allows concurrent assessment of the aortic valve, although its limited windows and coverage mean that it cannot be regarded as a comprehensive technique for the entire evaluation of the

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aorta. Computed tomography imaging is limited by its associated radiation dose, which means it is unfavourable for surveillance assessments of the aorta in the young, and is generally avoided in pregnant subjects outside the emergency setting of acute aortic pathology.

Although we did not include a

There are limitations of this study worthy of mention. Although we detected no adverse maternal or fetal outcomes following the use of MRI in this pilot study, the small sample size limits our ability to draw any firm conclusions regarding patient safety. Many centers are reticent to perform MRI in pregnant patients due to the potential heating effects on the fetus. All scans were performed at 1.5T field strength and we avoided using a sequence that required more than “level 1 power” to further minimise this potential risk but we are unable to provide information regarding the potential for ds-DNA breaks. While from a scientific perspective, it would have been of more robust to compare different methods of assessing the aorta (e.g. multislice SSFP, cine SSFP and Spin-Echo), for patient safety reasons it was deemed inappropriate to subject our patients to scanning protocols any longer in duration because of the increased chance of having an adverse haemodynamic effect on the gravid uterus. For the same reasons, we were unable to make an assessment of inter-study reproducibility. We did not perform signal-to-noise ratio (SNR) measurements although early reports have shown higher SNR values using this technique compared with reference standard contrast-enhanced MRA.[10,11] Finally, this study did not include a cohort of normal healthy pregnant subjects for comparison. Even accounting for body size, the mean aortic dimensions for subjects in the current study were generally greater than those quoted for a normal obese adult population.[14]

In conclusion, our data provide support for routine surveillance non-contrast MRA

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imaging of the aorta during the mid-trimester in high-risk subjects with an inherited aortopathy.

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REFERENCES

1. Confidential Enquiry into Maternal and Child Health (CEMACH). *Saving Mothers' Lives: reviewing maternal deaths to make motherhood safer 2006-2008.* London Centre for Maternal and Child Enquiries; March 2011.
2. Ray JG, Vermeulen MJ, Bharatha A, Montanera WJ, Park AL. Association Between MRI Exposure During Pregnancy and Fetal and Childhood Outcomes. *JAMA.* 2016;316(9):952-961.
3. Hiratzka LF, Bakris GL, Beckman JA, et al. 2010 ACCF/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/STS/SVM Guidelines for the diagnosis and management of patients with thoracic aortic disease. A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, American Association for Thoracic Surgery, American College of Radiology,American Stroke Association, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of Thoracic Surgeons,and Society for Vascular Medicine. *J Am Coll Cardiol.* 2010;55(14):e27-e129.
4. Erbel R, Aboyans V, Boileau C, et al. 2014 ESC Guidelines on the diagnosis and treatment of aortic diseases: Document covering acute and chronic aortic diseases of the thoracic and abdominal aorta of the adult. The Task Force for the Diagnosis and Treatment of Aortic Diseases of the European Society of Cardiology (ESC). *Eur Heart J.* 2014;35(41):2873-2926.
5. Regitz-Zagrosek V, Blomstrom Lundqvist C, Borghi C, et al. ESC Guidelines on the management of cardiovascular diseases during pregnancy: the Task Force on the Management of Cardiovascular Diseases during Pregnancy of the European Society of Cardiology (ESC). *Eur Heart J.* 2011;32(24):3147-3197.
6. von Knobelsdorff-Brenkenhoff F, Gruettner H, Trauzeddel RF, Greiser A, Schulz-Menger J. Comparison of native high-resolution 3D and contrast-enhanced MR angiography for assessing the thoracic aorta. *Eur Heart J Cardiovasc Imaging.* 2014;15(6):651-658.
7. Schulz-Menger J, Bluemke DA, Bremerich J, et al. Standardized image interpretation and post processing in cardiovascular magnetic resonance: Society for Cardiovascular Magnetic Resonance (SCMR) board of trustees task force on standardized post processing. *J Cardiovasc Magn Reson.* 2013;15:35.
8. National Health Service. Maternity Statistics England 2014-2015. Accessed 7th May 2017.
9. Francois CJ, Tuite D, Deshpande V, Jerecic R, Weale P, Carr JC. Unenhanced MR angiography of the thoracic aorta: initial clinical evaluation. *AJR Am J Roentgenol.* 2008;190(4):902-906.
10. Krishnam MS, Tomasian A, Deshpande V, et al. Noncontrast 3D steady-state free-precession magnetic resonance angiography of the whole chest using nonselective radiofrequency excitation over a large field of view: comparison with single-phase 3D contrast-enhanced magnetic resonance angiography. *Invest Radiol.* 2008;43(6):411-420.
11. Krishnam MS, Tomasian A, Malik S, Desphande V, Laub G, Ruehm SG. Image quality and diagnostic accuracy of unenhanced SSFP MR angiography compared with conventional contrast-enhanced MR angiography for the assessment of thoracic aortic diseases. *Eur Radiol.* 2010;20(6):1311-1320.
12. Potthast S, Mitsumori L, Stanescu LA, et al. Measuring aortic diameter with different MR techniques: comparison of three-dimensional (3D) navigated steady-state free-precession (SSFP), 3D contrast-enhanced magnetic resonance angiography (CE-MRA), 2D T2 black blood, and 2D cine SSFP. *J Magn Reson Imaging.* 2010;31(1):177-184.
13. Holloway BJ, Rosewarne D, Jones RG. Imaging of thoracic aortic disease. *Br J Radiol.* 2011;84 Spec No 3:S338-354.
14. Davis AE, Lewandowski AJ, Holloway CJ, et al. Observational study of regional aortic size referenced to body size: production of a cardiovascular magnetic resonance nomogram. *J Cardiovasc Magn Reson.* 2014;16:9.

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Table 1. Baseline characteristics and outcomes of pregnancy.

Variable	N = 15
Age, y	27 ± 4
Ethnicity	
White	14 (93)
Asian	0 (0)
Afro-Caribbean	1 (7)
Inherited Aortopathy	
Marfan	9 (60)
Ehlers-Danlos	2 (13)
Loeys-Dietz	1 (7)
Undefined	3 (20)
Beta-blocker	12 (80)
Systolic blood pressure, mmHg	121 ± 9
Diastolic blood pressure, mmHg	76 ± 4
Aortic dimensions	
Annulus, mm	25 ± 8
Sinus of Valsava, mm	35 ± 4
Sino-tubular junction, mm	29 ± 6
Proximal ascending, mm	27 ± 8
Mid aortic root, mm	26 ± 5
Proximal descending, mm	25 ± 11
Distal descending, mm	20 ± 4
Quality of study, 0 = poor, 3 = excellent	2.8 ± 0.4
Gestational age at delivery, wk	38.0 ± 0.5
Mode of delivery*	
Spontaneous vaginal delivery	6 (40)
Assisted (ventouse or forceps)	3 (20)
Induction	4 (27)
Elective Caesarean section	3 (20)
Emergency Caesarean section	3 (20)
Complications of pregnancy	
Maternal death	0 (0)
Adverse fetal outcome	0 (0)

Data are mean±SD or N(%)

*Not mutually exclusive

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Table 2. Intra- and interobserver variability of aortic measurements.

Aortic dimension (mm)	Variability	Mean difference ± SD (mm)	*P* Value	ICC (95% CI)
Annulus	Intraobserver	0.04 ± 0.81	0.77	0.99 (0.94 to 1.00)
	Interobserver	−0.61 ± 1.91	0.43	0.92 (0.62 to 1.00)
Sinus of Valsava	Intraobserver	0.43 ± 0.81	0.50	0.99 (0.95 to 1.00)
	Interobserver	−0.71 ± 0.91	0.37	0.96 (0.91 to 1.00)
Sino-tubular junction	Intraobserver	0.05 ± 0.32	0.71	0.99 (0.95 to 1.00)
	Interobserver	−0.07 ± 0.62	0.63	0.96 (0.91 to 1.00)
Proximal ascending	Intraobserver	0.23 ± 0.65	0.21	0.99 (0.97 to 1.00)
	Interobserver	0.29 ± 0.73	0.50	0.95 (0.92 to 1.00)
Mid aortic root	Intraobserver	0.19 ± 1.01	0.33	0.95 (0.97 to 1.00)
	Interobserver	−0.21 ± 1.25	0.27	0.93 (0.82 to 1.00)
Proximal descending	Intraobserver	0.21 ± 0.48	0.56	0.99 (0.97 to 1.00)
	Interobserver	0.36 ± 0.50	0.40	0.95 (0.92 to 1.00)
Distal descending	Intraobserver	−0.10 ± 0.45	0.32	0.99 (0.97 to 1.00)
	Interobserver	−0.15 ± 0.80	0.45	0.98 (0.96 to 1.00)