VILNIUS UNIVERSITY

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PALIONIS

The Importance and Clinical Application of Magnetic Resonance Tomography Contrast Unenhanced Sequences in Diagnostics of Aorta Pathology

SUMMARY OF DOCTORAL DISSERTATION

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This dissertation was written between 2013 and 2017 in Vilnius University.

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VILNIAUS UNIVERSITETAS

Darius

PALIONIS

Magnetinio rezonanso tomografijos bekontrastinių sekų reikšmė ir klinikinio taikymo galimybės aortos ligų diagnostikai

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ABBREVIATIONS

3D-MRA	three dimensional magnetic resonance angiography
AA	ascending aorta
ABP	arterial blood pressure
AO	aorta
AS	sinuses of aorta (Vansalva)
AT	applanation tonometry
AVS	aortic valve stenosis
b-SSFP	balanced steady state free precession sequence
WBS	white blood sequence
DA	descending aorta
BAOV	bicuspidal aortic valve
RA	right atrium
RPA	right pulmonary artery
RV	right ventricle
EF	ejection fraction
BBS	black-blood sequence
C/M	contrast media
BMI	body mass index
LA	left atrium
LPA	left pulmonary artery
BSA	body surface area
LV	left ventricle
LVH	left ventricular hypertrophy
LVOT	left ventricular outflow tract
CNR	contrast to noise ratio
MV	mitral valve

MPR	multiplanar reconstruction
MRA	magnetic resonance angiography
PA	pulmonary artery
PWV	pulse wave velocity
PH	pulmonary hypertension
SD	standard deviation
SSFP	steady state free precession sequence
STJ	sinotubular junction
SNR	signal to noise ratio
CT	computed tomography
MRI	magnetic resonance imaging
HR	heart rate
US	ultrasound examination (echocardiography)
TAOV	tricuspid aortic valve
TEE	transosophageal echocardiography
TTE	transthoracic echocardiography
LGE	late gadolinium enhancement
VUL SK	Vilnius University Hospital Santaros Klinikos

SUMMARY

1. RELEVANCE OF THE STUDY

In the last decade, the method of investigation - magnetic resonance imaging of the heart and large blood vessels - has been increasingly used in clinical practice. Because of many advantages, magnetic resonance imaging is widely used in many areas of diagnostics and one of them is the assessment of the aorta. This clinical method is very important for the detection of major vascular diseases, confirmation of clinical diagnosis and further evaluation and follow-up of treatment efficacy. Magnetic Resonance Angiography (MRA) with a contrast enhancement is a technique carried out using 3-dimensional (3D) fast gradient echo sequences after administration of gadolinium contrast media. This method allows to obtain ultra-high-quality vascular images and is considered a "gold standard". In recent years, magnetic resonance angiography with intravenous contrast has become one of the standard methods for evaluating the diseases of chest aorta and follow-up in many treatment and diagnostic centers over the world. Because of its high diagnostic accuracy for vascular pathology, rapid acquisition of images and ability to reconstruct images in 3D, magnetic resonance angiography has become an integral part of the research methodology not only in diagnosis, but also in the planning of further surgical or interventional therapies. Nevertheless, injection of intravenous contrast media and the possible undesirable consequences of this lead to a reconsideration of contrast unenhanced magnetic resonance imaging methods and their benefits in assessing cardiovascular diseases. In 2017 the use of gadolinium-containing linear contrasts in the European Union was limited, providing even greater need for alternatives to MRI angiography with contrast media. The doctoral dissertation presents an overview of the possibilities of native (contrast unenhanced) magnetic resonance imaging aorta examination and comparing it to the magnetic resonance angiography with a contrast agent for assessing the chest aorta and its segmental diameters, possibilities, advantages and disadvantages of these research methods, practical application possibilities.

Recent literature encourages the use of contrast unenhanced segmental analysis for measurement of lumen diameters in aorta, but the data are partially controversial and there is no unified contrast unenhanced aortic magnetic resonance imaging protocol in Lithuania. Intravenous contrast agents with gadolinium intravenous injection and the resulting undesirable effects motivate the study of contrast unenhanced magnetic resonance imaging methods and their benefits in assessing aortic diseases, diagnosis and treatment. In addition, there is an importance of an economical factor, as contrast enhanced MRI is more expensive due to the price of the contrast media itself and its supplemental equipment.

Possibility for measurement of aortic diameters without contrast media due to the good tissue contrast is one of the MRI strengths compared to other imaging modalities. However, MRI is also a functional imaging method that, as in the case of US, can be used to measure blood flow parameters in major blood vessels, including aorta, using Doppler technique. Aortic stiffness is the indicator of aging and pathological changes, as well as dependent factor to the central hemodynamics. Recent research has revealed that the MRI method is likely to be as successful as the ultrasound method (applanation tonometry) to be applied for pulsed wave velocity evaluation in aorta.

Studies have shown that, without using intravenous contrast in MRI studies, qualitative and quantitative parameters of thoracic aorta diameters do not underperform comparing to contrast enhanced MRA and other imaging methods or even surpass them in evaluating aortic wall changes. And while contrast enhanced MRA images can be obtained much faster than in native (unenhanced) MRI examinations, the lower risk to the patient and the lower cost of the test are unquestionably the benefits of contrast unenhanced MRI. So far, most of the comparative studies in the segmental measurements of the chest aorta have been performed with a constant free spin sequence (SSFP) and magnetic resonance imaging angiography (MRA) with contrast media, and this fact should not be astonishing, as the SSFP has an advanced and high probabilistic test method with its high diagnostic value.

2. THE AIM OF THE STUDY

To determine the practical application of MRI contrast unenhanced sequences in diagnosis of aortic diseases and to build up protocol for this study.

2.1 Objectives

1. Comparison of aortic contrast unenhanced MRI sequences with aortic contrast MRI angiography for the diagnosis of aortic dilatation in bicuspidal aortic valve (BAOV) and patients with primary arterial hypertension (PAH).
2. Comparison of aortic contrast unenhanced MRI sequences with aortic ultrasound (US) in diagnosing aortic dilatation in BAOV and PAH.
3. To evaluate the correlation of diagnostic accuracy of aortic stiffness in MRI comparing with applanation tonometry ("gold standard").
4. To evaluate the aortic stiffness diagnostic possibilities in the MRI method for patients with aortic pathology (BAOV and PAH) and control group patients.

3. SCIENTIFIC NOVELTY AND PRACTICAL SIGNIFICANCE

In cardiology patients, using an echocardiographic (US) method, due to poor echogenicity in patients or for other reasons, sometimes the cardiac and vascular anatomy cannot be reliably estimated; therefore, only two main alternatives - computed tomography (CT) and MRI remain for aortic dilatation diagnosis using imaging. The main disadvantages of the CT method are ionizing radiation and iodine-containing nephrotoxic contrast media. In the case of evaluation of the diameter of the aorta, the side effects of the CT examination are greater than the possible benefits of alternative methods.

MRI for aortic diameters measurement nowadays is also routinely performed using intravenous contrast media with gadolinium containing contrast agents. Following the ban on linear contrast media in 2017, MRI examination of aorta with no contrast media gets even more clinical significance. On the basis of dissertation’s goal and results, we see real practical benefits and we suggest, in the case of routine cases in Lithuania, to apply a contrast unenhanced MRI method to the assessment of maximal measurements of aorta according to the methodology described by dissertation. Especially, when cardiovascular diseases in Lithuania and in the world are not decreasing and the ways are sought for the simplest and most economical, but reliable research of aortic pathological changes. The MRI method is particularly relevant as it is a non-invasive and non-ionizing radiation examination.

To date, comparative studies have not been carried out in Lithuania to analyze MRI aortic angiography with and without contrast media. In the world, there are only isolated aortic stiffness and PWV comparative studies between MRI and AT methodologies, and research in Lithuania on these issues is not yet available. In addition, we were one of the first to perform comparative measurements for aortic PWV evaluation not only in the aortic arc but also in the aorta. We believe that due to aging or pathological changes, the varying diameter and elasticity of the aorta (whose decrease leads to an increasing overload and promotes other pathophysiological changes) can also be evaluated using the MRI method without contrast media as an alternative to other methodologies (especially when they cannot be applied or the results are non-informative).

4. PRINCIPLE STATEMENTS FOR DEFENCE

1. MRI aortic measurements without contrast enhancement using "white blood" sequences in the axial plane allow statistically reliable and most accurate estimation of the degree of dilatation of aortic aorta and other segments in the case of TAOV compared to the "black blood" sequences.
2. The results of all methods of measurement for aortic sinus and ascending aorta in MRI better correlate in-between that with US measurements for both TAOV and BAOV.
3. The PWV measurements using MRI method are most accurate in the aortic arch and statistically reliably correlate with the AT method (the "golden standard").
4. The MRI methodology for determining the PWV in the arch reflects the age-related and pathological changes in stiffness of the aorta and has statistically significant gender difference in PWV, therefore may be an alternative to the AT technique.

5. MATERIALS AND METHODS

The study was conducted in accordance with the recommendations of the Vilnius Regional Biomedical Research Ethics Committee issued on 2013 February 12 and supplemented on 2014 April 8 (Annexes 1 and 2) with permission No. 158200-13-576-178 (Supplement No. 158200-576-PP1 -14). Study Type: Clinical Prospective Study.

The study included all conscious and willing to participate (with written consent) in the study of adult patients (18-75 years of age) with cardiovascular disease, who had been assigned to perform heart and aorta MRI at the Center for Radiology and Nuclear Medicine of Santaros Klinikos of Vilnius University from April 2014 to April 2017.

Subjects for research:

1. Patients with primary arterial hypertension (including resistant to medical therapy) with TAOV.
2. Patients with bicuspidal AOV.
3. Patients without structural heart disease and with tricuspid AOV served as a control group.

Inclusion criteria:

1. The aforementioned pathology has been diagnosed.
2. A grown-up patient (18-75 years old).

Exclusion criteria:

1. Patient's refusal to conduct an examination.
2. The patient is a minor or unable to express his will.
3. Vulnerable persons.
4. Contraindications for the MRI study.

Control group: In addition to no structural heart disease - heart and aorta in other imaging studies appears to be unchanged.

During the study, MRI examinations were performed for 136 subjects. All subjects were divided into 3 main groups according to the selection criteria:

1. Patients with resistance to treatment for primary arterial hypertension (PAH) who were undergoing MRI testing prior to renal artery sympatic denervation (RASD) and after 6 months post RASD. In the PAH group: 52 patients with a mean age of 53.3 ± 8.1 years, 28 men and 24 women.
2. Patients with a bicuspidal aortic valve (BAOV) who were undergoing studies for the changes of the BAOV and the evaluation of ascending aorta dilatation. In the BAOV group: 42

patients with an average age of 30.8 ± 9.8, 31 males and 11 women.

3. The control group consisted of patients without structural heart disease and a tricuspid aortic valve (TAOV). TAOV group: 42 patients, mean age 36.6 ± 15.8, 26 men and 16 women.

5.1 Magnetic resonance tomography imaging protocol

Prospective study was performed using a 1.5 T Siemens Avanto (Germany, Erlangen) MRI machine using prospective ECG and breath holds (~15-20 s). All patients were examined in supine position. For a segmental and general left ventricle (LV) function evaluation, a special sequence of balanced steady state free precession sequences (b-SSFP) motion was used, characterized by a high signal-to-noise ratio (SNR), very good in blood and myocardial contrast ability and low sensitivity to motion artefacts. With the patient holding the breath, this cine sequence allowed to obtain images of four, three, two chamber views and short cardiac axes in 8 mm thick slices without any gaps (from 7 to 13 short axis slices).

Segmental diameters of the aorta were evaluated by "black blood" (HASTE) and "white blood" (TrueFISP, TRUFI) sequences as well with 3D contrast enhanced T1 isometric sequence.

Characteristics of the HASTE “black blood” sequence: field of view (FOV) - 420 mm, FOV phase - 75%, slice thickness - 6 mm, distance between slices - 0 mm, TR 649 ms, TE 42 ms, flip angle (FA) 160 °, volume element size - 2.2 × 1.3 × 6 mm.

Technical characteristics of TrueFISP “white blood” sequence: FOV - 340 mm, FOV phase - 87.5%, thickness of layer - 6 mm, distance between slices - 0 mm, TR 270 ms, TE 1.2 ms, FA 60 °, volume element (voxel) size - 2.1 × 1.3 × 6 mm.

Using phase velocity mapping sequence, the blood flow in aorta was scanned in 2 steps. The first slice was chosen so that the plane perpendicularly slices proximal ascending aorta (immediately above the sinotubular junction) and also covers the descending part of the aorta in the same plane. The scans in this plane were performed twice, and the result from the two measurements was averaged. The second slice was positioned in the distal part of the infrarenal aorta, perpendicular to the lumen, and immediately above the aortic bifurcation. The scan is also done 2 times. The result obtained from the two measurements was averaged.

Technical characteristics of the phase encoding sequence: field of view (FOV) - 320 mm, FOV phase - 69%, the thickness of slice - 5.5 mm, TR 47 ms, TE 1 ms, FA 30 °, the volume element size - 1.7 × 1.7 × 5.5 mm, 50 phases in 1 s (time resolution 20 ms / section. Note: according to international guidelines, the resolution time for flow analysis should be <30 ms/one slice, therefore our chosen sequence had a sufficient time resolution for recording a good quality flow curve). An analogous sequence was also applied for the determination of antegrade and retrograde flow through the aortic valve.

Aortic 3D angiography was performed using a T1 isometric sequence with 0.15 mmol/kg gadolinium containing gadofenetate dimeglumine or gadodiamide infusion via a brachial vein catheter using a special high-pressure automatic syringe. The scan time after contrast injection was chosen for each patient individually measuring the hemodynamic curve by injection of 1 ml of contrast media. 3D T1 angiography sequence technical characteristics: field of view (FOV) - 500 mm, FOV phase - 66%, thickness of slice - 1.4 mm, TR 3 ms, TE 1 ms, FA 25°, volume element size - 1.4 × 1.3 × 1.4 mm.

10-15 minutes after injection of gadolinium gadofenetate dimeglumine or gadodiamide (both containing gadolinium) via a special high-pressure automatic syringe, late gadolinium enhancement (LGE) sequence was performed to exclude structural myocardial pathology. A special gradient-echo sequence with an inversion recovery was used to determine delayed accumulation of contrast media. Technical parameters of the applied sequence: TR 700 ms, TE

3.2 ms, FA 25°; field of view size (FOV) 400 mm; volume element size 2.1 × 1.6 × 8 mm, scanned by inhalation of the patient. In order to suppress the myocardial signal, the optimal time was chosen between a premature inverse 180° pulse and a 90° radio pulse (typically from 240 ms to 330 ms). Images were obtained in the same four, two, three chamber view and short LV axis planes, as well as motion images. The planes of both long and short cardiac axes were identical in both the cine and the LGE images. Total duration of MRI study according to the protocol was 45-60 min.

5.2 Magnetic Resonance Imaging post-processing analysis

The analysis of MRI images was carried out in accordance with the recommendations of the Working Group on Image Reconstruction. An independent analysis of MRI for cardiac morphology and function was performed in each case using Siemens Argus software (version 4.01, Germany). The advantage of our work is that the images of MRI were evaluated by two experienced researchers (>10 years of practice with MRI, blinded to other available clinical data). Both researchers are accredited at EuroCMR II level at the London UCL Hospital with prof. James Moon. The fact that the performance of the research and the results of the assessment are influenced by the experience of the specialist is proved by other research studies.

LV volumes and functional indicators are estimated from LV short axes (basis-to-apex images) using the Argus program (Siemens). The endocardium and epicardial margin of the systole and the end of the diastole were defined manually by the usual method. LV wall thickness was measured at the end of the diastole perpendicular to the wall. The gender and body surface area (BSA) of each patient was adapted to normalize left ventricular final systolic volume (LVESV), final diastolic volume (LVEDV), and LV mass index (LVMI). The area of the left atrium (LA) was evaluated in the four-chamber view using the most appropriate plane with the best coverage of the LA (selecting one of 3 slices in 4-chamber view). The contours of the LA plot area were defined manually during the final systolic phase of the LV.

For the analysis of blood flow in the aorta, dedicated software "ART-FUN" (version 1.0, Laboratoire d'Imagerie Fonctionnelle, France) was used to measure aortic flow measurements as well as to determine the segmental PWV. This software is validated by other clinical studies. The aortic flow areas were defined in a semi-automated manner.

The length of the aorta was evaluated from T1 isometric images after intravenous contrast using the Lumen track software (Siemens, VesselView). Meanwhile, the AorteGeo software package was used to evaluate the length of the aortic arch as the initial and final measuring points were placed in the ascending and descending aortic flow central positions in the phase contrast sequence, while the remaining points were localized in the longitudinal aortic phase contrast image (the latter was obtained using semi-automatic triangulation, when in the axial images 3 main points of the plane were localized - in the ascending and descending aorta and aortic arch, with the maximum choice of position close to the center of the lumen).

The segmental diameters of the aorta were evaluated from the 3D T1 contrast enhanced sequence from the reconstructed transverse planes using MPR, measuring the maximum diameter 2 times and choosing a larger measured result. We used aortic segmental system by T. Kaiser et al., measuring 5 main aortic segments: 1) at the level of the aortic sinus, 2) ascending aorta at the right pulmonary artery (RPA) level, 3) aortic arch in the T2 segment, or between the first two branches (if there were only two branches of the aortic arch), 4) descending aorta at the left pulmonary artery (LPA) level. In the same manner, the same segments were measured in “black blood” sequences and in “white blood” sequences measuring the largest dimension in the axial plane of the body. Measurements of the maximum segmental diameter of the aorta in the true axial plane of the body are easier for the inexperienced researcher and is suitable for a wide range of routine applications, especially for researchers who have not been able to apply multiplanar reconstruction (which also takes up additional time).

A delayed gadolinium enhancement (LGE) sequence was used 10-15 minutes after administration of the contrast agent, using a 0.15 mmol/kg dose of gadolinium DTPA and using an inverted gradient echo sequence. The LGE sequence was performed on the planes of both long and short cardiac axes as in the preceding cine sequences in order to exclude a possible previously unknown myocardial pathology (myocardial infarction, chronic changes after previous myocarditis, etc.). The pre-pulse delay (time before inversion - TI) was individually evaluated with a pre-pulse sequence. The contrast agent was contraindicated if the glomerular filtration rate (GFR) was <30 ml/min. Therefore, two patients were not included in the sample and pulse rate (PWV) in the whole aorta was also not evaluated. Two radiologist technologists who have >10 years of experience of performing MRI performed all MRI examinations.

After 6 months, the MRI was repeated in PAH patients using the same protocol.

5.3 Arterial stiffness studies using applanation tonometry

Aortic stiffness and central blood pressure are evaluated using the Sphygmocor (AtCor Medical, Australia) applanation tonometry system with high precision piezoelectric crystal micromanometer (Millar®, Millar Instruments, USA). Finding the pulse of carotid, radial and femoral arteries where at the sites where they are closest to the body surface and based on solid anatomical structures - in the wrists, neck and groin areas. In these places, a special piezoelectric transducer of the transverse tonometry is sequentially applied during the study. The special software recorded patient data: height, weight, age, peripheral arterial pressure and measured distances. Sequential recording of the pulse wave velocity curves of the proximal (i.e., common carotid artery) and distal arteries (i.e., radial and femoral arteries). The pressure and pulse volume curves were recorded for 20 seconds in each measurement series (each curve is synchronized with an electrocardiogram R peak) and the results of each measurement are averaged. The goal is to have a calculated researcher's index of software >85%. By recording these curves, data are analyzed, arterial stiffness parameters are calculated: pulse wave rate, augmentation index and central arterial blood pressure. The pulse wave velocity between carotid and femoral arteries, the "gold standard" for the evaluation of arterial stiffness, is calculated automatically by dividing the distance (measured by using a flexible ruler) from time (meters per second) and multiplying it by 0.8, as recommended by the European expert guidelines. Estimates are based on literature and age-related and sex-dependent normal values in the software of the device.

5.4 Ultrasound protocol

A two-dimensional (2D) cardiac ultrasound examination (US) was performed using a color Doppler ultrasound system using a 1.0 to 5.0 MHz sensor (GE Vivid 7; General Motors Corporation, New York, USA). The following morphological parameters were evaluated: the final diastolic thickness (IVSd) of the mediastinal partition, the diastolic thickness (LVPWd) of the left ventricular (LV) and left diastolic diastolic diameter (LVd) of the left ventricle (LV). Following formulas have been used for calculations: body surface area (BSA) = $0.0061 \times$ height (cm) + $0.128 \times$ weight (kg) - 0.1529 (m^2), left ventricle mass (LVM) = $0.8 \times 1.04 \times [(IVSd + LVPWd + LVd)*3-LVd*3]+0.6$ (g), left ventricle mass index (LVMI) = LVM / BSA (g/m^2) and relative wall thickness (RWT) = (IVSd + LVPWd) / LVd * 6.7.

The LV ejection fraction (LVEF) was calculated using the Simpson BP method. The LV diastolic function evaluated the use of

Pulse Doppler for assessing the maximum early diastolic flow velocity (E) and the maximum rate of atrial contraction (A), E / A ratio, mitral valve (MV) A wavelength (Adur), E wave deceleration time (DTE), as well as tissue Doppler parameters with early (E ') and late (A') mitral valve speeds (MV rings). The E / E ratio was calculated as the LV filling pressure index. The isovolemic relaxation time (IVRT) was measured from the end of the flow of the aorta to the start of the flow through the mitral valve with a parallel representation of the AOV and MV flow.

The aortic measurements were performed in a 3-chamber view. The maximum diameters of the aortic sinus and the proximal part of the ascending aorta were measured.

Circular images of 4 and 2 chambers were obtained by evaluating the atrial length and area evaluation (from the middle of the MV plane to the back wall). The maximum area and length of the left atrium (LA) was prior to the mitral valve opening, excluding LA auriculum and pulmonary veins. The LA area was calculated and indexed to BSA. The original images were saved and the blind data was later analyzed using EchoPAC software (GE Medical Systems).

5.5 Statistical analysis

Statistical computations were performed using STATISTICA 64 statistical package. All results are presented with 95% confidence intervals.

The results of the different pulse wave rate measurement methods (AT and MRI comparison were performed using the Bland-Altman method).

$$S(x,y) = \left(\frac{S_1 + S_2}{2}, S_1 - S_2 \right)$$

The PWV measurements AT (S_1) and MRI (S_2) were performed independently and the resulting in 2n data array of data points. Each of the n samples is shown in the graph, assigning the average of both measurements as the abscissa (x-axis) value and the difference between the two values as the ordinate (y-axis) value.

The Pearson correlation coefficient (R) is calculated using the following method:

$$r = \frac{\sum_{i=1}^{n}(x_i - \bar{x})(y_i - \bar{y})}{\sqrt{\sum_{i=1}^{n}(x_i - \bar{x})^2}\sqrt{\sum_{i=1}^{n}(y_i - \bar{y})^2}}$$

,

when n is the sample size, x_i and y_i are the sample individual sample sizes in the position, and the sample meanings are calculated according to the following formula:

$$\bar{x} = \frac{1}{n}\sum_{i=1}^{n} x_i$$

If the correlation between the individual tests was high (R = 0.7 or higher) then measurements were considered as having a good level of testing and repeatability.

Independent and unequal group t-test (Welch) method was applied for the statistically significant difference between the PWV and aortic diameters for the determination of the groups. The t-test for groups whose averages and variations are different were calculated using the formula:

$$t = \frac{\bar{X}_1 - \bar{X}_2}{s_{\bar{\Delta}}}$$

, where

$$s_{\bar{\Delta}} = \sqrt{\frac{s_1^2}{n_1} + \frac{s_2^2}{n_2}}$$

4. RESULTS

After measurements of the aortic segments before and after 6 months, the PAH group revealed a very high repeatability of the measurements, both with contrast enhanced and contrast unenhanced methods. Although the measurements of all segments strongly correlated with the statistical significance ($p < 0.05$) in the contrast enhanced 3D-MRA method (in the aortic sinus region R = 0.92, in the ascending aorta R = 0.92, in the aortic arch R = 0.93, in the descending aorta R = 0.83 and in the diaphragmatic aortic part R = 0.91), but the strongest correlation was determined using the method of "white blood" sequences (in the aortic sinus region R = 0.94, in the ascending aorta R = 0.94, in the aortic arch R = 0.94, in the descending aorta R = 0.93 and diaphragm aortic part R = 0.94). These findings correspond to Krishnam and co. performed studies with 50 patients, when no significant difference was observed in the measurements of aortic segments between MRA with contrast media and "white blood" sequences. Although the Koktzoglou study found that the precision of measurement in the aortic sinus region in the "white blood" sequence was lower than in MRA with contrast, but using our "white blood" sequences, we obtained good reproducibility results in all segments. Meanwhile, using the measurements of "black blood" sequences, the worst correlation was found in the aortic sinuses (as in the Koktzoglou study) and diaphragmatic segments: in the aortic sinus region R = 0.88, in the ascending aorta R = 0.95, in the aortic arch R = 0.96, in the descending aorta R = 0.93 and in the diaphragmatic aortic part R = 0.87 ($p < 0.05$). It should also be noted that measurements of the maximum segmental diameters of aorta in the normal axial body planes (as we suggest in our methodology) are simpler for an inexperienced researcher and suitable for a wide range of routine applications, and are statistically insignificantly different from the "golden standard" (MRA with contrasting media) and also good reproducibility results have been achieved in the TAOV group. From the results obtained, it can be seen that although the "black blood" and "white blood" sequences are statistically reliably and strongly correlated with each other, but somewhat better reproducibility is observed in "white blood" sequences, therefore, when measuring aortic segmental diameters in the case of TAOV, without the contrast media, we recommend use these sequences. From 2017 July 20 Gadolinium containing linear MRI contrast media in the European Union and in Lithuania are no longer used. Since deposition of linear contrasts in the brain has been established since 2017, aortic MRI study (as in other body areas) without contrast media has gained even more clinical significance. Based on our work results, we see real practical benefits, and we suggest in Lithuania, in the case of routine cases, to apply a contrast unenhanced MRI method using "white blood" MRI sequences to evaluate the maximum measurements of aortic segments. The contrast unenhanced MRI 3D-SSFP with ECG synchronization during the study could not be applied due to technical limitations. This sequence is increasingly being applied in the world due to the availability of new MRI methods due to the updating of the hardware base, but it is not yet applicable in Lithuania. Therefore, we believe that our study will help reduce the number of aortic angiography in Lithuania with contrast media, until the next decade, it is likely in Lithuania that we will be able to fully switch to contrast unenhanced 3D angiography for aortic diameters and PWV measurements.

In the BAOV group, aortic contrast enhanced and contrast unenhanced measurements had the weakest correlations in the aortic sinus area. This can be explained by both the physiological pulsation of the aorta root (especially if ECG synchronization is not applicable) and a significant discrepancy between US and MRI measurements due to the asymmetry of the BAOV sinus. A significant discrepancy in the measurement of the size of the BAOV sinus with MRI and US methods was found during the initial study data collection. After analyzing the reasons, it was found that the difference is most likely due to the difference in measurement methodology. The MRI minimum and maximum diameters of aorta sinuses (AS) were determined by evaluating the image of a short-axis reconstructed by MPR, while the US plane is routed to AS from a 3-chamber image whose plane generally coincides with the smaller AS-dimension. Having detected the disadvantages of US methodology, VUL SK specialists in congenital and acquired heart disease took into account these differences in methodologies and started (in the case of BAOV and normal TAOV) measuring US diameters of the AS in a short axis image corresponding to the MRI reconstruction plane.

After analysis of aortic measurements in US and MRI studies, the following results were obtained: in the PAH group, US aortic sinus measurements correlated most closely with "white blood" sequences (R = 0.9, p <0.05), weaker with 3D MRA with c/m (R = 0.88, p <0.05), and the worst result was in “black blood” sequence (R = 0.83, p <0.05). The "black blood" sequence is usually used as an additional assessment of the morphology of the aortic wall, but with pulsation of the wall, we have found that it is more difficult to estimate it’s true wall position than in "white blood” sequences - this could be one of the main reasons, why in our results, in most cases, better results were obtained with "white blood" sequences. The US measurements of the ascending aorta strongly correlated with the "white blood" sequences and with the 3D MRA with c/m (R = 0.86, p <0.05). Minimal, but stronger correlation was observed in measurements with "black blood" sequences (R = 0.85, p <0.05). From the results obtained, it is seen that the strongest correlation in the PAH group was found between the US and "white blood" sequences. Since this trend has been established both between different MRI sequences (comparing sequences with and without c/m) and between different methods (US vs. MRI), therefore, in the measurement of aortic segmental diameters in TAOV, we recommend using “white blood” sequences without contrast media.

In the BAOV group, aortic sinus US measurements were most strongly correlated with "black blood" sequences (R = 0.86, p <0.05), weaker with 3D MRA with c/m (R = 0.80, p <0.05) and the worst result was with "white blood" sequences (R = 0.77, p <0.05). In the BAOV group, the ascending aorta US measurements correlated strongly with the 3D MRA with c/m (R = 0.70, p <0.05), much weaker with "black blood" sequences (R = 0, 68, p <0.05), and the worst result was with "white blood" sequences (R = 0.60, p <0.05). From the results, it is seen that the lowest correlation in the BAOV group (unlike PAH) was found between the US and "white blood" sequences for both aortic sinus and ascending aortic measurements. According to some authors, the aortic diameters are measured most accurate in “white blood” sequences because of the excellent contrast between the aortic wall and the lungs, but this trend was not observed only in the BAOV group.

Analyzing the results, we found that the results of the US measurements were more varied than in the MRI. We believe that this is mainly due to the fact that the US measurements were performed by different researchers and is more researcher-dependent, which results in a greater variation between the research methodology, the researchers' experience and the results of the measurements.

Measurements of applanation tonometry and MRI for the PWV in the aorta statistically reliably, but weakly correlated (R = 0.35, P <0.05). According to the linear regression equation, we have found that PWV_AT = (PWV_MRI – 3.58) / 0.49 (R = 0.354, P <0.05). A statistically significant correlation between PWV in the whole aorta and AT was not obtained (R = 0.225961, P> 0.05), but the determination of PWV by MRI method in the aortic arch and in the whole aorta was statistically reliably correlated (R = 0.306, P <0. 05). The determination of PWV in the aortic arch is performed in one scan, so, as we have found, this measurement method is more precise than setting the PWV throughout the aorta. The method for determining the PWV in the whole aorta determines the time interval according to the blood flow curves recorded from two separate sequential scans, which is likely to significantly increase the error comparing to the one-time scan flow curves, and therefore the resulting measurement has sufficiently significant higher hardware and/or measurement errors. The AT PWV measurements statistically reliably correlate with the age of patients ($R = 0.354$, $P < 0.05$) as also has been determined by Doupis and co-authors. Bland Altman's analysis showed that the mean total PWV measurements between the AT and MRI in aortic arch were 1.46 m/s higher in the AT methodology. Jehill D. Parikh research have published similar data as our analysis. Their measured PWV values were measured using the MRI method and were found to be lower than in the AT method. The values of our MRI PWV were on average 1.46 m / s lower compared to 1.6 m / s in D. Parikh's studio, which indicates a similar difference between AT and MRI. The PWV measurements by the MRI method in the PAH group, the BAOV and the control group have found statistically significant difference for the PWV ($p < 0.01$) between PAH and control groups, as well as between PAH and BAOV groups. There was no statistically significant difference between the BAOV and the control group. This could be explained by the fact that changes in PWV depend more on age than on aortic and pathological changes in AOV at younger age. In addition, in all 3 groups, PWV was statistically significantly higher in males ($p < 0.01$) than in women as in previously published healthy population studies.

In our study, accurate anthropometric measurements of the total length of the aorta were also measured using MRI. The total length of the aorta had statistically significant difference ($p < 0.01$) in all 3 groups. Longer aortic length of the PAH group may be explained by the loss of elastic properties of the aorta with age due to the aging process and PAH (106). Meanwhile, the statistically significant difference between the lengths of the aortic BAOV and the control group is likely due to the fact that patients with BAOV loose elasticity in aortic wall at a younger age than those with TAOV.

When measuring aortic flow velocity in different aortic segments, an accidental finding was detected - in all 3 groups, the average flow rate of the distal abdominal aorta was practically identical (~1.97-1.99 m/s) and had a significantly lowest standard deviations than in the remaining aortic segments. This interesting finding predisposes the hypothesis that, irrespectively of aortic stiffness and other indicators of hemodynamics, the aortic flow in the distal part of aorta is bound up to ~ 2 m/s. In literature, we did not find work (in vivo or in vitro) that would explain the convergence of such blood flow rates, which could be the subject of new scientific studies.

5. CONCLUSIONS

1. Using contrast unenhanced magnetic resonance imaging sequences, the most reliable of all aortic segments can be measured the diameters of an ascending aorta and the choice of priority is to apply "white blood" sequences for better accuracy of results compared to the "gold standard" - magnetic resonance angiography with contrast media.

2. The results of the measurements of magnetic resonance imaging of the aortic sinuses and the ascending part of aorta were more strongly correlated in-between than with the ultrasound measurements with both tricuspid and the bicuspid aortic valve. Therefore, we determined that ultrasound measurements of the aortic sinus and the ascending part have lower diagnostic accuracy than in magnetic resonance angiography (both in contrast enhanced and unenhanced sequences).

3. Pulse wave velocity measurements using the magnetic resonance tomography technique are the most accurate in aortic arch and statistically reliably correlate with measurements using the applanation tonometry method with a 1.46 m/s difference between the methods. Therefore, the method of measuring pulse wave velocity with the magnetic resonance imaging in aorta is considered as an alternative to applanation tonometry study.

4. The method of magnetic resonance imaging has statistically reliably determined pulse wave rate differences in the test groups that reflect the age-related, sex-related and pathological changes in stiffness in the aorta; therefore, it is proposed that the methodology should be used to determine aortic pulse wave velocity in both healthy population and patients with aortic pathology.

6. PRACTICAL RECOMMENDATIONS

1. It is recommended to apply a magnetic resonance imaging in accordance with the methodology we have developed and proposed (see Magnetic Resonance Imaging Protocol), with the priority of "white blood" instead of computer tomography or in the absence of cardiac ultrasound, for the detection and follow-up of maximum diameters of aorta using contrast unenhanced methodology.

2. It is recommended to use the contrast unenhanced method of magnetic resonance imaging to apply for pulsed wave velocity determination in the aortic arch as an alternative to the applanation tonometry study.

3. It is recommended to evaluate the diameters of the bicuspidal aortic valve in short-axis images in all imaging techniques, in order to avoid measurement inaccuracy due to congenital aortic sinus asymmetry.

LIST OF AUTHOR PUBLICATIONS, SUMMARIES AND NOTIFICATIONS

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1. Baltic Congress of Radiology 2014. Congenital vascular malformations using MRI. Parnu, Estonia.
2. Radiology 2015. Vilnius, Lithuania. Changes in morphology and hemodynamics of left ventricle and aorta after sympathic denervation of renal arteries.
3. Multimodality Imaging in Cardiology 2016. Cardiac CT: principles, role and future perspectives.
4. Ultrasound 2016. Should we make MRI immediately?
5. Evolutionaty medicine: prie-existing mechanisms and patterns of current health issues 2016. Cardiovascular Magnetic Resonance (CMR) of Left Ventricle (LV) and Aorta in Patients prior and after Renal Artery Sympatic Denervation (RASD). Best phD student oral presentation award.
6. Baltic Congress of Radiology 2016. Measurement of segmental diameters and pulse wave velocity using contrast unenhanced MRI.

BRIEF INFORMATION ABOUT THE AUTHOR

Darius Palionis was born in Panevėžys, Lithuania, on July 24, 1980.

1998–2004 - medicine studies at the Faculty of Medicine, Vilnius University.

2004–2005 - residency in General Medicine, Vilnius University.

2008–2009 - residency in Radiology, Vilnius University and Vilnius University Hospital Santaros Klinikos.

2014–2017 - doctoral (Ph. D.) studies in Vilnius University at the Faculty of Medicine.

2009–onwards - doctor radiologist at Vilnius University Hospital Santaros Klinikos, specializing in Cardiothoracic Imaging.

2007 - three weeks internship on cardiac MRI in The University Hospital of Essen, Germany.

2009 - work experience in medical radio station.

2009 - two weeks on cardiac SPECT-CT and VCT training in Zurich University hospital, Switzerland.

2012 - accredited at EuroCMR II level at the London UCL Hospital by prof. James Moon.

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