SUMMARY

Background

Fibromuscular dysplasia (FMD) is an idiopathic, segmental, non-atherosclerotic and non-inflammatory disease of the musculature of arterial wall, most frequently affecting small and medium-sized arteries. It is rather considered as a systemic disease which may involve multiple vascular beds in one patient and may be present with various features including arterial stenosis, occlusion, tortuosity, aneurysms, dissections. Therefore, there are limited data on coronary and thoracic aorta involvement in patients diagnosed with extra-coronary FMD.

Objective

The main aims of the study:

1. Assessment of the frequency of FMD unifocal and multifocal lesions in coronary arteries in patients with extra-coronary FMD.
2. Evaluation of the frequency of vascular complications, especially aneurysms and dissections in coronary arteries in patients with extra-coronary FMD and compare to the control group.
3. Assessment of other possible phenotype of coronary arteries, including measurements of lumen areas and diameters of coronary arteries and evaluation of arterial tortuosity in coronary arteries in patients with extra-coronary FMD and compare to the control group.
4. Evaluation of thoracic aorta phenotype with precisely dimensions of aortic root and diameters of ascending and descending aorta in patients with confirmed extra-coronary FMD and compare to the control group.

Material and methods

This study was conducted with the Research Grant of the National Institute of Cardiology in Warsaw titled "Evaluation of structural lesions in coronary arteries in patients with fibromuscular dysplasia in relation to changes in other vascular beds and genetic profile. ARCADIA-Pol BIS Study" (No 2.40/III/19) in the Department of Hypertension, National

Institute of Cardiology in Warsaw. This study obtained a consent of the Bioethical Committee (No 1805). Patients enrolled in ARCADIA-Pol study in 2015-2019. Of 232 patients with confirmed diagnosis of FMD in at least one vascular bed, 149 patients were agreed to perform angio-CT examination of coronary arteries and ascending and descending aorta.

In the first part of the study, 103 consecutive patients (82 women, age 45,7 ± 13,2) with confirmed FMD and any signs of coronary atherosclerosis and with calcium score "0" were enrolled in analysis. The control group consists of 96 patients (75 women, age 47,3 ± 12,2) sex and age matched to examine group with no coronary atherosclerosis. In all subjects coronary computed tomography angiography (CCTA) was performed. Coronary arteries were classified in segments based on Society of Cardiovascular Computed Tomography classification. Evaluation of the frequency of FMD focal and multifocal lesions in coronary arteries in FMD patients were analyzed and assessment of presence of vascular complications, especially aneurysms and dissections, stenosis in coronary arteries in patients with extra-coronary FMD and control group were conducted. Additionally, the assessment of Tortuosity Index (TI) defined as number of curves *(n)* multiplied by artery length (centerline) *(A)* and divided by vector artery start-end *(B)* was performed per coronary segment and per coronary artery. Moreover, in every segment of coronary artery number and measure of bends were made manually and segregate in categories: >30° ; >45°; >90°. Additional markers of tortuosity – intravessel symmetry sign, multivessel symmetry sign and corkscrew sign were identified in FMD patients and compare to the control group. Moreover, detailed analysis of coronary arteries with regard to the dimensions, including lumen area (LA), length and diameters (LD) of coronary arteries were performed.

In the second part of the study, 149 patients with FMD (121 women, age 48,5 ± 14,3) and 139 patients (112 women, age 50,2 ± 13,6) sex and age matched controls were enrolled in analysis of aortic root and ascending and descending aorta. Dimensions of aorta were made manually using a dedicated workstation and including aortic annulus, sinus of Valsalva, sinotubular junction, right and left coronary heights, diameters of origins of right and left coronary arteries and diameters of ascending and descending aorta.

Results

In the first part of the study, coronary arteries in FMD patients were analyzed. There were no focal and multifocal FMD lesions in examined cohort and no coronary aneurysms, ectasias or dissections were found in both groups. FMD patients had longer coronary arteries

(RCA 116,3 mm vs 109,7 mm, p=0,019; LM 10,2 mm vs 8,5 mm, p=0,007; LAD 141,1 mm vs 123,2 mm, p<0,001; LCx 85,1 mm vs 78,5 mm, p=0,202) and smaller lumen area of coronary arteries (RCA 8,5 mm^2 vs 9,7 mm^2, p=0,017; LM 18,0 mm^2 vs 19,6 mm^2, p=0,003; LAD 6,4 mm^2 vs 6,9 mm^2, p=0,109; LCx 12,3 mm^2 vs 13,6 mm^2, p=0,027) and smaller diameters of coronary arteries (RCA 3,3 mm vs 3,5 mm, p=0,014; LM 4,8 mm vs 5,0 mm, p=0,003; LAD 2,7 mm vs 2,8 mm, p=0,494; LCx 5,3 mm vs 6,9 mm, p<0,001) compared to control group. Additional markers of tortuosity were more common in patients with FMD than in controls (57 vs 12, p<0,00001; 15 vs 0, p<0,0001; 11 vs 0, p=0,0008).

Coronary arteries in FMD patients had significant higher Tortuosity Indexes (TI) than in controls (TI RCA 10,3 vs 6,6, p<0,001; TI LM 0 vs 0, p<0,001; TI LAD 15,9 vs 8,5, p<0,001; TI LCx 11,3 vs 6,6, p<0,001). TI of coronary segments identified for FMD patients were higher than in control group, expect proximal segments of LAD and LCx (0 vs 1, p=0,569; 1,1 vs 1,1, p=0,385) where no significant difference was observed. The highest predictive value for FMD was found in TI determined for the distal LAD segment 8 (AUC 0,866; 95%CI: 0,811–0,910), indicating that the most optimal sensitivity and specificity values were obtained for TI > 4,9, at 72,8% and 87,5% respectively. The second FMD predictor, after TI segment 8, was number of curves >30° in segment 8 (AUC 0,842; 95% CI: 0,784–0,890) and number of curves >45° in segment 8 (AUC 0,820; 95%CI: 0,760–0,871). For number of curves of the distal LAD segment (segment 8) the most optimal sensitivity and specificity values were >4,5 for curves >30°: at 65,1% and 90,6 and >3,5 for curves >45° at 69,9% and 79,2% respectively. In a multivariate logistic regression analysis TI for segment 8 was an independent predictor of FMD (OR: 3,17; 95%CI: 1,07-9,41, p=0,037).

In the second part of the study, the dimensions of the ascending and the descending aorta with detailed evaluation of aortic root were analysed in FMD and control groups. Measured parameters of the aorta and aortic root were smaller in FMD patients, however, statistical significance was reached by dimensions of aortic annulus (2,3 cm vs 2,9 cm, p<0,001), sinus of Valsalva (3,0 cm vs 3,2 cm, p=0,03) and the heights of origins of right and left coronary arteries (1,1 cm vs 1,3 cm, p<0,001; 1,2 cm vs 1,3 cm, p<0,001). The dimensions of the ascending aorta and the descending aorta did not differ significantly between examined cohort and control group. Multivariate logistic regression shown that the differences between the analysed morphological parameters of the aortic root between the study FMD group and the control group were independent of clinical variables.

Conclusions

1. No focal and multifocal FMD lesions had been identified in coronary arteries in FMD patients. No vascular abnormalities associated with FMD like stenosis, ectasia, aneurysm or dissection had been reported in coronary arteries in examined and control groups. The fact of the absence of FMD lesions in coronary arteries in patients with extracoronary FMD is unexplained in pathogenesis of this arteriopathy.
2. Coronary arteries in FMD patients had significantly higher Tortuosity Indexes (TI) than controls. The revealed method of measurement of coronary tortuosity may constitute a basis for the definition of „excessive arterial tortuosity".
3. In FMD patients there were no significant differences in coronary tortuosity in relation to the FMD type (focal or multifocal) and number of involved vascular beds (1 or 2 and more involved vascular beds in one patient).
4. Coronary arteries in FMD patients were longer and had smaller lumen areas and average diameters compared to control group. These data suggest a relationship between FMD in extracoronary vascular bed and the phenotype of coronary arteries, which may emphasize the systemic nature of FMD.
5. The highest predictive value for FMD was observed in excessive tortuosity for TI for distal LAD segment (segment 8). For distal LAD segment the most optimal values of sensitivity and specificity were received for TI > 4,9. For number of curves of distal LAD segment (segment 8) the most optimal sensitivity and specificity values were >4,5 for curves >30° and >3,5 for curves >45°. These data may determine precise criteria in assessment excessive coronary tortuosity in patients with suspected FMD.
6. The dimensions of ascending and descending aorta and aortic root were smaller in FMD patients than in control group. This study confirmed systemic character of FMD and revealed multiple clinical presentations of this disease. Also, it indicating the phenotype of FMD which can manifest in large arteries, as aorta.