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Original Article

Histopathological evidence of aortopathy in newborns and infants with Tetralogy of Fallot at the time of the surgical repair

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ABSTRACT

Objectives: The purpose of this study was to evaluate the microscopic structural abnormalities of the ascending aorta in infants with Tetralogy of Fallot (ToF) and compare them with aortic samples from control group of small children that died of other diseases. We aimed at identification of the specific histopathological changes associated with ToF and correlation of the severity of these changes with time to surgery and mean levels of saturation in the ToF group, and age at death in control group.
Methods: The full-thickness ascending aortic wall sample was taken from 23 children with ToF at the time of surgical reconstruction (age spread 2 to 19 months) and evaluated by light microscopy. Corresponding samples were taken from 16 cadaverous cases of children with other diseases (0–76 months). The assessed morphological variables included elastic fiber fragmentation/loss, thinning and disorganisation, presence of laminar medial necrosis, intralamellar and translamellar mucoid extracellular matrix accumulations, smooth muscle cell disorganisation, presence of fibrosis, calcifications and neovascularisation and finally grade of overall medial degeneration.
Results: No difference was found between the two groups in the individual morphological variables. However, there was a difference in the distribution of the grades of the overall medial degeneration ($P = .016$). ToF group showed uniform mild degenerative changes, whereas control group harboured spectrum of changes ranging from normal to moderate. The presence of the given histopathological changes and their severity were associated neither with age at surgery or mean levels of saturation in ToF group, nor with the age at death in the control group.
Conclusions: This study emphasizes the histopathological assessment of the bioptic samples of the ascending aorta during the surgical repair of ToF, since the patients demonstrating moderate or severe degenerative changes already in the early childhood may be in increased risk of the subsequent late complications.

1. Introduction

Tetralogy of Fallot (ToF) represents the most frequent cyanotic congenital heart disease (CHD), occurring in approximately 1 in 3600 live-born children and accounts for 5% of all CHD [1,2]. Development of surgical repair techniques during last 40 years significantly improved prognosis of these patients. In the western world, one-year survival rate after the reconstruction reaches 97% and the majority of the children survive to the adult age [1,3]. It increased demands for recognizing and proper management of delayed complications contributing to late morbidity. Previous studies illustrate intrinsic structural abnormalities of the aortic wall in the majority of the patients with ToF, which may, in addition to long-standing volume overload, play a role in certain delayed complications such as progressive aortic root dilatation [4–7]. However, it remains unclear, whether the histopathological abnormalities of the aortic wall can be regarded as a causative factor.

In this prospective study we aim to 1) evaluate the microscopic structural abnormalities of the ascending aorta in infants and small toddlers with ToF at the time of surgical reconstruction; 2) compare the severity of the pathological changes with cadaverous aortic samples from small children that died from other diseases; 3) identify the specific histopathological variables associated with ToF; and finally 4) correlate the severity of the microscopic changes with age at surgery or at death respectively.

2. Materials and methods

Between June 2014 and October 2017, 23 patients with ToF (12 males) and 16 autoptic cases of children with various diseases (10 males) were enrolled in this prospective study. The age at surgical correction was 2 to 19 months (median 6.5 months, interquartile range 4–9 months), age at death in the second, control group was 0 to 76 months (median 9, interquartile range 3.25–16.75 months). In the

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Table 1
Causes of death of the control group of the patients

Patient	Cause of death
1	Primary fibroelastosis of the heart
2	ALL, mycotic sepsis
3	Generalised rhabdoid tumor of the kidney
4	Primary immunodeficiency, ascending cholangitis
5	cerebellar ETANTR
6	Ommen syndrome, adenovirus sepsis
7	Generalised alveolar RMS
8	Pierre-Robin sequence, aspiration pneumonia
9	Congenital valvar aortic stenosis
10	AML
11	Primary immunodeficiency, sepsis
12	Diffuse midline glioma of the pons
13	Intrauterine hypoxia, hypoxic ischemic encephalopathy
14	Congenital nephrotic syndrome, kidney failure
15	Intracranial hemorrhage
16	GALD

ALL, acute lymphoblastic leukemia; ETANTR, embryonal tumor with abundant neuropil and true rosettes; RMS, rhabdomyosarcoma; AML, acute myeloid leukemia; GALD, gestational alloimmune liver disease

ToF group, the mean levels of saturation in the period before surgery were also recorded. The clinical details of the individual patients are given in Table 2. Table 1 summarizes the causes of deaths of the children in the control group. A standardized full-thickness aortic wall sample of proportions 10 × 5 mm was taken from the ascending aorta during the surgical reconstruction or post-mortem. The specimens were sampled from the standardized locality just above the sinotubar junction. The samples were subjected to histopathological evaluation by light microscopy.

Each bioptic and necroptic specimen was fixed in 10% buffered formalin, embedded in paraffin block and sections of 4 um thickness were taken. The slides were stained with hematoxylin and eosin, Masson trichrome, Alcian blue/periodic acid-Schiff and Weigert's resorcin fuchsin. The microscopical slides were consecutively evaluated by two independent senior cardiovascular pathologists. The assessed morphological variables included elastic fiber fragmentation/loss, elastic fiber thinning, elastic fiber disorganisation, presence of laminar medial necrosis, intralamellar and translamellar mucoid extracellular matrix accumulations (MEMA), smooth muscle cell disorganisation, presence of fibrosis, calcifications and neovascularisation. The standard definitions of the given variables correspond with the international consensus statement for degenerative aortic diseases from the Society of Cardiovascular Pathology and the Association for European Cardiovascular Pathology [8]. The most of the variables were graded 0 to 3 (absent, mild, moderate, severe), except for fibrosis, calcifications and neovascularisation that were graded 0 or 1 (absent or present). Ultimately, the grade of the overall medial degeneration was established.

Table 2
Clinical characteristics and grading of degenerative changes of the aortic wall in individual patients

Patients	Sex	Age at operation (months)	Age at death (months)	Sat (%)	MEMA _I Grade	MEMA _T Grade	ELA_F Grade	ELA_T Grade	LMC Grade	SM_D Grade	FIBR	CALC	NEO	Overall Grade
ToF														
1	F	4	N/A	85	1	0	1	1	0	0	0	0	0	**1**
2	F	6	N/A	82	1	0	1	0	0	0	0	0	0	**1**
3	F	9	N/A	95	2	0	1	0	0	0	0	0	0	**1**
4	F	8	N/A	91	0	0	1	0	0	0	0	0	0	**1**
5	M	12	N/A	93	1	0	1	1	0	0	0	0	0	**1**
6	M	7	N/A	87	1	0	0	0	0	0	0	0	0	**1**
7	M	6	N/A	93	1	0	1	0	0	0	0	0	0	**1**
8	F	3	N/A	90	1	0	1	1	0	0	0	0	0	**1**
9	F	N/A	N/A	78	1	0	1	1	0	0	0	0	0	**1**
10	M	11	N/A	82	1	0	1	0	0	0	0	0	0	**1**
11	M	9	N/A	90	0	0	2	0	0	0	0	0	0	**1**
12	F	6	N/A	87	0	0	2	0	0	0	0	0	0	**1**
13	M	8	N/A	84	1	0	0	0	0	0	0	0	0	**1**
14	F	12	N/A	91	1	0	1	0	0	0	0	0	0	**1**
15	F	6	N/A	83	0	0	0	0	0	0	0	0	0	**0**
16	F	7	N/A	78	1	0	1	0	0	0	0	0	0	**1**
17	M	9	N/A	84	1	0	1	0	0	0	0	0	0	**1**
18	M	4	N/A	76	1	0	0	0	0	0	0	0	0	**1**
19	M	6	N/A	86	1	0	0	0	0	0	0	0	0	**1**
20	M	3	N/A	88	1	0	1	0	0	0	0	0	0	**1**
21	M	4	N/A	88	2	0	1	0	0	0	0	0	0	**1**
22	F	8	N/A	78	0	0	1	0	0	0	0	0	0	**1**
23	M	2	N/A	90	1	0	2	1	0	0	0	0	0	**1**
Control														
1	M	N/A	10	N/A	0	0	0	0	0	0	0	0	0	**0**
2	F	N/A	5	N/A	1	0	1	1	0	0	0	0	0	**1**
3	M	N/A	13	N/A	1	0	1	0	0	0	0	0	0	**1**
4	M	N/A	3	N/A	2	0	1	1	0	0	0	0	0	**1**
5	M	N/A	9	N/A	1	0	0	0	0	0	0	0	0	**1**
6	M	N/A	9	N/A	1	0	1	0	0	0	0	0	0	**1**
7	M	N/A	17	N/A	1	0	1	0	0	0	0	0	0	**1**
8	M	N/A	5	N/A	0	0	0	0	0	0	0	0	0	**0**
9	F	N/A	4	N/A	2	1	0	0	0	0	0	0	0	**1**
10	F	N/A	16	N/A	0	0	0	0	0	0	0	0	0	**0**
11	M	N/A	40	N/A	0	0	1	0	0	0	0	0	0	**1**
12	F	N/A	76	N/A	1	0	1	0	0	0	0	0	0	**1**
13	F	N/A	0	N/A	2	0	2	2	0	0	0	0	0	**2**
14	M	N/A	1	N/A	0	0	1	1	0	0	0	0	0	**1**
15	F	N/A	24	N/A	0	0	0	0	0	0	0	0	0	**0**
16	M	N/A	0	N/A	2	1	2	1	0	0	0	0	0	**2**

ToF, Tetralogy of Fallot; F, Female; M, Male; Sat, Mean level of saturations till the surgical reconstruction; MEMA_I, Intralamellar mucoid extracellular matrix accumulations; MEMA_T, Translamellar mucoid extracellular matrix accumulations; ELA_F, Elastic fiber fragmentation/loss; ELA_T, Elastic fiber thinning; LMC, Laminar medial collapse; SM_D, Smooth muscle cell disorganisation; FIBR, Fibrosis; CALC, Calcification; NEO, Neovascularisation; Overall, Overall medial degeneration.

However, due to the small size of the tissue samples, the focality of the changes (focal, multifocal, extensive) could not been properly assessed and the official grading scheme established in the aforementioned consensus document could not been used. Therefore, the evaluation of the overall medial degeneration was based on the presence and severity of the individual alterations only.

3. Statistical analysis

We used statistical software R-project (R Core Team, version 3.5.1) for data analysis, including packages "tidyr" and "ggplot2" for data visualization. A Fisher's exact test was used to compare the proportional distribution of the grades in the ToF and control group in the individual morphological variables as well as the overall medial degeneration. The same test was used to tell, whether the severity of medial degeneration in individual morphological components and grade of overall degeneration in both groups were independent on the gender, time to surgical reconstruction or age at death. Finally, the Fisher' s exact test was used to verify the association between the severity of medial degeneration in the aforementioned variables and the mean levels of saturation in ToF group. Probability (P) values $<.05$ were considered significant. A 95% confidence interval was used.

4. Results

The summary of all morphological variables in individual patients is given Table 2. No interobserver disagreement on the interpretation of the given variables was recorded.

4.1. Alterations of elastic membranes

Eighteen patients (78.2%) from ToF group had elastic fiber fragmentation/loss, graded as mild (Grade 1) in 15 cases and moderate (Grade 2) in 3 cases. In the control group, elastic fiber fragmentation/loss showed 10 (62%) children (8 cases Grade 1, 2 cases Grade 2). Thinning of elastic fibers was present in 5 (21.7%) specimens in ToF group (all graded as mild) and 2 cases (12.5%) in control group (both of them Grade 1). No statistically significant difference was found between the two groups neither in the individual variables nor in the summarized counts of the overall elastic fiber alteration.

4.2. Mucoid extracellular matrix accumulations

Intralamellar MEMA were present in eighteen (78%) ToF specimens, from which 16 were Grade 1 and two specimens Grade 2 (Fig. 1). Control group demonstrated 10 cases (62%) with MEMA (6 cases Grade 1, 4 cases Grade 2). Translamellar MEMA were found only in two cases in control group and were graded as mild. There was no statistically significant difference between ToF and control group, neither in the separate intralamellar and translamellar counts nor in overall MEMA counts.

4.3. Other histopathological findings

Not a single case harboured smooth muscle cell alterations, fibrosis, calcifications, neovascularisation or laminar medial collapse.

4.4. Overall medial degeneration

In the ToF group, all patients except for one showed some structural aortic wall abnormality. The overall medial degeneration was considered mild in 22 patients and 1 child had a normal aorta. In the control group, the histopathological changes were more uneven. Four patients were devoid of any morphological alteration, 10 cases demonstrated Grade 1 overall degeneration and 2 patients, Grade 2. This difference between the groups was statistically significant ($P = .016$, Fig. 2). (See Figs. 3 and 4.)

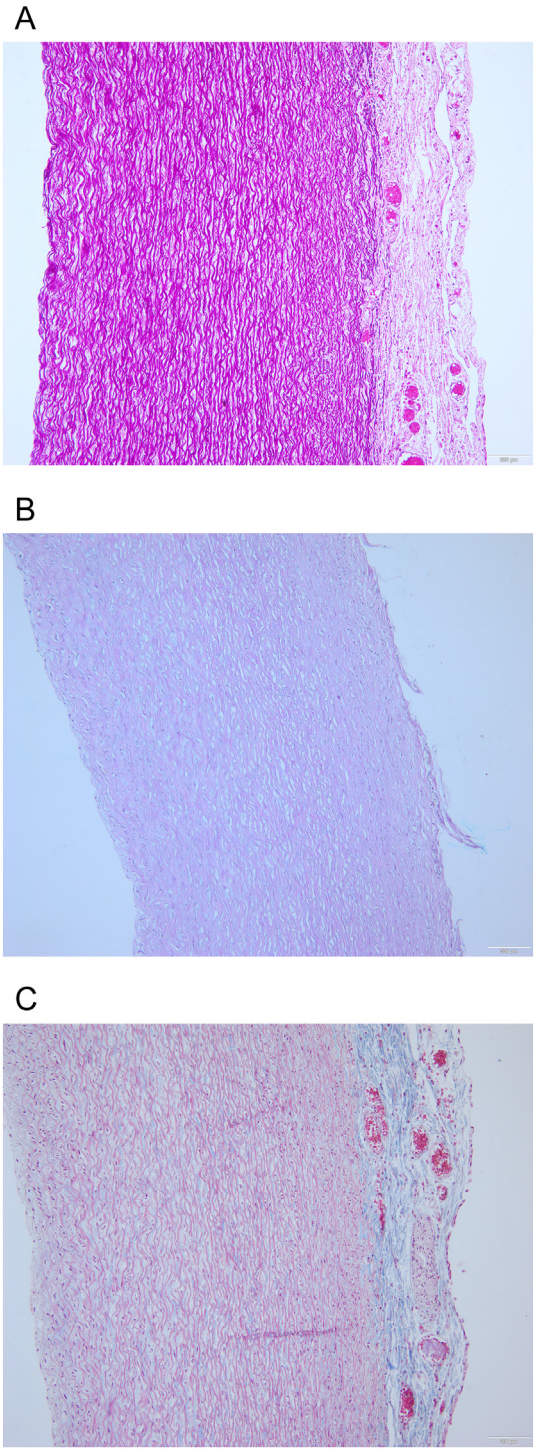

Fig. 1. Photomicrograph of the normal ascending aorta. (A) Normal arrangement of the elastic membranes, Weigert's resorcin fuchsin stain, original magnification ×100. (B) Absence of mucoid extracellular matrix accumulations, Alcian blue/periodic acid-Schiff stain, original magnification ×100. (C) Absence of fibrosis or smooth muscle alterations, Masson's trichrome, original magnification ×100

4.5. Clinical variables

Individual histopathological alterations as well as overall grade of medial degeneration were not associated with the gender of the patients. The presence or absence of the given microscopical changes and their severity were independent on the time to surgical reconstruction in the ToF group or age at death in the control group. We did not

demonstrate any association between these alterations and mean levels of saturation in the ToF group.

5. Ethical considerations

Legal representatives of the patients signed an informed consent form for inclusion into the study. The study was approved by the Ethics Committee of Motol University Hospital.

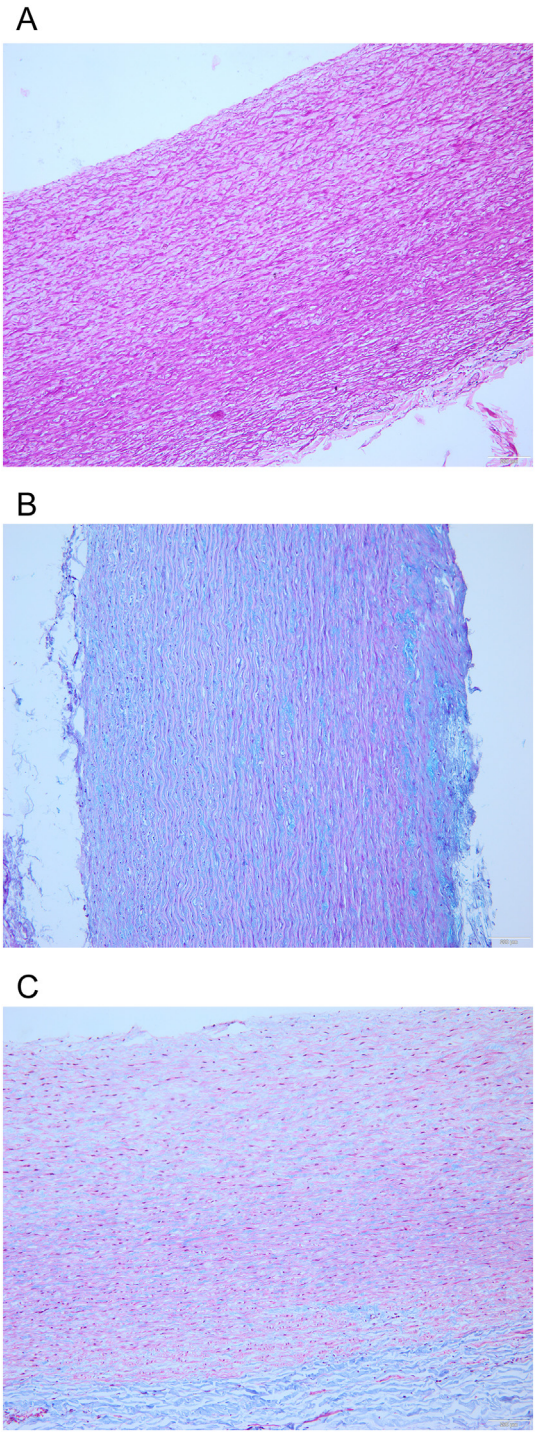

Fig. 2. Photomicrograph of the ascending aorta with mild medial degeneration. (A) Mild fragmentation and thinning of the elastic membranes especially in the subintimal zone, Weigert's resorcin fuchsin stain, original magnification ×100. (B) Mild intralamellar mucoid extracellular matrix accumulations, Alcian blue/periodic acid-Schiff stain, original magnification ×100. (C) Absence of fibrosis or smooth muscle alterations, Masson's trichrome, original magnification ×100.

6. Discussion

Microscopic structural alterations of the aortic media accompany various diseases [8] and can be present in patients with hypertension [9], during pregnancy [10], as a secondary change related to atherosclerosis [11] or, in a lesser extent, as a physiological aging process [12,13]. Given changes can be demonstrated also in patients with congenital

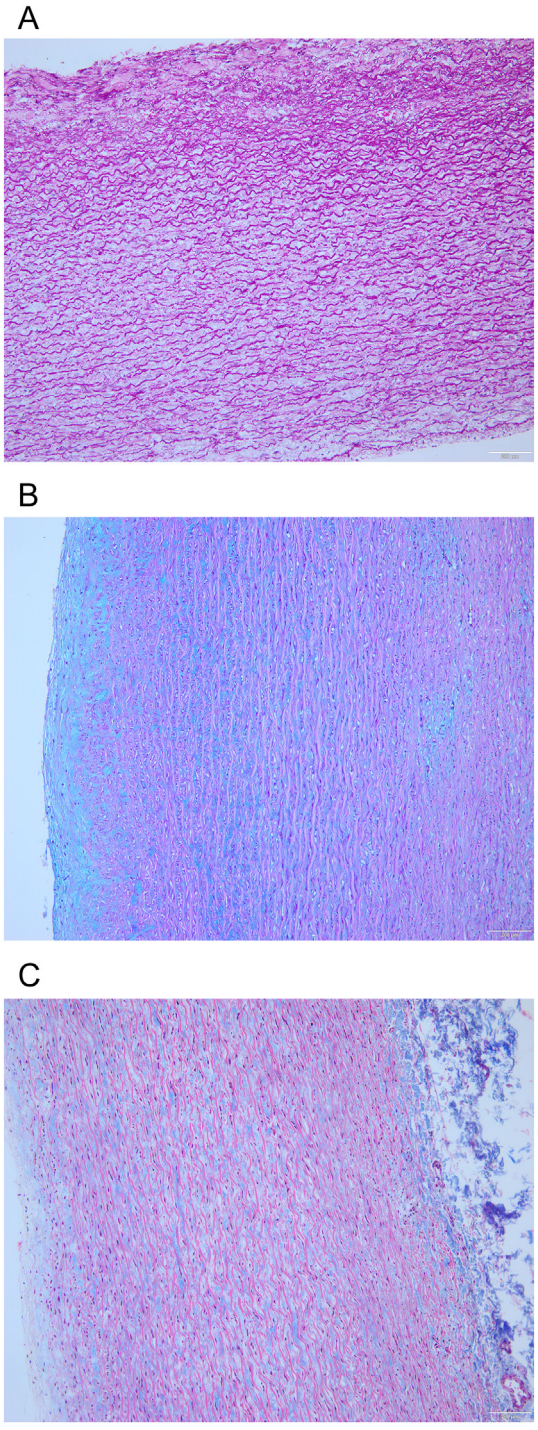

Fig. 3. Photomicrograph of the ascending aorta with moderate medial degeneration. (A) Moderate fragmentation and loss and mild thinning of the elastic membranes in almost full thickness of the aortic wall, Weigert's resorcin fuchsin stain, original magnification ×100. (B) Moderate intralamellar and translamellar mucoid extracellular matrix accumulations predominantly in subintimal region, Alcian blue/periodic acid-Schiff stain, original magnification ×100. (C) Absence of fibrosis or smooth muscle alterations, Masson's trichrome, original magnification ×100.

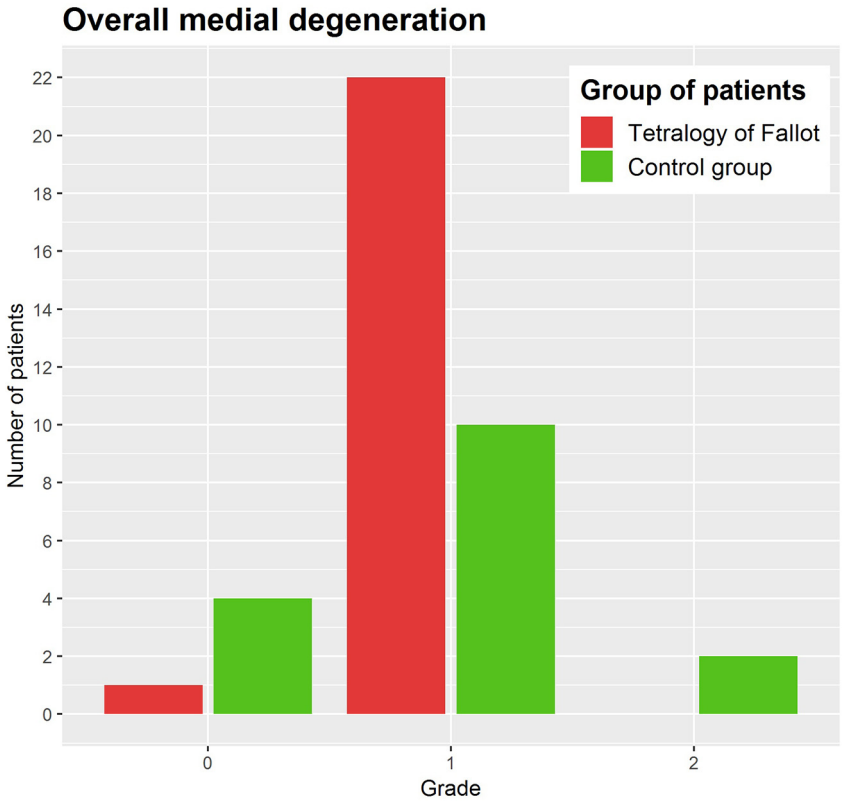

Fig. 4. A bar plot comparing individual grades of overall medial degeneration in the ToF and control group of the patients.

connective tissue disorders (CTD) [9]. Some specific components of the medial degeneration seem to be more pronounced in concrete CTD (as marked elastic fiber fragmentation and fibrosis in patients with Loeys-Dietz syndrome or more prevalent mucoid matrix accumulations in Marfan and Ehlers-Danlos syndrome) [8,14,15]. However, these slight differences are unreliable and cannot justify diagnosis of specific CTD based solely on the histopathological appearance of the aorta. Morphology of medial degeneration represents entirely nonspecific and stereotypic finding and neither its overall severity nor proportional occurrence of the individual components can be tied to a specific disease.

Regarding the surgical pathology of the ascending aorta, the most of the knowledge stem from old case reports, largely referring to syphilitic aortitis or mycotic aneurysms [16,17]. We are aware of three comprehensive studies from years 1977, 1983, and 2006 with large cohorts of the patients, describing histopathological changes of the aortic wall in various inflammatory and non-inflammatory conditions. However, none of them proved any association between individual components of medial degeneration and specific diseases [18–20].

In CHD, the aortic histopathological abnormalities are common and according to some authors may represent even an integral component of the given malformations [4,9,21]. In case of ToF, data are sparse due to low number of studies, which are often limited to necroptic cases, include small groups of the patients with restricted observations or encompass non-homogenous groups of patients with wide age distribution [4,6,7]. One from the most comprehensive studies regarding this topic comes from Chowdhury et al. [5]. This study examined bioptic specimens of the ascending aorta from 98 patients with ToF at the time of the surgical repair, with age distribution ranging from 6 to 47 years. Authors demonstrated microscopical abnormalities in 73 patients in the study, with elastic fiber fragmentation and mucoid extracellular matrix accumulations in the highest prevalence. The severity of the changes increased with age and may have accounted for the progressive aortic dilatation after the surgical correction, but it remained unclear till what extent they were caused by hemodynamic factors or chronic hypoxia. Their conclusions reflect general dilemma in this sphere. Up to now it remains unclear, whether structural abnormalities of the ascending aorta represent integral part of the congenital heart malformation with progressive worsening during the time, or can be understood rather as a consequence of long-term volume overload. ToF is no longer a fatal heart disease and, as stated above, the majority of the patients survive till the adult age and may suffer from the late complications. It is therefore reasonable to search for proper predictors of the postoperative course and raise the question, whether we can rely on the histopathology in this case.

In our work, we focused at histopathological evaluation of the medial degeneration of the ascending aorta in newborns and small infants. To the best of our knowledge, no previous study aimed at children in this age nor had such a homogenous group of the patients. Furthermore, our study seems to be the first one using the standardized nomenclature and current valid definitions from the aforementioned international consensus of the surgical pathology of the aorta [8]. The vast majority of the patients in the ToF group showed histopathological evidence of the medial degeneration. Our results support the well-known fact that these changes are not specific, since the same alterations were present in the majority of the patients with various other illnesses in the control group. The occurrence of individual morphological variables was not different among the groups and therefore no specific variable could be linked together with ToF. However, there was a significant difference in the distribution of the grades of the overall medial degeneration. In ToF group, all patients except for one had Grade 1 changes, whereas the control group included patients with normal aortas as well as those with moderate changes. The proportion of the individual variables and also the severity of overall medial degeneration were independent on time factor - age at death in the control group and time to surgical repair in ToF group. Two patients from the control group with Grade 2 changes were even newborns. The severity of the medial degeneration therefore cannot be explained by the duration of the disease only.

A fundamental question is the effect of hypoxia on the structure of the aortic wall, which was also one of the considered pathophysiological mechanisms in the aforementioned study from Chowdhury et al. However, studies concerned with this topic are sporadic. Some authors declare ultrasonographic thickening of the aortic wall in fetuses with intrauterine growth retardation, where the main causation is considered to be a placental insufficiency and prolonged hypoxia [22,23]. There are also some animal studies on mouse models with long term intraabdominal sepsis, documenting accelerated atherosclerosis in this setting [24]. In our study, the both patients from control group that manifested Grade 2 overall medial degeneration were newborns with history of protracted hypoxia. First baby suffered from ill-defined intrauterine asphyxia, which resulted in severe hypoxic-ischemic encephalopathy, the second child died from multiorgan failure due to gestational alloimmune liver disease and also had showed signs of intrauterine asphyxia. That is why the correlation of histopathological changes in ToF group with mean levels of saturation in ToF group was included in our study. However, we failed to prove any association between individual components of the medial degeneration and mean levels of saturation and considering the fact, that all patients in ToF group had the same grade of the overall medial degeneration, the relationship between the microscopic alterations of the aortic wall and presence of hypoxia could not been confirmed.

There are some limitations of the study that may result mostly from the small size of the tissue samples. The anatomical relationships in the small children do not allow harvesting larger pieces of the aortic wall during the surgical correction of ToF. The histopathological assessment of the morphological variables relied solely on their severity and the evaluation of the focality of those changes, as recommended in the consensus document, could not been properly addressed. Therefore, the final grade of the overall medial degeneration does not correspond with the official grading scheme and the individual grades in this work may reflect more subtle changes. Also the assessment of the elastic fiber alterations, which are often subtle, can be subjective and prone to interpersonal variability. The mutual comparison of the given variables may be challenging as well, because the elastic fiber changes are often grouped together. However, since there was no disagreement between the two independent assessing pathologists, we strongly believe in reproducibility and objectiveness of this scheme even in the borders of the small tissue samples.

7. Conclusions

We did not demonstrate any association between individual microscopic alterations of the ascending aorta and diagnosis of ToF. On the other hand, we found a significant difference in the severity of the overall medial degeneration between ToF and control group, as the children in the control group demonstrated uneven and haphazard alterations independent on the duration of the disease, whilst the patients with ToF showed uniform mild changes unrelated to the level of saturation or time to operation. This might justify the histopathological assessment of the bioptic samples of the ascending aorta during the surgical correction of ToF. We speculate that the vast majority of the children embody only mild microscopic changes at the time of the first surgical repair. Patients with more severe alterations could be therefore in increased risk of the subsequent late complications. However, further studies with long-term prospective follow up are required to foster this premise and confirm the intrinsic structural abnormality of the aortic wall as an independent risk factor.

Conflict of interest

None

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