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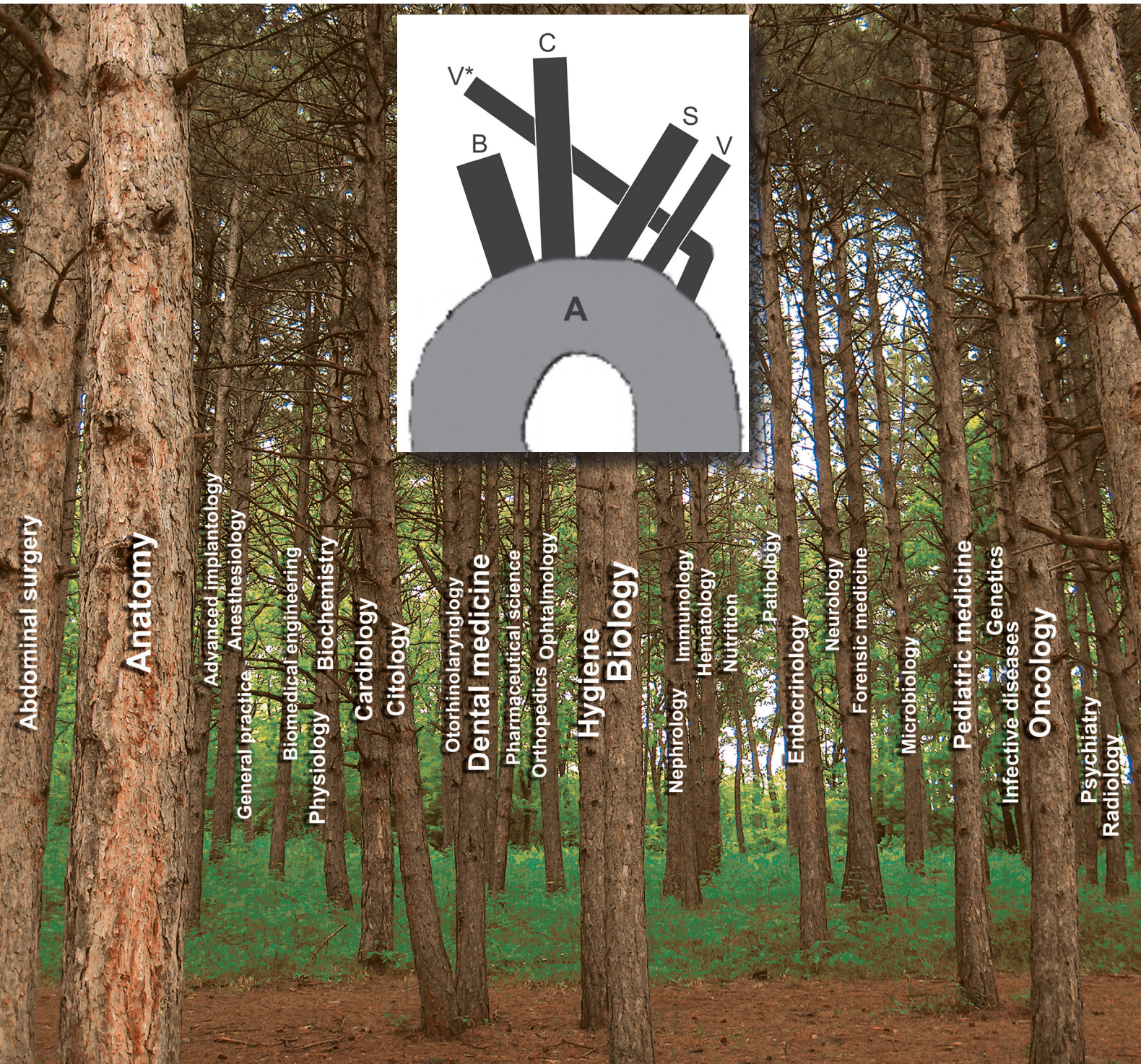

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1. Kuroda S, Ishikawa T, Houkin K, Nanba R, Hokari M, Iwasaki Y. Incidence and clinical features of disease progression in adult Moyamoya disease. Stroke 2005; 36:2148–2153.
2. Papantchev V, Hristov S, Todorova D, et al. Some variations of the circle of Willis, important for cerebral protection in aortic surgery — a study in Eastern Europeans. Eur J Cardiothorac Surg 2007; 31:982–998.
3. Jovanović S, Gajić I, Mandić B, Mandić J, Radivojević V. Oral lesions in patients with psychiatric disorders. Srp Arh Celok Lek 2010; 138:564–569. (Serbian)
4. Valença MM, Martins C, Andrade-Valença LPA. Trigeminal neuralgia associated with persistent primitive trigeminal artery. Migrâneas cefaléias (Brasil) 2008; 11:30–32.
5. Belenkaya RM. Structural variants of the brain base arteries. Vopr neirokhir 1974; 5:23–29. (Russian)

Abstract:

6. Tontisirin N, Muangman SL, Suz P, et al. Early childhood gender in anterior and posterior cerebral blood flow velocity and autoregulation. In Abstract of Pediatrics 2007. (doi:10.1542/peds. 2006-2110; published online February 5).

Books:

7. Patten MB. Human embryology, 3rd edn. McGraw-Hill: New York, 1968.
8. Marinković S, Milisavljević M, Antunović V. Arterije mozga i kičmene moždine—Anatomske i kliničke karakteristike. Bit inžerenjering: Beograd, 2001. (Serbian)

Chapters:

9. Lie TA. Congenital malformations of the carotid and vertebral arterial systems, including the persistent anastomoses. In: Vinken PJ, Bruyn GW (eds) Handbook of clinical neurology, vol. 12. North Holland: Amsterdam, 1972; pp 289–339.

Unpublished data:

10. Reed ML. *Si-SiO_2 interface trap anneal kinetics*, PhD thesis. Stanford University: Stanford, 1987.

Online document:

11. Apostolides PJ, Lawton MT, David CA, Spetzler RF. Clinical images: persistent primitive trigeminal artery with and without aneurysm. Barrow Quarterly 1997; 13(4). http://www.thebarrow.org/Education_And_Resources/Barrow_Quarterly/204843
12. Cerebrovascular embryology, in: power point; 2000. http://brainavm.oci.utoronto.ca/staff/Wallace/2000_curriculum/index.html

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Table and figure legends should be included within the text file and contain sufficient data to be understood without reference to the text. Each should begin with a short title for the figure. All symbols and abbreviations should be explained within the legend. If the magnification is quoted in a sentence, it should appear in parentheses, e.g. (x400); at the end of legend it should appear, e.g., "... fibrils. X20 000".Tables must be typed on separate pages. All tables should be simple without duplicating information given in the text. Numerical results should be expressed as means with the relevant standard errors and/or statistically significant differences, quoting probability levels (p-value).

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Review Article

VARIABLE LEFT AND/OR RIGHT VERTEBRAL ARTERY IN PREVERTEBRAL PART: A REVIEW OF FEATURES IN THE POSTNATAL PERIOD

Ljiljana Vasović[1], Goran Radenković[2], Milena Trandafilović[1*], Gordana Đorđević[3]

Faculty of Medicine, University of Niš, [1]Department of Anatomy, [2]Department of Histology and Embryology, Niš, Serbia
[3]Health Center of Niš, Niš, Serbia

Abstract. *The vertebral artery (VA), as the first upstream branch of the subclavian artery on both sides courses having four topographical parts — prevertebral, cervical, atlantic and intracranial to the interlocking connection into basilar artery. However, its amenability to the variations can be at the origin, and/or course and/or termination. The review of postnatal features of variable VA origin and its prevertebral part was performed according to the 171 literature case reports. Among them, 94 cases of variable left VA, 30 cases of variable left and right VAs and 47 cases of variable right VA have been analyzed. The left and/or right VAs were showed as simple or common vessels or segmentally duplicated at their origin from the aorta and/or subclavian or common carotid or external carotid artery or unusual arterial stems. Different patterns of single VA origin and/or arrangement associated with main supra-aortic arteries variants were presented as 30 primary (basic) and 32 complementary models. Nine different vascular and/or visceral pathological processes were common independently of unilateral or bilateral variability of the VA; however, there were only eight patients with pathological changes in variable VA.*

Key words: *Human vertebral artery, morphologic variants, postnatal status, associated disorders*

Introduction

The cardiovascular system is the first system functioning in the developing animal or human embryo [1]. As cited by Bhatia et al. [2], the development of blood vessels is associated with local release of certain growth factors such as the placental growth factor, fibroblast growth factor-2, angiopoietins and vascular endothelial growth factor.

The development of the cardiovascular system is associated with the formation of the endocardial tube and paired primitive aortae. The endocardial tube begins to beat during the third week of gestation. It consists of four parts: (1) sinus venosus; (2) primitive atrium; (3) primitive ventricle; and (4) bulbus cordis that continues as the truncus arteriosus. Six primitive aortic arches bilaterally diverge from a dilatation of the truncus arteriosus (aortic sac) to the dorsal aortas that run through the entire length of the embryo and their segmental branches correspond to the somites. The dorsal aorta gives off thirty pairs of dorsal intersegmental arteries (DIAs), which supply the spinal cord and the developing somites. Each segment has the same number as the intersegmental artery bounding it caudally. The fusion of paired dorsal aortas could be seen just caudal to pharyngeal arches, during the 4th week. The first pair of aortic arches embedded in the mandibular arch courses around the rostral part of the pharynx. Actually it is formed by the curving of a ventral segment of the primitive aorta ("ventral aorta") into dorsal segment ("dorsal aorta"), between days 22–24. The first aortic arch will contribute to the development of maxillary and external carotid arteries. A second pair of aortic arches that embedded into tissue of the hyoid arch springs from the cephalic end of the heart dorsal to the ventral root of the first aortic arch. It participates in the formation of hyoid artery and its stapedial branch. The further course of development is followed by appearance of other aortic arches; five pairs (I–IV and VI) are developed between days 22–29. The development of the fifth aortic arch is followed by the disappearance of the first two arches. A proximal segment of the *third pair* will form the common carotid artery (CCA), whereas the distal part of the third arch together with some segments of the dorsal aorta will contribute to the formation of the internal carotid artery (ICA). The left *fourth* arch will form the segment of adult arch of the aorta between the left CCA and subclavian (SA) arteries; the right fourth arch will form the proximal right SA [3, 4].

There is a disagreement in the literature about the complete development of the SA. Some authors noted that the distal right SA will derive from a portion of the right dorsal aorta and the right sixth cervical intersegmental artery (CIA), whereas the left SA will be formed entirely from the left sixth CIA [5–16]. However, some embryologists [1, 3, 4], as well as most cited anatomists

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and clinicians in this paper described that the seventh CIA is a precursor of future SA and VA.

The segment of the ventral aortic roots between the fourth and third aortic arches will incorporate into the brachiocephalic trunk on the right and into the ascending aorta on the left side. The arch of the aorta will develop from the aortic sac, left 4th aortic arch, and a part of the left dorsal aorta. The *left sixth aortic arch* will participate to the formation of the pulmonary trunk, left pulmonary artery and ductus arteriosus; the right sixth arch will contribute to the right pulmonary artery. The branches of the arch of the aorta develop during the 5th and 6th weeks of gestation, and during the 8th week transformation of the aortic arch arteries leads to the development of an adult arterial system. This adult pattern is caused by degeneration or hypertrophy or anastomosis of some embryonic vessels and/or separation of one primitive vessel into two and/or formation of new arteries [3, 4, 6]. However, isolated anomalies of the arch of the aorta and its branches with normal heart can associate with chromosome 22q11 deletion [17].

Summarizing the developmental changes from stereomicroradiographic images of timed-gestation embryos, Effman et al. [1] noted the following: (1) partitioning of the truncus arteniosus; (2) initial symmetry of primitive III, IV and VI aortic arches and dorsal aortae; (3) development of the SAs from seventh CIAs caudally to their final location on the primitive aortic arch; (4) progressive decrease in the size of right IV and VI aortic arch derivatives; (5) attenuation of a segment of the right dorsal aorta distal to the right SA; (6) progressive rounding of the aortic arch; and (7) persisting large main pulmonary trunk and ductus arteriosus through late gestation.

As cited [16], primary VA stem contains three parts: (1) cervical VA with prevertebral and transversal segments; (2) atlantic part; and (3) subarachnoid part—a metencephalic longitudinal anastomosis in the direction of primitive ICA caudal branch. Any interruption or regression and reformation in the developmental process of VA can give rise to anomalies such as fenestration or duplication [12, 16, 18], as well as the variable origin [12, 16,] and/or involvement of only one VA in the BA origin [19].

Although these VA anomalies can be found both in the fetal [12, 16, 20] and adult period, in continuation of review of morphological features of the VA from prenatal to the postnatal age 21 [16], anatomo-pathological specificities of VA in a special sample of left and/or right VA variants will be highlighted.

Material and Methods

Case reports of the left and/or right VA variants from online available articles and library archives at the Faculty of Medicine of Niš dated from year 1928 to 2015 have been examined. These variants in 171 adult cases—patients and cadavers of (un)known gender that were investigated in 32 countries have been reviewed (Table 1).

Systematization of variable VAs was performed according to the location and relationships of variable VA with other supra-aortic arteries in the form of primary and complementary models. The capital letter ─ M (or M*) with corresponding Arabic number was used for labeling the patterns of variable left (or right) VA origin, respectively; two letters ─ MM* (with corresponding Arabic number) were used for marking different patterns of variable origin of both VAs. Marking of complementary model (variable VA origin associated with variation of the main supra-aortic arteries) was as follows: appropriate characters of primary models (M1… or M*1… or MM*1…) received a small letter of the alphabet. All models were personally sketched.

Unilateral and bilateral VA variability

Routine anatomy dissection of human cadavers during students' exercises, as well as surgical interventions and/or some radiological methods (aortography, or cerebral angiography, or selective vertebral angiography, or retrograde brachial angiography, or computer tomography angiography, or magnetic resonance angiography, or digital subtraction angiography, or color Doppler sonography) were applied as therapeutic and/or diagnostic procedures in patients because of different diseases during which variable VA and other vascular and/or visceral (ab)normalities were detected.

Left VA

General data

Only on the left side, a variable VA was found in 94/171 or 54.97% of cases (52 of male, 25 of female and 17 of unknown gender), from age 6 [21] to 95 [22].

Variable left VA was discovered in patients with different initial symptoms—headache [11, 13, 18, 23, 24], or motor weakness in the right upper limb [25, 26] and lower limb [27], or weakness and vertigo [23, 28], or dizziness [29] and gait instability [30, 31], or tingling on one side of the body [23] followed by cardiac murmur [21], or paresthesia in the left arm [32] and left limb [33], or chest pain [34, 35], or presyncope [36], or stroke [37, 38], or known presence of arterial aneurysm [38, 39], or transient ischemic attack [40], or dysphagia, dehydration and respiratory distress [7]. However, this VA variability was also discovered during health screening [41–43], or preoperative examination [9, 44], or suspected pacemaker failure [45], as well as in single angiographic images [15, 46–49].

Status of vessel stem

The left VA was presented as a simple or common vessel or total and segmentally duplicated at the origin from different vascular sources—the left SA and/or the arch of the aorta, or left CCA, or left external carotid artery (ECA), or left thyrocervical trunk, or so-called left brachiocephalic artery, or special left lateral SA (Fig. 1).

Table 1. Distribution of single cases of the variable vertebral artery origin

Country*	Case numbers			Σ
	Side			
	Left	Right	Left + Right	
	Patients + Cadavers (m / f / u)			
1 Argentina	2 (2u)			2
2 Austria		1 (m)	1 (f)	2
3 Brazil	1(m)	1 (m)		2
4 Canada	1 (m)		1 (m)	2
5 China			2 (2f)	2
6 Croatia	1 (f)		1 (f)	2
7 Ethiopia	1 (m)			1
8 France		2 (m+f)	2 (2f)	4
9 Germany	6 (2m+4f)	2 (m+f)	1(f)	9
10 Greece	1 (u)	1 (u)		2
11 Grenada		1 (m)		1
12 India	32 (18m+3f+11u)	7 (2m+3f+2u)	5 (3m+1f+1u)	44
13 Iran	1 (m)			1
14 Ireland	1 (m)			1
15 Italy		1 (f)	2 (m+f)	3
16 Japan	12(5m+7f)	8 (5m+3f)	1 (m)	21
17 Korea	3 (2m+1f)	4 (2m+2f)	2 (2f)	9
18 Lithuania			1 (u)	1
19 Netherlands			1 (f)	1
20 Pakistan		1 (m)		1
21 Poland	1 (m)			1
22 Romania	1 (m)			1
23 Serbia	1 (m)			1
24 Slovakia	1 (f)			1
25 South Africa	6 (5m+1u)	1 (m)		7
26 Spain	1 (m)			1
27 Switzerland		1 (f)	1 (m)	2
28 Tanzania	1 (m)			1
29 Trinidad and Tobago	1 (m)			1
30 Turkey	5 (2m+2f+1u)	4 (3m+1f)	3 (3f)	12
31 UK	2 (f+u)	2 (m+u)	1 (f)	5
32 USA	12 (7m+5f)	10 (5m+4f+1u)	5 (2m+3f+1u)	26
Σ	94 (52m+25f+17u)	47 (25m+17f+5u)	30 (9m+18f+3u)	171 (85m+60f+26u)

*Alphabetical order

m, male; *f*, female; *u*, unknown gender

A single left VA of aortic origin was found between a brachiocarotid trunk and left SA [34, 46, 50], distally from the left SA [21, 23, 26, 35, 39, 48], and between the left CCA and left SA in most cases. Although infrequently, the left VA was found between the brachiocephalic trunk (BT) and left CCA [51], between the right SA and bicarotid trunk [24], between the left internal carotid artery (ICA) and left SA [52], and between the left CCA and left internal thoracic artery (InTA) [53] in single cases. Such unique cases were also the origins of the left VA from the left CCA [27] or so-called left brachiocephalic artery [45] or special left lateral SA [54]. The left VA had a common origin with the left SA at the arch of the aorta [53, 55–57], and with the left inferior thyroid artery (ITA) originating from ipsilateral SA or the arch of the aorta [41].

The left VA was totally duplicated in a female case described by Poonam et al. [58]. Namely, the authors discovered one hypoplastic VA of SA origin that coursed only in the V1 and V2 parts, and entered the C VI foramen transversarium, whereas the second VA of ECA origin was dominant and took the course through V3 and V4 parts without entering any foramen transversarium. The left VA was segmentally duplicated while both segments originated from ipsilateral SA [28, 29, 47, 59], or SA and the arch of aorta [9, 13, 23, 25, 30, 32, 36–38, 40, 43, 49, 53, 59, 60], or the thyrocervical trunk and aorta [61].

The patterns of the variability of 93 left VAs and its association with variable main supra-aortic arteries are presented by 12 primary and 12 complementary models, respectively (Table 2).

Caliber

Some authors described that variable left VA was hypoplastic [26] and had 0.9 mm diameter [58], or was small with mild ostial narrowing [23, 45], or dilated [34, 81].

The diameter of the left VA of aortic origin ranged from 2 mm [62] to 8.4 mm [77]. A 9.5 mm diameter

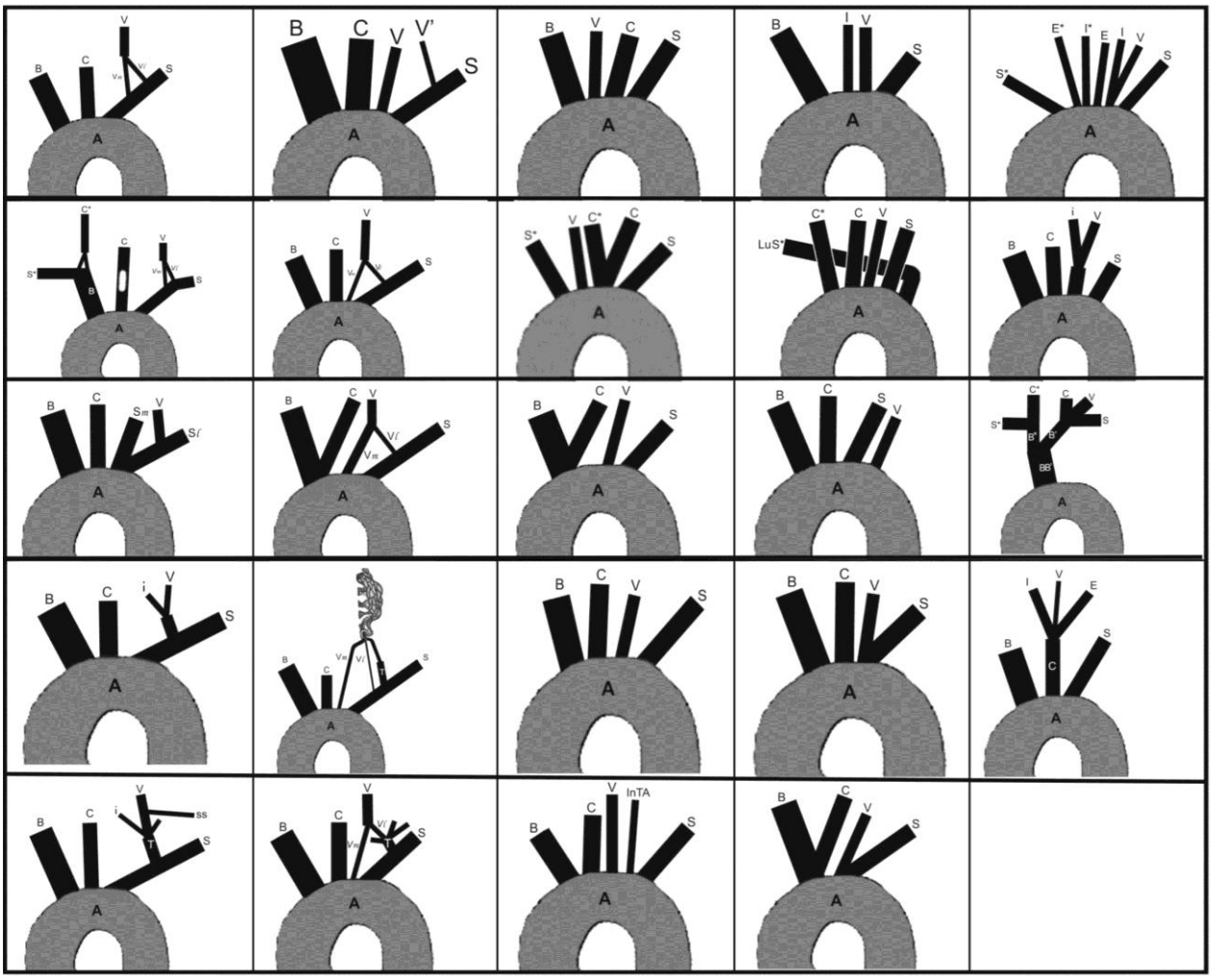


Fig. 1. Twenty four patterns of relationships of the variable left vertebral and main supra-aortic arteries.
A, arch of the aorta; *B*, brachiocephalic trunk; *C* (*C**), left (right) common carotid a.; *S* (*S**), left (right) subclavian a.; *Vl* (*Vm*), lateral (medial) segment of duplicated left vertebral artery in prevertebral part; *V*, left vertebral a.; *Sl* (*Sm*), lateral (medial) subclavian a.; *i*, left inferior thyroid a.; *T*, left thyrocervical trunk; *ss*, left suprascapular a.; *LuS**, so-called lusoria right subclavian a.; *BB'*, common trunk of so-called brachiocephalic arteries; *B** (*B'*), so-called right (left) brachiocephalic a.; *I*, left internal carotid a.; *E*, left external carotid a.; *InTA*, left internal thoracic a.

was noted in a common stem of the left VA and SA in the first [56], and 10.08 mm in the second case [57].

Sikka and Jain [81] revealed that the diameters of the left VA at origin and at the entry of the corresponding cervical foramen transversarium were different — 4.9 mm and 3.9 mm, respectively. Ikegami et al. [64] described a pyramidal commencement of the left VA on the arch of the aorta with 8 mm in diameter, and its decrease to 4 mm at a point about 2 cm away from the origin.

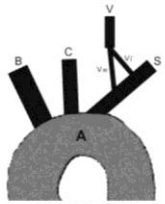
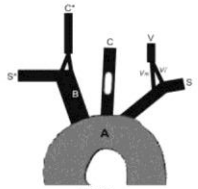
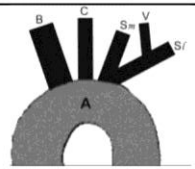
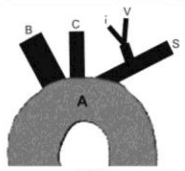
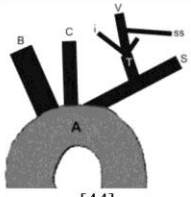
Course in V1 part

There was no note about some special course of the variable VA in V1 part in relation to the course of the normal VA. There were descriptions that the left VA of aortic origin ascended upward and backward lying behind the left vagus, left brachiocephalic vein and left CCA [84], or in close to the left vagus and the apex of the left lung [56], sometimes of tortuous course [81]. The VA was crossed anteriorly by ITA [71], or by sympathetic trunk [77], or by thoracic duct [74]. Posteriorly, the VA was related to the longus cervicis muscle before entering the foramen transversarium of the cervical (C) vertebra at a higher level than that of the sixth [71].

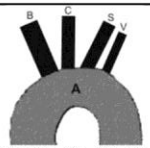
There were reports about different levels of the single (left) VA entry at the foramen transversarium of cervical vertebra — C VII [49, 56], C VI [54, 58, 65, 68–70, 72, 74, 75, 80, 82, 84], C V [11, 33, 62, 64, 71, 77], C IV [49, 55, 71, 81], C III [76, 87] and C I [27]. Moreover, in a case described by Poonam et al. [58], the left VA of aortic origin bifurcated at V1 part, where one vessel entered C VI, whereas the second vessel entered C V foramen transversarium. Unusual extension of the left VA of thyrocervical origin outside of the transverse foramina and penetration of dura in the level of foramen magnum was described in a 36-year-old woman [44].

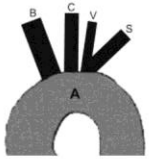
Medial and lateral segments of duplicated left VA also penetrated foramen transversarium at different levels [9, 28, 30, 38]. Their fusion differed from case to case — C VII [36], C VI [37], C V [13, 18, 23, 30, 32, 49], C IV [38, 43], or above C II [28].

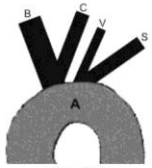
Table 2. Display of primary and complementary models of left vertebral artery (VA)[1] variants in 94 cases[2]

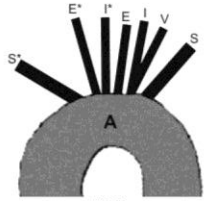
<table>
<tr><th colspan="3">Vascular source(s)</th><th colspan="2">Schemes and description of primary models of variable left VA</th><th colspan="2">Schemes and description of complementary models of variable left VA</th></tr>
<tr><td rowspan="5">Left subclavian a. (SA)</td><td rowspan="2">Subclavian stem (S)</td><td></td><td> 
[18, 28, 47]</td><td>M1:
Segmental duplication of the left VA of SA origin.</td><td> 
[29]</td><td>M1a:
Additionally, fenestration of the left common carotid a. (CCA) and segmental duplication of the right CCA.</td></tr>
<tr><td colspan="3">M1(M1a): Vℓ / S + Vm / S</td><td colspan="2"></td></tr>
<tr><td rowspan="3">Sub-clavian branch</td><td>So-called lateral left subclavian a (Sℓ)</td><td colspan="2"></td><td> 
[54]</td><td>M2a:
Left VA origin from so-called left lateral SA associated with a presence of a left medial SA.</td></tr>
<tr><td colspan="3"></td><td colspan="2">M2a: V / Sℓ</td></tr>
<tr><td>Vertebral -inferior thyroid trunk (V-i)</td><td> 
[41]</td><td>M3:
Common trunk of the left VA and inferior thyroid artery of SA origin.</td><td colspan="2" rowspan="2"></td></tr>
<tr><td colspan="2">M3: V-i / S</td></tr>
<tr><td>Thyro-cervical trunk (T)</td><td> 
[44]</td><td>M4:
Left VA originates from the left thyrocervical trunk (TT).</td><td colspan="2"></td></tr>
<tr><td colspan="2">M4: V / T</td><td colspan="2"></td></tr>
</table>

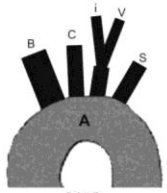
Left subclavian a. and arch (A) of the aorta						
Subclavian stem and aortic arch (S + A)	[22]	**M5:** Left VA originates with two separate vessels from the arch and left SA.				
	M5: V/A +V/S					
	[9, 13, 23, 25, 30, 32, 37, 38, 40, 43, 49, 53, 59]	**M6:** Segmental duplication of the left VA of SA and aortic origin.	[36]	[60]		**M6a**: Additionally, common stem of brachiocephalic trunk (BT) and left CCA–brachiocarotid trunk [36]. ---------- **M6b:** Additionally, an angiomatous vascular formation on the left side of the neck and connection of segmentally duplicated left VA with left TT [60].
	M6 (M6a–b): V*ℓ* / S + V*m* / A					
Thyrocervical trunk and aortic arch (T + A)	[61]	**M7:** Segmental duplication of the left VA of TT and aortic origin.				
	M7: V*ℓ* / T + V*m* / A					
Arch of the aorta	[51]	**M8:** Left VA originates from the arch as the second branch.	[24]	[34, 46, 50]		**M8a:** Additionally, BT aplasia; right SA as the first branch of the arch; common stem of the left and right CCA (bicarotid trunk) [24]. ---------- **M8b:** Additionally, brachiocarotid trunk [34, 46, 50].
	[7, 11, 15, 31, 32, 41, 49, 53, 58, 62–88]	**M9:** Left VA originates from the arch as the third branch.	[53]	[52]	[89]	**M9a:** Additionally, left InTA as the fourth branch of the arch [53] ---------- **M9b:** Additionally, absence of both CCAs; left ICA as the second branch of the arch [52]. ---------- **M9c:** Additionally, BT aplasia; right CCA and SA as the first and last branch of the arch, respectively [89].

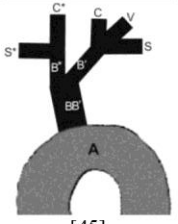
<table>
<tr><td rowspan="8"></td><td rowspan="8"></td><td> 

[21, 23, 26, 35, 39, 48, 49]</td><td>M10:
Left VA originates from the arch as the fourth (last) branch.</td><td colspan="4"></td></tr>
<tr><td colspan="6">M8 (M8a–b); M9 (M9a–c); M10: V / A</td></tr>
<tr><td> 

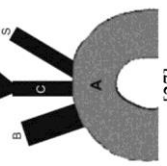
[53, 55]</td><td>M11:
Common beginning of the left VA and SA from the arch.</td><td> 

[56, 57]</td><td></td><td></td><td>M11a:
Additionally, brachiocarotid trunk [56, 57].</td></tr>
<tr><td colspan="6">M11 (M11a): V-S / A</td></tr>
<tr><td></td><td></td><td> 

[42]</td><td colspan="2">M12a:
Common beginning of the left VA and internal carotid a. Additionally, right SA as the first branch of the arch; right external carotid and internal carotid aa. as separated branches of the arch[42].</td></tr>
<tr><td></td><td></td><td colspan="3">M12a: V-I / A</td></tr>
<tr><td> 

[41]</td><td>M13:
Common stem of the left VA and inferior thyroid artery originates from the arch.</td><td colspan="4"></td></tr>
<tr><td colspan="2">M13: V-i / A</td><td colspan="4"></td></tr>
<tr><td colspan="2">So-called left brachiocephalic a. (B’)</td><td></td><td colspan="4"></td></tr>
<tr><td colspan="3"> 

[45]</td><td colspan="2">M14a:
Left VA is a branch of so-called left brachiocephalic artery trifurcation; additionally, common stem of the left and right brachiocephalic arteries is the only branch of the arch.</td></tr>
<tr><td colspan="3">M14a: V / B’</td></tr>
</table>

Left common carotid a. (C)	 [27]	**M15: V / C**	**M15:** Left VA is a branch of the left CCA trifurcation.

[1]Abbreviations of arteries in the text are explained during description of each pattern; abbreviations of same arteries in schemas include only the first capital letter of corresponding previous abbreviation because of practical reasons. The current relationship of VA and the main supra-aortic arteries is personally presented by "mathematical relation" in the row below corresponding pattern.
[2]The number of reported cases does not correspond to the number of cited references, because some authors discovered two or three same cases.
Abbreviations of arteries in inserts: *A*, arch of the aorta; *B*, brachiocephalic trunk; *C* (*C**), left (right) common carotid a.; *S* (*S**), left (right) subclavian a.; *Vl* (*Vm*), lateral (medial) segment of duplicated left vertebral artery in prevertebral part; *V*, left vertebral a.; *Sl* (*Sm*), lateral (medial) subclavian a.; *i*, left inferior thyroid a.; *T*, left thyrocervical trunk; *ss*, left suprascapular a.; *LuS**, so-called lusoria right subclavian a.; *BB'*, common trunk of so-called brachiocephalic arteries; *B* (B')*, so-called right (left) brachiocephalic a.; *I*, left internal carotid a.; *E*, left external carotid a.; *InTA*, left internal thoracic a.

Collaterals

Although normally VA does not distribute collaterals in V1 part, some authors noted side branches of the variable left VA as follows: (1) suprascapular artery [44]; (2) InTA [35]; and (3) bronchial artery [31, 62].

An early bifurcation of VA of aortic origin in two vessels was also evidenced, but without description about their further course and termination [58].

Additional vascular variants

VA. A fenestration of the left VA stem after fusion of its initial double segments in 42-year-old woman [25] and 73-year-old man was also reported [30].

Distal duplication of the right VA at the craniocervical region [38], or ectatic diameter of the right VA followed segmental left VA duplication of aortic and subclavian origin [25] in two separate cases.

Aorta. There was variable number (1–6) and/or arrangement of branches of the arch (and descending aorta). The arch of the aorta with four branches of different arrangement was the most frequent in cases of variable left VA.

Rare cases of these patterns were as follows: (a) one branch—a common trunk of so-called brachiocephalic arteries [45]; (b) two branches—a brachiocarotid and left VA-SA stems [56, 57]; (c) three (variable) branches—brachiocarotid stem, a medial segment of the left VA and left SA in one [36], and BT, left CCA and left VA-SA stem in two cases [53, 55]; (d) five branches—right CCA, left CCA, left VA, left SA and lusoria right SA in the first [89], and BT, left CCA, left VA, left InTA and left SA in the second case [53]; (e) six branches—right SA, right ECA, right internal carotid artery (ICA), left ICA-VA stem, and left SA in the one case [42].

In addition, a mild dilatation of ascending aorta [26], or kinked and elongated arch of the aorta [21], or dilated arch and descending aorta [39] were associated with aortic origin of left VA distally from the left SA. Hypoplastic descending aorta was associated with segmental duplication of the left VA in one case [60].

Brachiocephalic trunk (BT). There were some cases of absence of normal BT [24, 45, 89], or the presence of a brachiocarotid stem [34, 36, 46, 50, 56, 57]. One case of BT aplasia was especially characteristic because of the presence of unusual common brachiocephalic stem that divided into two so-called brachiocephalic arteries, while the left vessel distributed the left CCA, VA and SA, whereas the right vessel bifurcated in the right CCA and SA [45].

The right ITA [64], and a variable thyroid ima artery of BT origin [86] were found in two separate cases of aortic origin of the left VA.

Common carotid artery (CCA). A common trunk of the left CCA and BT or brachiocarotid trunk was revealed in association with single left VA of aortic origin [34, 36, 46, 50, 56, 57], and segmental VA duplication [36].

The right CCA was the first branch of the arch of the aorta in a case of BT aplasia and aortic origin of left VA [89].

Fenestration of the left CCA and initial segmental duplication of the right CCA were followed by segmental duplication of the left VA [29]. Bilateral absence of CCA was discovered in two cases of aortic origin of VA [42, 52].

Subclavian artery (SA). A very interesting case was a seemingly normal left SA of aortic origin that immediately bifurcated into medial SA that gives most of the branches and the lateral ones that continue as the axillary artery [54]. The right SA as the first branch of the arch of the aorta was found in two cases of aortic origin of the left VA [24, 42]. So-called lusoria right SA (last branch of the arch of the aorta) persisted only in a case of BT aplasia and associated with aortic origin of the single VA [89].

In three separate cases of aortic origin of the left VA, InTA was revealed from the left VA [35], or the arch of the aorta [53], or the right SA about 1 cm before its continuation into axillary artery [85]. A bronchial artery was noted as a variable branch of the left SA in one case of aortic left VA origin [62]. There were two cases of variable ITA origin in the shape of ITA-VA common trunk originated from the arch of the aorta and from the left SA [41], and the third case of the right ITA branching from BT and in the presence of aortic origin of the left VA [64]. Aplasia of both ITAs was associated with aortic origin of single VA [75], and in a case of persistent thyroid ima artery [86].

Anterior cerebral artery (ACA). Right ACA branch supplying right MCA territory was associated with a common trunk of the left VA and ITA of SA origin [41]. Aplasia of the precommunicating part of the right ACA was associated with CCA origin of the left VA [27].

Posterior cerebral artery (PCA). There were two reports with data about fetal origin of the right PCA associated with segmental duplication [36], and single aortic origin of the left VA [15] .

Persistent primitive arteries. Vasović et al. [7] and Lotfi et al. [24] discovered persistent left primitive trigeminal artery (PPTA) in association with aortic origin of the left VA, whereas Meila et al. [38] discovered the persistent right lateral spinal artery in a case of segmental duplication of the left VA.

Veins. Duplicate left vertebral veins at C V level [62] and between C III–IV and C V–VI [28] were revealed in cases of single aortic origin and segmental duplication of the left VA, respectively. Kawate et al. [62] also found a draining of these veins into venous angles on both sides. Ikegami et al. [64] noted enlarged veins in the neck and abdominal region in association with aortic origin of the left VA. Nathan and Seidel [89] revealed a termination of the thoracic duct in the right venous angle associated with aortic origin of left VA in a 64-year-old male.

An arteriovenous fistula between the right VA and ipsilateral veins was discovered in a 42-year-old female with a segmental duplication of the left VA [25].

Associated disorders

Basic congenital anomalies

1. Ehlers–Danlos syndrome (a group of inherited disorders that affect primarily skin, joints and blood vessel walls) and segmental left VA duplication of SA origin were presented in a 43-year- old male [18].
2. Chiari malformation (malformation of the skull) was associated with an absence of C IV foramen transversarium and VA origin from the left thyrocervical trunk in a 36-year-old female [44].
3. Dumbell neurofibroma (a type of tumor that can involve both the spinal canal and the posterior thoracic cavity) and a finding of a common trunk of left VA and ITA of aortic origin (between the left CCA and left SA) were found in a 33-year-old male [41].

Acquired pathological disorders

1. Dissections of some arteries — left VA [11], or both CCAs [34], or the right ICA [18] in a case of segmental duplication of the left VA of SA origin [18], or aortic origin of single left VA [11, 34] were noted.
2. Cerebral infarction (of different localization) was followed by segmental duplication of the left VA [18, 49], or by aortic origin of the left VA distal to the left SA [23], or by CCA origin of the left VA [27].
3. Aneurysms of different arteries — left VA and both ICAs [13], left PCA [23], left anterior temporal artery [43], ICA [38] were associated with segmental VA duplication, whereas an aneurysm of the descending aorta [39], or anterior communicating artery [41], or unnamed artery [49] was followed by aortic origin of single VA.
4. Partial thrombotic occlusion of different arteries — left ICA followed by a common trunk of the left VA and ITA [41], or the right VA and both ICAs followed by origin of the left VA from so-called left brachiocephalic artery [45].
5. Stenosis of some arteries of different grade — so-called left brachiocephalic artery [45], or the left VA [11, 37], or ICAs and/or left VA [23], or the right VA [51] was also noted.
6. Coarctation of the aorta (distally to the left SA origin) followed by segmental VA duplication was found in a 15-year-old girl [60]; pseudocoarctation of the aorta and perimembranous ventricular septal defect was associated with aortic origin of the left VA (distally to the left SA) in a 6-year-old boy [21].
7. Cerebral hemorrhage was presented in a 60-year-old woman with aortic VA origin distally to the left SA [49], whereas ventricular hemorrhage was diagnosed in a 46-year-old man with aortic origin of the left VA (between the right SA and bicarotid trunk) [24].
8. Subarachnoid hemorrhage was presented in a 52-year-old female with aortic origin of the left VA between the left CCA and left SA [41].
9. Angiomatous formation and segmental duplication of the left VA were revealed on the left side of the neck in a 15-year-old girl [60].

10. Tumor at the left cerebellopontine angle and segmental duplication of the left VA were discovered in a 27-year-old female [9].

Left and right VAs

General data

An association of variable left and right VAs, single or associated with supra-aortic arteries' variants was found in 30/171 (9 of male, 18 of female and 3 of unknown gender) or 17.54% of cases from age 4 [90] to 83 [91].

Variable left and right VAs were discovered in patients with different initial symptoms or reasons of investigation — a headache [25, 92, 93], followed by vertigo [94, 95], or cognitive impairment [91], or pain in the left eye and ear [8], or hemisensory disturbance [10], or trauma [96, 97], or subarachnoid hemorrhage [38],or personality change [98], or right-sided numbness [99], or right upper and lower limb weakness [90], or stroke [100], or central chest pain [101], or myocardial infarction [102], or carcinoma [103, 104], or spondyloepiphyseal dysplasia [105], or angiographic evaluation [106–109], or aortic valve replacement [110] or swallowing difficulties [111].

Status of vessels' stems

Variable left and right VAs were presented as simple or common vessels or segmentally duplicated at their origin. Vascular sources of variable VAs were SAs, arch of the aorta and descending aorta, BT and its common stem with the left CCA—brachiocarotid trunk, and right CCA (Fig. 2).

There were some cases of similar vascular sources —left and right SA in 2/28 cases [8, 91] and aorta in 5/28 cases [92, 96, 97, 104, 105]. Different vascular sources were found in other 21 cases while aorta and right common carotid artery were more frequent vascular sources of the left and right VAs, respectively. Only Takasato et al. [8] described an association of double left (rudimentary and accessory) VAs with segmentally duplicated right VA of SA origin.

A variability of both VAs is presented by nine primary and nine complementary models (Table 3).

Caliber

Very interesting finding in some papers was relatively larger caliber of the variable right VA in relation to the same of the left VA. Namely, Rameshbabu et al. [108] noted that medial segment (2.2 mm in diameter) and lateral segment (2.4 mm in diameter) of the left VA united into single vessel of 3.2 mm in diameter. Simultaneously, medial segment (3.9 mm in diameter) and lateral segment (2.4 mm in diameter) of the right VA fused to form a single vessel of 4.4 mm in diameter. Diameter of the left VA of aortic origin was 3.3 mm, whereas the one of the right VA of CCA origin was 3.8 mm [114]. Diameter of the left VA of aortic origin was 6 mm, whereas the one of the right VA of BT origin was 7 mm [112].

Karcaltincaaba et al. [97] described a widening or so-called Kommerell's diverticulum at aortic origin of the right VA.

Course in V1 part

Special course of variable (left or right) VA related to the unusual retroesophageal course of the right VA in cases of aortic origin of both VAs [96, 97, 102, 104]. They were also related to a location of the right VA in retrothyroid area and close to the thyroid gland in cases of its CCA origin [107] or segmental duplication of both VAs [38, 91, 100].

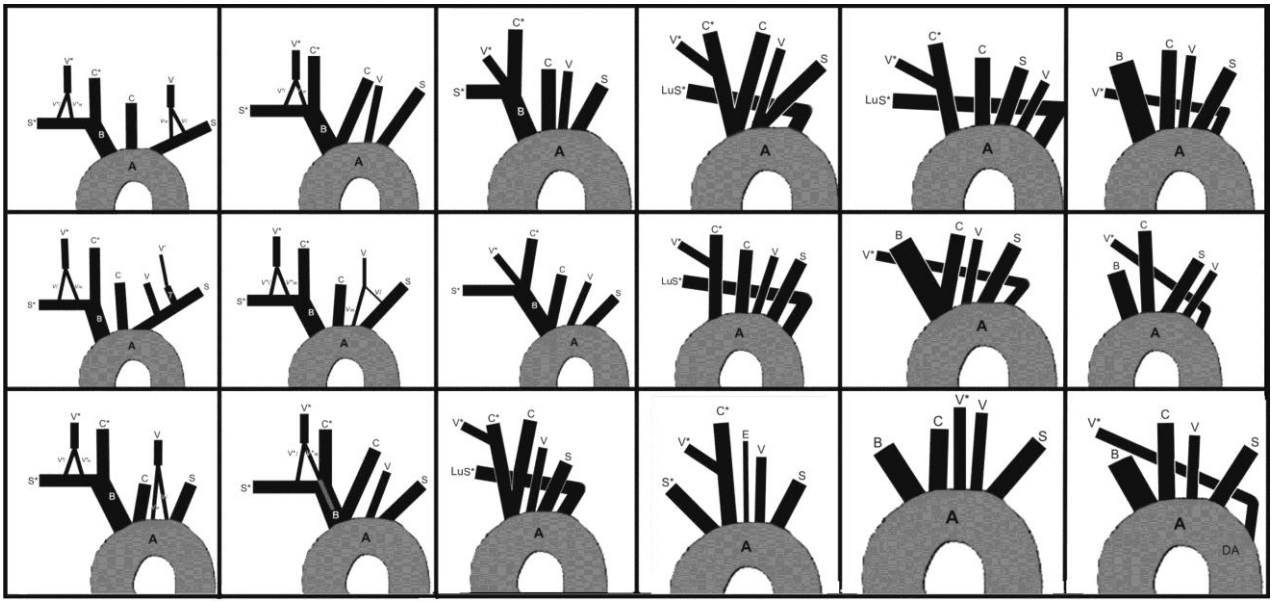
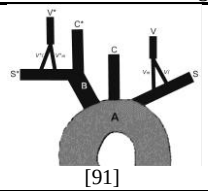
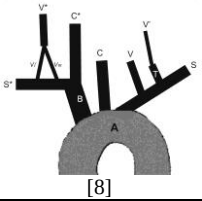
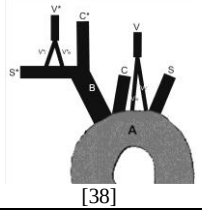
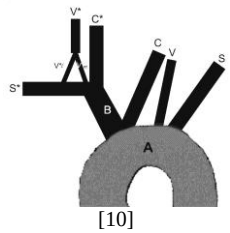
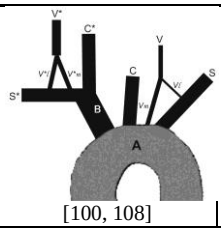
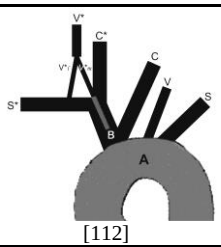
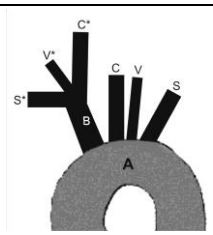
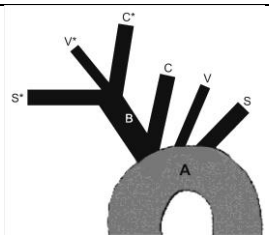
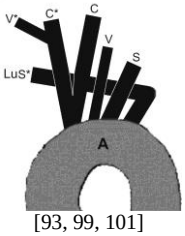
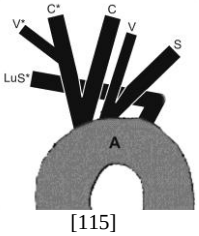
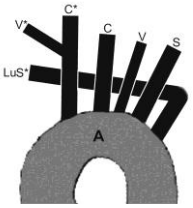
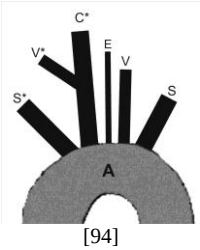
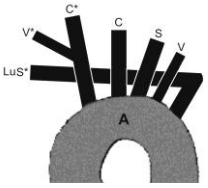


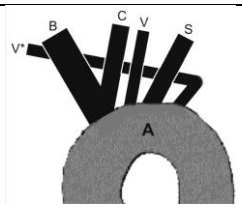
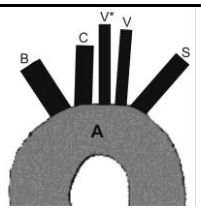
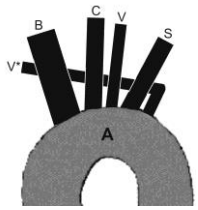
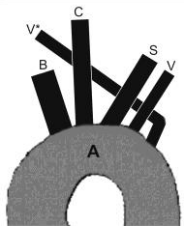
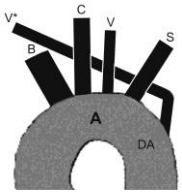
Fig. 2. Eighteen patterns of relationships of variable both vertebral and main supra-aortic arteries.
V (*V**), left (right) vertebral a.; *Vl* (*V***l*) + *Vm* (*V***m*), lateral and medial segments of duplicated left (right) vertebral artery at prevertebral part; *S* (*S**), left (right) subclavian a.; *LuS**, so-called lusoria right subclavian a.; *A*, arch of the aorta; *DA*, descending aorta; *B*, brachiocephalic trunk; *C* (*C**), left (right) common carotid a.; *E*, left external carotid a.

Table 3. Display of primary and complementary models of left and right vertebral arteries (VAs)[1] variants in 30 cases[2]

Vascular source(s)	Schemes and description of primary models of variable left and right VAs		Schemes and description of complementary models of variable left and right VAs	
(Left subclavian a..) + (Right subclavian a.) (S + S*))	 [91]	**MM*1:** Bilateral segmental duplication of vertebral aa. of subclavian (SA) origin.		
	MM*1: (V𝓁/ S + V𝓂 / S) + (V*𝓁 / S* + V*𝓂 / S*)			
(Left thyrocervical trunk) + (Right subclavian a.) (T + S*))	 [8]	**MM*2:** Total duplication of the left VA of SA origin and segmental duplication of the right VA of SA origin.		
	MM*2: (V' / T) + (V*𝓁/ S* + V*𝓂 / S*)			
(Arch of aorta) + (Right subclavian a.) (A + S*))	 [38]	**MM*3:** Bilateral segmental duplication of vertebral aa. of aortic origin on the left and SA origin on the right side.		
	MM*3: (V𝓁/ A + V𝓂 / A) + (V*𝓁 / S* + V*𝓂 / S*)			
			 [10]	**MM*4a:** Aortic origin of single left VA and segmental duplication of the right VA of SA origin. Additionally, common stem of brachiocephalic trunk (BT) and left common carotid artery (CCA) —brachiocarotid trunk.
			MM*4a: (V / A) + (V*𝓁/ S* + V*𝓂 / S*)	
(Arch of aorta + left subclavian a.) + (Right subclavian a.) (A + S) + (S*))	 [100, 108]	**MM*5:** Bilateral segmental duplication of vertebral aa. of aortic and SA origin on the left and SA origin on the right side.		
	MM*5: (V𝓁/ S + V𝓂 / A) + (V*𝓁 / S* + V*𝓂 / S*)			
(Arch of aorta) + (Brachiocephalic trunk + right subclavian a.) (A) + (B +S*))			 [112]	**MM*6a:** Aortic origin of single left VA and segmental duplication of the right VA of SA origin of brachiocephalic origin. Additionally, brachiocarotid trunk.
			MM*6a: (V / A) + (V*l / S* + V*m / BC)	

<table>
<tr><td rowspan="2">(Arch of aorta + Brachiocephalic trunk)
(A + B))</td><td> 
[113]</td><td>MM*7:
Aortic origin of single left VA and BT origin of the right VA.</td><td> 
[114]</td><td>MM*7a:
Additionally, brachiocarotid trunk.</td></tr>
<tr><td colspan="2">MM*7:
(V / A) + (V* / B)</td><td colspan="2">MM*7a:
(V / A) + (V* / BC)</td></tr>
<tr><td rowspan="6">(Arch of aorta) + (Right common carotid a.)
(A + C*))</td><td colspan="2" rowspan="2"></td><td> 
[93, 99, 101]</td><td> 
[115]</td><td>MM*8a:
Aortic origin of single left VA (second branch) and CCA origin of the right VA. Additionally, common stem of the left and right CCA ―bicarotid trunk; right SA is the last branch of the arch [93, 99, 101].

MM*8b:
Common stem of the left VA and SA (second branch) of aortic origin, and CCA origin of the right VA. Additionally, bicarotid trunk and right SA as the last branch of the arch [115].</td></tr>
<tr><td>MM*8a:
(V / A) +
(V* / C*C)</td><td>MM*8b:
(VS / A) +
(V* / C*C)</td></tr>
<tr><td colspan="2"></td><td colspan="2"> 
[90, 95, 103, 106, 107, 110, 116, 117]</td><td>MM*9a:
Aortic origin of single left VA (third branch) and CCA origin of the right VA. Additionally, right SA is the last branch of the arch.</td></tr>
<tr><td colspan="2"></td><td> 
[94]</td><td> 
[98, 111]</td><td>MM*10a:
Aortic origin of single left VA (fourth branch) and CCA origin of the right VA. Additionally, right SA is the first branch of the arch. Left CCA aplasia; left external carotid artery originated from the arch [94].
MM*10b:
Aortic origin of single left VA (fourth branch) and CCA origin of the right VA. Additionally, right SA is the last branch of the arch [98, 111].</td></tr>
<tr><td colspan="2"></td><td colspan="2">MM*9a; MM*10a–b:
(V / A) + (V* / C*)</td></tr>
</table>

				 [104]	**MM*11a:** Aortic origin of the left (second branch) and right VAs (fourth branch). Additionally, brachiocarotid trunk.
Aorta	Arch of aorta (A)	 [92]	**MM*12:** Aortic origin of the right (third branch) and left VAs (fourth branch).		
		 [102]	**MM*13:** Aortic origin of the left (third branch) and right VAs (fifth branch).		
		 [105]	**MM*14:** Aortic origin of the left (fourth branch) and right VAs (fifth branch).		
		MM*11a; MM*12–14: (V / A) + (V* / A)			
	(Arch of aorta) + (Descen-ding aorta) (A + DA))	 [96]	**MM*15:** Origin of the left VA (third branch) from the arch and right VA from descending aorta.		
		MM*15: (V / A) + (V* / DA)			

[1]Abbreviations of arteries in the text are explained during description of each pattern; abbreviations of same arteries in schemas include only the first capital letter from corresponding previous because of practical reasons. The current relationship of VA and the main supra-aortic arteries is personally presented by "mathematical relation" in the row below corresponding pattern.

[2]Patterns are based on 29 cases because one report was without data about precise location of variable left and right VAs on the arch of the aorta [109]

Abbreviations of arteries in inserts: *V* (*V**), left (right) vertebral a.; *Vℓ* (*V**ℓ*)+ *Vm* (*V***m*), lateral and medial segments of duplicated left (right) vertebral artery at prevertebral part; *V'*, left accessory vertebral a.; *S* (*S**), left (right) subclavian a.; *LuS**, so-called lusoria right subclavian a.; *A*, arch of the aorta; *DA*, descending aorta; *B*, brachiocephalic trunk; *C* (*C**), left (right) common carotid a.; *E*, left external carotoid a.

Ionete and Omojola [91] and Mordasini et al. [100] described the course of both segmentally duplicated VAs as follows: The right medial segment originated proximally beyond the origin of SA and after a short loop it entered the carotid space, whereas the right lateral segment emanated from SA, coursed straight and entered the foramen transversarium of C VII vertebra. Both vessels joined in C IV–C V disk level to continue as the single right VA. On the left side, medial segment began from SA, looped slightly forward, and coursed straight up behind the left CCA, whereas lateral segment emanated just distal to the medial segment and entered the foramen transversarium of C VII vertebra; both vessels joined at C V–C VI disk level into single left VA. Meila et al. [38] presented the right lateral and medial segments at entry of the foramen transversarium of C VI and C IV vertebrae, respectively. They also found that left lateral segment entered the foramen transversarium of C V vertebra, whereas the medial segment entered it at C IV vertebra. Pauliukas [109] noted aortic origin of both VAs, but the left VA was the one which was strangulated by the sympathetic trunk and compressed at the entrance into C V foramen transversarium by longus colli muscle tendon.

Some variable VAs of single stems entered the foramen transversarium of the same cervical vertebra level on both sides [103, 105, 107, 112, 115], whereas some VAs entered the foramen transversarium at different levels [58, 102, 109]. So, the right VA of CCA origin penetrated CVI foramen transversarium, whereas the left VA of aortic origin penetrated C VII [109]; the left VA of aortic origin penetrated C VI foramen transversarium, whereas the right VA of aortic origin penetrated C IV foramen transversarium [102] or the left VA of aortic origin penetrated C IV, while the right VA of aortic origin penetrated C VII foramen transversarium [58].

Collaterals

Schwarzacher and Krammer [102] described ITA as a side branch of the left VA in a case of aortic origin of both VAs.

Additional vascular variants

Aorta. There was a variable number (3–5) and/or arrangement of branches of its arch and descending part. In addition, cervical location of the arch of the aorta above the level of the manubrium of sternum was found in a 77-year-old woman [102].

BT. Its aplasia [90, 93–95, 98, 99, 101, 103, 106, 107, 110, 114–116] was noted in 14/29 or 46.4% of the cases, whereas a common trunk of the BT and left CCA (brachiocarotid trunk) [10, 104, 111, 113] was found in 4/29 or 14.2% of the cases. BT was a vascular source of the thyroid ima artery in one case [102].

SA. So-called lusoria right SA (LuS) was found in previously mentioned 12 cases of BT aplasia, except in a case described by Abas et al. [94], when right SA was the first branch of the arch of the aorta. Besides, LuS coursed retroesophageally in most of these cases.

An early bifurcation of the left SA in two axillary arteries was associated with aortic origin of the left VA and segmental duplication of the right VA in a 46-year-old man [111]. Aplasia of the left thyrocervical trunk was revealed in an 83-year-old woman with aortic origin of both VAs [102].

CCA. A common trunk of BT and left CCA (brachiocarotid trunk) at the arch of the aorta was described in four cases [10, 104, 111, 113], a common trunk of left and right CCAs (bicarotid trunk) at the arch of the aorta was also found in four cases [93, 99, 101, 114]. Right CCA was the first single branch of the arch of the aorta in nine cases [90, 95, 98, 103, 106, 107, 110, 115, 116]. Both ECAs supplied intracranial collaterals through their dural branches in a 4-year-old girl with Moyamoya disease [90].

Aplasia of the left CCA and ICA followed by the aortic origin of the left VA and CCA origin of the right VA were discovered in a 43-year-old woman [94].

Posterior cerebral artery (PCA). Fetal origin of both PCAs associated with aortic origin of the left and right VAs was found in a 53-year-old man [92].

Associated disorders

Basic congenital anomaly

1. Down syndrome (trisomy 21) was a known congenital anomaly in a 4-year-old girl where an aortic origin of the left VA and CCA origin of the right VA was discovered [90].
2. Klippel-Feil syndrome (congenital fusion of any two of seven cervical vertebrae) was presented in a 43-year-old woman with aortic origin of the left VA and CCA origin of the right VA [94].

Acquired pathological disorders

1. Pseudocoarctation of aorta associated with aortic origin of both VAs was discovered in a 35-year-old woman after trauma [96].
2. Aneurysms of different arteries—right anterior cerebral artery [92], posterior communicating artery [38, 115], and descending aorta [101] were proved in 4/28 cases.
3. Partial stenosis of the left ICA [91, 100], or right SA [98, 99] was also associated with variable VA origin.
4. Partial occlusions of the right VA [101], or left internal jugular vein and sigmoid sinus [93] were proved in 40-year-old and 50-year-old women, respectively.
5. Cerebral infarct was developed in a 60-year-old woman with aortic origin of the left VA and segmental duplication of the right VA [10].
6. Thyroid carcinoma was primary reason of a preoperative evaluation in a 67-year-old woman when aortic origin of the left VA and CCA origin of the right VA were discovered [107].
7. Pial siderosis along the sulci of the right cerebral hemisphere were proved by MRI in a 68-year-old female with aortic origin of the left VA and CCA origin of the right VA [116].

Right VA

General data

Only unilaterally, variable right VA was found in 47/171 (25 of male, 17 of female and 5 of unknown gender) or 27.48% of cases from age 2 [118] to 76 [49, 119].

Variable right VA was discovered in patients with different initial symptoms or reasons of investigations— headache [26, 120, 121], or dizziness [30, 115, 122], or weakness [36], or blurred vision dizziness [123], or paresthesias [124], or transitory ischemic attacks [38, 125–128], or shortness of breath [118], or loss of consciousness [129], or progressive memory loss with incoherent behavior [130], or retrosternal chest pain [131], or carotid stenosis [132], or left hemiplegia [98], as well as after trauma [133, 134], or during preoperative evaluation [106, 135], or evaluation of mediastinal enlarged lymph nodes [136], or doubt for the left middle cerebral artery infartcion [137] or by angiographic images [15, 49, 138–140].

Status of vessel stem

The vascular sources of variable right VA were the right SA and its (in)direct branches, the arch of the aorta, ascending and descending aorta, the brachiocephalic trunk, right CCA and right ECA (Fig. 3).

Segmentally duplicated right VA was revealed in seven cases [30, 38, 49, 122, 134, 141, 142]. Single right VA as a side branch of ipsilateral CCA was found in 10 cases [23, 49, 107, 115, 120, 125, 138, 143–145], whereas it was terminal branch of the right CCA in a case described by Morasch [140].

The right VA was of aortic origin in most cases; among them, it originated from the ascending aorta in one [131], and from descending aorta in another case [118].

In three cases the right VA originated singly from the brachiocephalic trunk [15], right thyrocervical trunk [146] and right supreme intercostal artery [147].

The right VA was presented as a simple or common vessel or segmentally duplicated at its origin; there were 9 primary and 9 complementary models (Table 4).

Caliber

Single right VA of aortic origin was described as “small” [131], or hypoplastic [26], or dilated with so-called Kommerell’s diverticulum at its beginning [133, 135, 136]. Right VA originating from the supreme intercostal artery [146], and thyrocervical trunk [147], measured 1 mm and 1.8 mm in diameter, respectively. Thomas et al. [134] described that the medial segment of duplicated right VA measured 1.3 mm in diameter and had a beaded appearance, whereas the lateral segment was of regular lumen and measured 3.1 mm in diameter.

Course in V1 part

There were some examples of unusual course of the variable right VA from the beginning to the entry at the foramen transversarium of cervical vertebra. So, Higashi et al. [119] observed that the right VA of aortic origin coursed into the first intercostal space and entered the first costotransverse foramen, and then all of the transverse foramina from C VII to C I vertebra. Retroesophageal course of the right VA of aortic origin was also noted by some authors [26, 106, 121, 133, 135, 136, 139]. In addition, Fazan et al. [143] discovered that the right VA was crossed anterior to the ITA and upstream outside and anterior to the transverse foramina from C VII to C III, whereas Park et al. [107] reported about a location of the right VA in the retro-thyroid area and very close to the thyroid gland.

Segmentally duplicated right VA of SA origin were kinked at V1 part in one case [122], whereas simple VA stem was underdeveloped at intracranial part after fusion of its double segments in another case [113].

Hypoplastic right VA of supreme intercostal artery (SIA) origin anastomosed with the right persistent primitive hypoglossal artery (PPHA) at the internal opening of the hypoglossal canal in a 74-year-old Japanese male cadaver [146].

Collaterals

Only Higashi et al. [119] discovered the esophageal, prevertebral and second right posterior intercostal arteries as the right VA branches in V1 part.

Additional vascular variants

Left VA. It ended as the posterior inferior cerebellar artery in a case of aortic origin [36], or segmental duplication [122], or it made terminal trifurcation in a case of CCA origin [125]. Mild tortuosity and constricted portion of the left VA in a case of thyrocervical origin [147], or its hypoplasia in a case of external carotid origin of the right VA [129] were revealed.

There was a description of an anastomosis of the left VA and anterior inferior cerebellar artery in a case of SIA origin of the right VA [146].

Aorta. Multiple aortopulmonary collaterals supplying the left lung were found in a 2-year-old child [118].

BT. Aplasia of BT existed in 16/47 cases [23, 49, 98, 107, 116, 118, 120, 123, 125, 127, 131, 137, 138, 143, 145, 148]. A brachiocarotid trunk was found in two cases [106, 139].

CCA. This artery on the right side was noted usually as the first single or a common branch of the arch of the aorta in cases of BT aplasia and/or origin of the right VA from ipsilateral CCA [23, 49, 98, 107, 116, 120, 123, 125, 127, 131, 137, 138, 143, 145], or aorta [118, 148]. Above mentioned brachiocarotid trunk was associated with CCA or aortic origin of the right VA, respectively [106, 139]. The right CCA in a case described by Morasch [140] was bifurcated into right VA and ECA, because the right ICA was aplastic.

SA. Lusoria right SA was associated with origin of the right VA from ipsilateral CCA [23, 49, 98, 107, 116, 120, 125, 137, 138, 140, 143, 145], or the arch of the aorta [148], or ascending [131], or descending aorta [118]. Right SA, as the third branch of the arch of the aorta, passed behind the two CCAs and in front of the right VA in a case of CCA origin of the right VA [123].

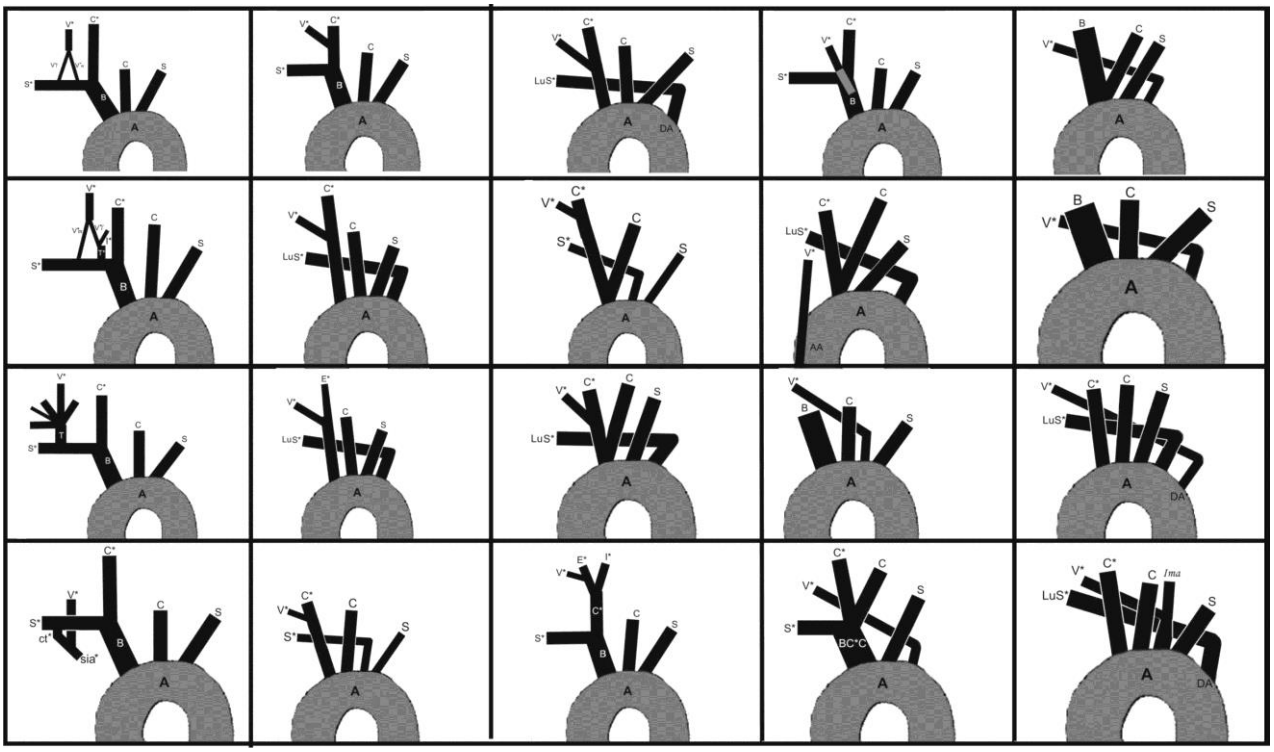


Fig. 3. Twenty patterns of relationships of the variable right vertebral and main supra-aortic arteries.
*V**, right vertebral a.; (*V*ſ+ V*m*), lateral and medial segments of duplicated right vertebral artery at prevertebral part, *S** (*S*), right (left) subclavian a.; *C** (*C*), right (left) common carotid a.; *B*, brachiocephalic trunk; *A*, arch of the aorta; *T**, right thyrocervical trunk; *ct**; right costocervical trunk; *sia**, right supreme intercostal a.; *AA*, ascending aorta; *LuS**, so-called lusoria right subclavian a.; *DA*, descending aorta; E*, right external carotid a.; I*, right internal carotid a.; *BC*C*, brachiobicarotid trunk; *Ima*, thyroid ima a.

Aplasia of ITA was associated with the persistence of a common trunk of the right VA and thyroid ima artery at the arch of the aorta [148].

Persistent primitive arteries. Right PPTA was associated with CCA origin of the right VA [120], whereas the right PPHA was associated with SIA origin of the right VA [146].

Associated disorders

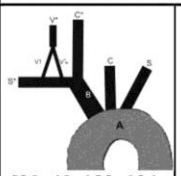
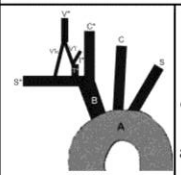
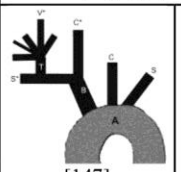
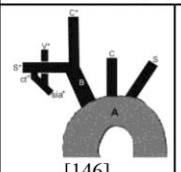
Basic congenital anomaly

1. Cardiac anomaly (atrioventriculoarterial discordance, double outlet right ventricle, multiple muscular ventricular septal defects, and right ventricular outflow tract obstruction with hypoplastic right ventricle) was a primary reason of discovery of aortic origin of the right VA in a 2-year-old child [118].

Acquired pathological disorders

1. Dissection of the right VA was associated with its segmental duplication in a 49-year-old woman [134].
2. Aneurysms of different arteries—some cerebral artery [49], ascending [106] and abdominal aorta [135], anterior communicating [129] and basilar arteries [134] were discovered in the presence of different origin of the right VA.
3. Infarction of the cerebrum [49], or cerebellum [36, 141], or the myocardium [23] was associated with segmental duplication, or aortic origin, or CCA origin of the right VA.
4. Partial stenosis of different arteries—right SA [98, 125] and right CCA [23, 125] was associated with CCA origin of the right VA.
5. Intracerebral hemorrhage was diagnosed simultaneously with aortic origin of the right VA after a cerebrovascular accident in a 40-year-old man [128].
6. Subarachnoid hemorrhage was diagnosed in a 32-year-old woman with CCA origin of the right VA [120].
7. Arteriovenous malformation in the right cerebellopontine angle was diagnosed simultaneously with CCA origin of the right VA in a 52-year-old woman [116].
8. Spinal neurinoma was a primary reason in a 57-year-old patient when the right VA of aortic origin was discovered [124].
9. Thyroglossal duct cyst was associated with CCA origin of the right VA in a 30-year-old man [107].

Table 4. Display of primary and complementary models of variants of the right vertebral artery (VA)[1] in 47 cases

Vascular source(s)			Schemes and description of primary models of variable right VA		Schemes and description of complementary models of variable right VA
Right subclavian a.	Subclavian stem (S*)		 [30, 49, 122, 134, 141, 142]	**M*1:** Segmental duplication of the right VA of subclavian (SA) origin.	
			M*1: **V*ℓ+ V*m / S***		
	Subclavian stem + thyrocervical trunk (S* + T*)		 [38]	**M*2:** Segmental duplication of the right VA of subclavian (SA) and thyro-cervical (TT) origin.	
			M*2: **V*ℓ/ S*+ V*m / T***		
	Branch	Thyrocervical trunk (T*)	 [147]	**M*3:** Single right VA of TT origin.	
			M*3: **V* / T***		
		Supreme intercostal a. (sia*)	 [146]	**M*4:** Single right VA originates from the supreme intercostal a.	
			M*4: **V* / sia***		

Right common carotid a. (C*)								
	[49, 53, 144]	**M*5:** Single right VA of common carotid (CCA) origin.	[23, 98, 107, 115, 125, 137, 138, 143]	[140]	[123]	[120]	[127]	[49, 130, 145]
	M*5 (M*5a–d): V* / C*						**M*5e–f: V* / CC***	

M*5a:
Additionally, aplasia of the brachiocephalic trunk (BT); right CCA is the first branch and LuS* is the last branch of the arch of the aorta [23, 98, 107, 115, 125, 137, 138, 143]

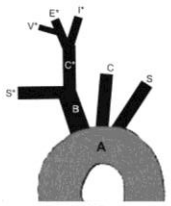
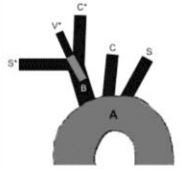
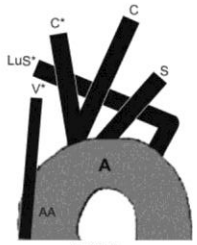
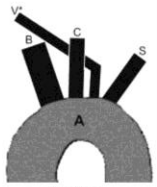
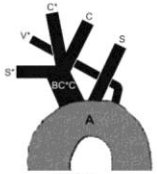
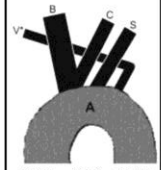
M*5b:
Additionally, aplasia of the brachiocephalic trunk (BT); right CCA as the first aortic branch bifurcated into right VA and ECA, left CCA is the second; right SA is the third and left SA is the fourth branch of the arch [140].

M5c:
Additionally, aplasia of the brachiocephalic trunk (BT); right CCA is the first, left CCA is the second; right SA is the third and left SA is the fourth branch [123].

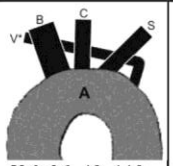
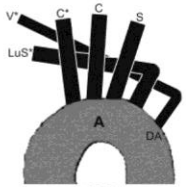
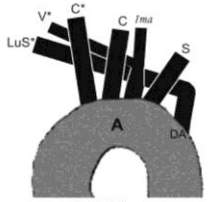
M*5d:
Additionally, aplasia of BT; right CCA is the first branch of the descending aorta [120].

M*5e:
Additionally, aplasia of BT; common stem of the right and left CCAs (bicarotid trunk) is the first branch of the arch; right SA is the second branch of the arch of the aorta [127].

M*5f:
Additionally, aplasia of BT; common stem of the right and left CCAs (bicarotid trunk) is the first branch of the arch; LuS* is the last branch of the arch of the aorta [49, 130, 145].

<table>
<tr><td colspan="2">Right external carotid a.
(E*)</td><td> 
[129]</td><td>M*6:
Single right VA of the right ECA origin.</td><td colspan="3" rowspan="2"></td></tr>
<tr><td colspan="2"></td><td colspan="2">M*6:
V* / E*</td></tr>
<tr><td colspan="2">Brachiocephalic trunk
(B)</td><td> 
[15]</td><td>M*7:
Single right VA of BT origin.</td><td colspan="3" rowspan="2"></td></tr>
<tr><td colspan="2"></td><td colspan="2">M*7:
V* / B</td></tr>
<tr><td rowspan="4">Aorta</td><td rowspan="2">Ascending aorta (AA)</td><td colspan="2" rowspan="2"></td><td colspan="3" rowspan="2"> 
[131]</td><td>M*8a:
Right VA originates from ascending aorta. Additionally, aplasia of BT; bicarotid trunk is the first branch of the arch; LuS* is the last branch of the arch of the aorta</td></tr>
<tr><td>M*8a:</td><td>V* / AA</td></tr>
<tr><td rowspan="2">Arch of the aorta (A) and descending aorta (DA)</td><td rowspan="2">Single vessel</td><td rowspan="2"> 
[126]</td><td rowspan="2">M*8:
Right VA, as the third branch of the arch of the aorta.</td><td> 
[106]</td><td> 
[121, 128, 139]</td><td></td><td>M*8a:
Additionally,
common stem of so-called brachiocephalic aa. [106].

M*8b:
Additionally,
brachiocarotid trunk is the first branch of the arch of the aorta. Right VA had retroesophageal course [121, 128, 139].</td></tr>
</table>

			 [26, 36, 49, 119, 124, 128, 132, 133, 135, 136]	**M*9:** Right VA, as the fourth branch originates from the arch of the aorta distal to the left SA.		
			M*8 (M*8a–b): M*9: V* / A			
				 [118]	**M*10a:** Right VA originates from the descending aorta. Additionally, BT aplasia; right CCA is the first branch of the arch; LuS* is the branch of the arch.	
				M*10a: V* / DA		
		Common trunk		 [148]	**M*11a:** Common stem of the right VA and thyroid ima artery originates from the arch of the aorta. Additionally, BT aplasia; right CCA is the first branch of the arch; right SA is the branch of the descending aorta.	
				M*11a: *Ima*V* / A		

[1]Abbreviations of arteries in the text are explained during description of each pattern; abbreviations of same arteries in schemas include only the first capital letter from corresponding previous because of practical reasons. The current relationship of VA and the main supra-aortic arteries is personally presented by "mathematical relation" in the row below corresponding pattern.
Abbreviations of arteries in inserts: *V**, right vertebral a.; (*V*ſ+ V*m*), lateral and medial segments of duplicated right vertebral artery at prevertebral part, *S** (*S*), right (left) subclavian a.; *C** (*C*), right (left) common carotid a.; *B*, brachiocephalic trunk; *A*, arch of the aorta; *T**, right thyrocervical trunk; *ct**; right costocervical trunk; *sia**, right supreme intercostal a.; *AA*, ascending aorta; *LuS**, so-called lusoria right subclavian a.; *DA*, descending aorta; *BC*C*, brachiobicarotid trunk; *Ima*, thyroid ima a.

Concluding Remarks

Common morphological features

Vascular sources. There were one or two or three vascular sources in the presence of variable left and/or right VA. The arch of the aorta was the most frequent source of single left VA and bilateral VA variabilities. Segmentally duplication of the VA was more frequent on the left side, while the vascular sources were the arch of aorta and left SA.

Although the right CCA was the vascular source of the single right VA in one third of cases, it was a vascular source of the right VA in almost half of cases with bilateral VA variability.

A specificity of the VA represented a pyramidal widening or so-called Kommerell' diverticulum of its beginning.

The origin of variable VA from the CCA (33 cases on the right and one on the left side) or right ECA in one case opens a problem of its denotation and differentiation from some of the persistent primitive CIA or PPIA.

Frequency of variable single VA origin. It was selected 94/171 cases of variable left VA, 30/171 cases of variable left and right VA and 47/171 cases of variable right VA. Our hypothesis is that the variability of the single left VA was two times higher than the variability of the right VA.

Unilateral vs. bilateral VA variability. Our hypothesis is that the variability of the single left or right VA was more frequent than bilateral variability of VA — three times for the left and 50% for the right side. In that manner, one cannot confirm the claim where one VA has an anomalous origin and the incidence of contralateral VA anomaly increases.

Sex difference. A variability of the left VA was more frequent in male specimens, whereas a variability of both VA was more frequent in female specimens, although there was no marking of gender for 25/171 cases.

Patterns of VA vs. total number of VA variability. The finding of 62 (30 of primary and 32 of complementary) patterns from 171 cases of unilateral or bilateral VA variability could suggest that in every third case can expect a special relationship of the VA and main supraaortic arteries.

Primary models vs. complementary models. Two thirds of total number of primary patterns or models of variable VA on one or both sides could indicate that it is the only vascular variation. However, most primary models were presented as single cases on the left and/or the right side, whereas 7/30 — four primary models on the left and three primary models on the right side were showed by three and more authors; this may mean that presented arrangements of VA(s) could be expected as isolated variation. Five complementary models (5/32) — one on the left, two on the right and two on both sides presented by three and more authors could indicate that only these VA variabilities are not isolated.

Course of VA. Retroesophageal course of the right VA of aortic origin could be expected in cases of aortic origin of both VAs, or aortic origin of single right VA distally from the left SA. From a morphofunctional view of point, the VA could be compressed at the higher level of entry at the foramen transversarium of cervical vertebra.

Although variable single VAs or their lateral or medial segments penetrated foramen transversarium from C IV to C VI vertebra in about one third of cases for each level, there was not a rule in relation to the VA beginning.

Caliber. It is well known that the posterior circulation is more vulnerable to ischemia in patients with VA severe hypoplasia, although most of these individuals remain asymptomatic if additional atherosclerotic factors are not associated. Having in mind only a few reports about the hypoplasia of VA, we can conclude that a way of the VA origin does not affect its caliber.

Side branches. The finding of unusual collaterals—the suprascapular artery, or ITA, or InTA, or bronchial artery, which branched from the left VA, as well as the esophageal, prevertebral and second right posterior intercostal arteries from the right VA, can point out on the VA variability.

Status of the arch of the aorta. Different patterns of branching of the arch of the aorta with respect to the number (from one to six), and/or position of these branches at the arch were main associated vascular variants with variable VA origin.

Associated supra-aortic arterial variants. A finding of lusoria right SA in almost half of the bilateral VA variability cases and in one third of variable right VA cases could be accepted as an indirect sign that variable right VA can be found, and vice versa.

Persistent primitive carotidbasilar anastomoses. According to the finding of only 5/171 cases—three PPTA, one PPHA and one lateral spinal artery, one can conclude that association of carotid-basilar anastomoses (CBAs) and a variable left VA origin was a coincidence, especially because of different embryologic base of VA and CBAs.

Common pathoanatomical conditions

Basic diseases. Nine different pathological processes — arterial dissections, aneurysms, cerebral infarction, partial thrombotic occlusion, stenosis, intracerebral hemorrhage, subarachnoid hemorrhage, (pseudo)coarctation of the aorta and different tumors, although rare, were common independently from unilateral or bilateral variability of the VA.

Pathologic changes of variable VA. On one side, some authors claimed that anomalous VA origin does not result in clinical symptoms, what was proved on the example of variable left VA where the right VA of normal (SA) origin was stenosed approximately of 60%. On the other hand, some authors described that higher incidence of spontaneous dissection was presented in cases of variable VA. However we revealed only eight patients with some

pathological changes — a dissection, or aneurysm, or stenosis of the left VA, and a dissection or thrombotic occlusion of the right VA.

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Original Article

RISK FACTORS AND INDICATORS OF CARDIOVASCULAR ILLNESSES IN LATE ADOLESCENT PERIOD

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Abstract. *Epidemiological studies of previous decades indicate that cardiovascular illnesses present a dominant part of the structure of mortality in the majority of developed countries in the world. The goal of this research was to establish the most common risk factors of this group of illnesses, as well as statistically significant differences and correlations between risk factors and cardiovascular illnesses in the late adolescent period. A cross-study was performed in three high school graduate classes in Serbia (Valjevo), in April 2015, on an incidental sample of 240 subjects of both genders, aged (19 ± 0.5 years). A statistically significant difference in the frequency of hypertension in male adolescents (2.54%) and female adolescents (0.0%) was not established. Obesity was significantly more manifested in male graduates (6.93%), with a significant level, than in female graduates (1.10%). Abdominal obesity is, with a confidence interval – range (99% CI), much more common in male graduates (10.01%), than in female graduates (1.26%). Among smokers, a significant gender difference was not established Alcohol was, with a probability level ($p \leq 0.01$) consumed much more by male graduates (19.93%) than female graduates (8.01%). A statistically significant linear correlation between variables of systolic and diastolic blood pressure, body mass index, and waist circumference was observed. Risk factors in late adolescents are significantly different when it comes to gender. With a goal of prevention of cardiovascular diseases in high school graduate students, it is imperative to reduce obesity, cigarette smoking, and alcohol consumption, as well as implementation of regular physical activity*.

Key words: *High school graduates, risk factors, hypertension, obesity, cigarette smoking, alcohol consumption*

Introduction

The first and second decade of the 21st century is characterized by a rise in cardiovascular diseases (CVDs) which have become a dominant cause of morbidity and mortality in the developed countries of the world. CVDs are a result of interaction of different somatic, environmental, and behavioral factors. Risk factors (RFs) comprise certain illnesses, pathological states, traits or habits that cause or contribute to the development of a certain illness or its complications. The most significant traditional risk factors for CVDs include genetic predisposition, obesity, arterial hypertension (HTN), insufficient physical activity, improper diet (food rich with fats of animal origin), nicotinism – habit of cigarette smoking, diabetes mellitus (DM), men older than 55 years, post-menopausal women, acute stress disorder (ASD), and other [1]. Recognizing these RFs, as well as their mutual relationships will enable a new approach to the phenomenon of disease of the cardiovascular system, but to the personality of the diseased individual as well [2].

According to data of the World Health Organization (WHO) – by year 2030, 24.000.000 people will die of cardiovascular diseases (CVDs) every year [3], while in the Republic of Serbia, one third of males and one fourth of females die from this disease. In more than 90% of cases the cause of the disease is atherosclerosis of coronary arteries, which starts with damage of the inner layer of the artery, thickening of the vessel wall, narrowing of the artery (AS), and ischemia of the heart muscle (IHD).

European Association of Cardiology (ESC) has proposed a model for prevention of CVDs (0-3-5-140-5-3-0), which directs to a healthy way of living, and suppression of standard risk factors: 0 – no smoking (neither active nor passive), 3 – a minimum of 3 km of walking or 0.5 h of mild physical activity is recommended, 5 – it is desirable to have 5 meals consisting of fruit and vegetables every day (minimum 400–600g), 140 – systolic blood pressure (SBP) < than 140 mmHg, 5 – total cholesterol < than 5 mmol/l, 3 – LDL cholesterol < than 3 mmol/l.0 – no obesity and no diabetes [4].

Medical researchers have turned the attention to the existence of significant mutual dependence between traditional cardiovascular risk factors (RFs) and

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pathological states, as well as mortality from CVDs in humans [5]. The majority of RFs in adolescents manifest a tendency to remain at the same degree in later period of life as well [6]. Effects of each of the individual factors are cumulative, and the conformation of factors, as well as their simultaneous appearance, cause multiplication and increased threat in later life, especially after 30 years of life [7]. During adolescent age, individuals who are exposed to stimuli that contribute to CVDs usually remain in that group later in life, which amplifies the need of early diagnosed diseases, that are not visible at first sight, and a need for their prevention as well. Prevention and protection from diseases in order to reduce and weaken the effects of cardiovascular risk factors has shown to be efficient in a significant number of cases in different age groups, especially in adolescents [8].

Despite numerous researches dealing with CVDs, there isn't a sufficient number dealing with standard RFs that cause the mentioned diseases, which is why it is expected that the obtained results in this research can contribute to a change in understanding RFs as contributors of CVDs in the adolescent population.

The basic goal of this empiric cross-sectional study was directed towards evaluation of the most frequent RFs for CVDs, as well as statistically significant differences and correlations between RFs and CVDs in subjects of both genders in late adolescent period.

Material and Methods

Sample

Research was performed in Technical, Economic, and Agricultural-Veterinary school in Valjevo, in June, 2015. By a transverse study, an incidental sample of 240 graduate students was encompassed (122 female graduates and 118 male graduates), with a mean age of 19 years (± 0.5 months).

Student evaluation, measurement of morphological characteristics, alimentary status and functional capability of the cardiorespiratory system was conducted by the authors of this paper. Before initiating this process, subjects were introduced with the goal and the method of the study, after which they gave a written consent to use their data in the planned study.

Instruments

Based on the questionnaires that were fulfilled anonymously, information regarding gender and age were analyzed, as well as habits regarding physical activity, cigarette smoking and alcohol consumption.

Information regarding gender and age were obtained through an anonymous questionnaire. The questionnaire and the results of measurements of the subject were registered under the same coded number.

In regard to the category variable cigarette smoking, subjects declared in one of the following ways: never smoked cigarettes, former smoker, and active cigarette smoker. Smokers are defined as individuals who have declared to smoke every day. Former or occasional smokers are classified as non-smokers.

On the category variable alcohol consumption, subjects could respond in one of the following ways: does not consume alcohol, occasional consumption, and everyday consumption.

Variable for estimation of physical inactivity of graduate is defined through the criteria of conducting mild physical activity (speed walking, housework, sport-recreational activities). Subjects who claimed that they exercise at least three times weekly, in duration of 45 minutes or more, were classified as individuals with regular physical activity.

Morphological indicators and alimentary status

By using standardized anthropometric instruments, having in mind the principles of the International Biological Program, body height, body mass (BM), and waist circumference were measured. All measurements of subjects, who were lightly dressed and without shoes, were conducted during morning hours at the same time (± 2 hours), with the same instruments, using the same techniques, and according to standard procedure. Measurements were performed three times, after which the arithmetic mean was automatically calculated.

Continued variable body height (BH) of subjects were measured in a standing position, by using the *Harpenden* anthropometer (*Holtain Ltd, Crosswell, UK*), from head to toe, with joined feet. Heels, scalp, and scapulae were in the same plane, and the head was in parallel position to the "Frankfurt plane" (an imagined plane that passes through the line that connects the apical point on the external ear canal – orbits, with the point that is located on the lowest part of the inferior margin of the orbit – *porion*), with a precision of ± 0.1 cm. Measurement of BM was conducted using a medical decimal scale with mobile weights, with precision of 0.1 kg. Waist circumference measurement (WC) was conducted in a standing position with the *Holtain* measuring tape (on the level of the lowest rib and anterior iliac spine), at the end of normal expiration, with a precision of ± 0.1 cm.

In order to evaluate the alimentary status, body mass index (BMI) was calculated, which presents the relation between the body mass and body height expressed in meters squared, based on the mathematical formula: $BMI = BM/height^2$ (kg/m^2). According to the criteria of World Health Organization (WHO), alimentary status is classified in the following way: underweight ($BMI < 18.50$ kg/m^2), normal ($BMI = 18.50–24.99$ kg/m^2), overweight (BMI = 25.00–29.99 kg/m2) and obese ($BMI \geq 30$ kg/m^2).

For evaluation of the amount of abdominal obesity waist circumference values were used. Based on the criteria of WHO (NCEP ATP III criteria from the *National Cholesterol Education Program, Adult Treatment Panel* III, or AL II from *action level* II), the adopted borderline values for waist circumference in females of ≥ 80 cm matched to an increased cardiovascular risk, while

values of ≥ 88 cm in males matched to an increased cardiovascular risk.

Indicators of functional capabilities of cardiorespiratory system

The discrete variable blood pressure (BP) was measured using a standard calibrated lead manometer and and adequate cuff on the upper arm above the brachial artery, after a rest of at least 10 minutes. Subjects were in a sitting position, on a chair with a back, with feet on the floor. The cuff was pumped 20–30 mmHg above the values of expected SBP, and it was released with the speed of 2–3 mmHg/s. The mean value of BP in three subsequent measurements was used.

Hypertension is defined as SBP ≥ 140 mmHg and/or diastolic blood pressure (DBP) ≥ 90 mmHg, and prehypertension as: SBP of 130–140 mmHg and/or DBP between 85–90 mmHg.

Statistical analysis

Depending on the tested variables, methods of descriptive statistics were used: parameter variables that were observed were presented with arithmetic mean (AM) and standard deviation (SD), while category values were presented through a percentage structure. In order to establish statistical presence of certain risk factors and significant differences of frequencies of certain variables between genders, the nonparametric Pearson's χ^2 test was used (chi-square test). In order to establish correlations between parametric variables of certain risk factors (in female and male gender separately), Pearson's coefficient of bivariate correlation (r) was used. The borderline of statistical significance was defined for the probability level ($p \leq .05$ or $p \leq .01$).

Data were analyzed by using the program – *Statistical Package for Social Science* (SPSS) for Windows (version 15.0).

Results

Table 1 depicts statistical magnitudes of BP and frequency of HTN in the examined gender groups. The obtained empiric findings suggest that the frequency of increased BP is minimal (4.09% in males and 0.90% in females). Frequency of prehypertension is also minimal: only three subjects (2.54%) are distributed into the cluster with "borderline hypertension".

Consideration of the empiric values of BMI with the assumed has turned the attention to the fact that, with a 99% confidence interval, every third graduate student is distributed in the cluster of overweight, while 6.93% of subjects are obese (Table 2). The mean value of BMI in male subjects is around 24 kg/m^2, which denominates the borderline value of normal alimentary status. On the other hand, chi-square distribution analysis, with a significance ($p \leq 0.0001$) showed a significantly decreased presence of obesity in female subjects – 1.10% female subjects are obese, while 8.03% of female subjects are distributed into the cluster of overweight.

Based on the provided empiric results of nonparametric chi-square distribution (Table 3), it can be observed that the squares of differences between the obtained (observed) and expected (theoretical) frequencies in abdominal obesity, with a confidence interval – range (99% CI), are a much more common issue in male graduates than in female classmates. Every 24th graduate student in our sample had a WC value on the interval scale that proposed a risk of CVDs, while in female subjects; the presence of AG was 1.26%.

Table 1. Comparison of values of blood pressure (BP) and frequency of hypertension in the examined high school graduate population

Subjects	SBP (mmHg)	DBP (mmHg)	Frequency of prehypertension	Frequency of hypertension
	AM ± SD	AM ± SD	(%)	(%)
Male graduates	123.2 ± 7.2	68.1 ± 6.4	0	4.09
Female graduates	109.5 ± 8.7	70.2 ± 6.3	2.54	0.90
All subjects	117.6 ± 10.4	70.1 ± 10.0	0.49	0.49

Statistically significant difference (males/females): $p < 0.01$; SBP, systolic blood pressure; DBP, diastolic blood pressure; AM, arithmetic mean; SD, standard deviation.

Table 2. Distribution of body mass index (BMI) and the frequency of obesity in the examined high school graduate population

Gender	BMI (kg/m^2)			Frequency of preobesity	Frequency of obesity	p*
	AM ± SD	Min	Max	(%)	(%)	
Male graduates	24.9 ± 2.16	18.2	36.0	37.93	6.93	≤ 0.001
Female graduates	20.8 ± 2.47	17.4	29.3	8.03	1.10	
All subjects	21.7 ± 3.11	17.5	36.2	15.86	3.42	

*Nonparametric Pearson's χ- test (goodness of fit model). AM – arithmetic mean; SD – standard deviation; Min – minimal value; Max – maximal value; p – statistical significance at the level $p \leq 0.001$.

Table 3. Differences in frequencies of waist circumference and abdominal obesity values in the examined population of high school graduates

Gender	Waist circumference (cm)			Prevalence of abdominal obesity	*p**
	AS ± SD	Min	Max	(%)	
Male graduates	89.15 ± 8.79	70	114	9.09	≤ 0.001
Female graduates	68.60 ± 6.55	58	93	1.26	
All subjects	74.08 ± 1.61	58	114	16.02	

*Nonparametric Pearson's χ- test (goodness of fit model). AM, arithmetic mean; SD, standard deviation; Min, minimal value; Max, maximal value; *p* – statistical significance at the level $p \leq 0.001$.

According to the data calculated by the sum of squares of Pearson's χ- test shown in Table 4 and theoretical, i.e. borderline table values, there is no statistically significant difference in the examined sample in the variable cigarette smoking when it comes to gender. Every fourth subject, regardless of gender, is a cigarette smoker: among male subjects, 20.14% are active smokers, and 14.36% of female subjects are smokers, respectively.

Table 4. Differences in frequencies of smoking habits, alcohol consumption and physical inactivity

Variables	Gender	Frequency (%)	p
Cigarette smoking	male	25.42	
	female	25.23	
Alcohol consumption	male	18.18	≤ 0.001
	female	2.65	
Physical inactivity	male	36.32	≤ 0.001
(< 3.5 hours/week)	female	66.90	

Pearson's χ- test (goodness of fit model) for comparison of the analyzed category variables between genders

Alcohol consumption is statistically more common in male students than in female ($p \leq 0.001$). A significant statistic difference between empiric and theoretical frequencies in alcohol consumption was established: 19.93% of male graduates and 8.01% regularly consume alcohol. Additionally, every other female graduate (48.34%) and 18.2% of male graduates do not consume alcoholic beverages at all. With a 99% CI confidence interval, statistically significant squared differences between the obtained and expected frequencies in relation to the expected frequencies were obtained in the nonmetric parameter physical inactivity as well. Male subjects are by far more physically active than female subjects. The prevalence of physical inactivity in male subjects is 34.51%, with a *p*-value (level of significance) ≤ 0.001. On the other hand, 65.12% of female subject claimed that they have mild physical activity (speed walking, mild housework, swimming, and other sport-recreational activities), less than 3.5h during the week.

In order to establish a statistically significant correlation in the frequencies of the two attributive characteristics, or between the obtained (observed) frequencies and theoretical frequencies, the Pearson's coefficient of correlation was used (Table 5). With bivariate correlational analysis of cardiovascular risk factors, it was shown that in the group of male graduate students, the frequency of the size of the discrete variable – SBP – is statistically significant and mildly positively correlated with DBP ($r = 0.59$, $p \leq 0.01$), BMI ($r = 0.39$, $p \leq 0.01$), and WC ($r = 0.40$, $p \leq 0.05$), as well as the fact that DBP was statistically significantly different than zero, together with BMI ($r = 0.41$, $p \leq 0.01$) and WC ($r = 0.28$, $p \leq 0.05$). In the population of female graduates, age was, with a level of significance of $p \leq 0.05$, in positive and weak correlation with SBP ($r = 0.33$), WC ($r = 0.30$), and cigarette smoking ($r = 0.28$). Also, SBP is in statistically significant and positive mutual dependence with DBP ($r = 0.62$, $p \leq 0.01$), BMI ($r = 0.27$, $p \leq 0.01$) and WC ($r = 0.19$, $p \leq 0.05$) in female subjects. Results of DBP in female graduate students are statistically significantly positive and exhibit mild mutual relation with BMI ($r = 0.20$, $p \leq 0.05$), and are in negative with the category variable physical inactivity ($r = 0.19$, $p \leq 0.05$). Additionally,

Table 5. Correlation of cardiovascular risk factors of male graduates (under the diagonal) and female graduates (over the diagonal)

Male graduates/ variables	Female graduates/variables							
	SBP	DBP	BMI	Waist circumference	Cigarette smoking	Alcohol consumption	Physical inactivity	Age
SBP (mmHg)	1.0	0.62**	0.27**	0.19**	0.07	0.07	0.01	0.05
DBP (mmHg)	0.59	1.0	0.20**	0.15*	0.13*	0.04	-0.19**	0.11*
BMI (kg/m2)	0.39**	0.41**	1.0	0.78**	0.13*	0.07	-0.05	-0.02
Waist circumference (cm)	0.40**	0.32**	0.80**	1.0	-0.03	0.04	-0.26**	-0.03
Cigarette smoking	0.08	0.07	-0.26**	0.01	1.0	0.39**	-0.15*	0.19**
Alcohol consumption	0.21**	-0.03	-0.09	-0.08	0.13*	1.0	0.01	-0.13*
Physical inactivity	0.16*	-0.02	-0.20**	-0.23**	-0.04	-0.04	1.0	-0.08
Age	0.33**	0.25**	0.10	0.30**	0.28**	0.15*	0.14	1.0

SBP, systolic blood pressue; DBP, diastolic blood pressure; BMI, body mass index.
Values of Pearson's coefficient of correlation (*r*).
*$p \leq 0.05$; **$p \leq 0.01$

frequencies of values of BMI and waist circumference, cigarette smoking, and age of female graduate students are with a p-value ≤ 0.01, statistically highly significant and positively correlated ($r = 0.80$, $p = 0.19$).

The obtained positive and statistically significant linear correlations between cardiovascular RFs point to the fact that an increase in value of one variable stipulates higher scores in another variable, i.e. a higher degree of RFs for the onset of CVDs in the examined high school graduate population.

Discussion

HTN is a dominant cause of cardiovascular mortality. The fact that the values of SBP in the range between 140–159 mmHg and diastolic pressure between 90–99 mmHg cause about 60% mortality amplifies the need for empiric research of this silent and insidious disease [9]. Research conducted in Croatia showed that HTN was registered in 45.6% of males and 43% of female subjects [10]. However, despite clear evidence about the positive effects of treatment, and awareness of the relevance of the problem, HTN is still not sufficiently diagnosed, and inappropriately treated [11, 12]. Increased BP can occur in adolescents, but it is characterized by an insidious and atypical symptomatology, so that it often goes undiagnosed. The obtained results in our research, together with the results in the Croatian study [13], have manifested minimal HTN in the late adolescent period. Research that was also conducted in Croatia on a school population showed increased values of arterial pressure in 38.9% of subjects, with a much higher prevalence in male subjects than in female (44.5%, i.e. 32.5%, respectively) [14]. It is important to emphasize the fact that prevalence of HTN is significantly higher in relation to male graduate students (4.09%) and female graduates (0.90%) in our study.

Obesity is a chronic metabolic disorder that is characterized by excessive buildup of fat tissue in the organism, and because it is drastically more present today, it becomes one of the more dominant health priorities, both in developed and underdeveloped countries, and even in Serbia. The majority of referenced studies indicate that obesity occurs as a consequence of lifestyle (improper diet and markedly decreased physical activity). It significantly affects the cardiovascular system (CVS), as well as endocrine, digestive, metabolic, locomotor, and mental health as well [15, 16]. The obtained results in our study point to the fact that male graduates are more obese than female subjects, which is consistent with the findings of other authors [17]. However, it is assumed that female adolescents take more care about their constitution, about the food they eat, as well as the amount of food they eat [18]. They are often unsatisfied with their body, and strive to be more slim [19]. Additionally, findings from this research turn the attention to the fact that younger female subjects have a lower BMI and are less obese than their older classmates of the same gender [20].

Abdominal obesity and/or insulin resistance IR is an indirect indicator of risk for development of CVDs in adolescent age [21]. The obtained results in our empiric study signify that male adolescents are particularly prone to this risk, while female adolescents had a much lower prevalence of WC over optimal values.

Regardless of the harmful effects of the bad habit of cigarette smoking in the examined population, it is still present in a certain number of adolescents. A quarter of the examined subjects of both genders smoke every day, which matches to the findings of research conducted in other parts of the world [22]. According to these results, prohibition of cigarette smoking is much lower in female adolescents than in male, and in mature age, due to different external environmental factors, cigarette smoking detains on the same level, or tends to increase over time.

The obtained results regarding alcohol consumption in this research are typical for adolescents, which is compatible with the results from Croatian research [23]. Results of other foreign authors point to the fact that different environmental factors (traditional habits, socioeconomic state, family habits, level of education, and individual personality traits) influence alcohol consumption in adolescents [24].

There are a significant number of researches that turn the attention to the significance of mild physical activity in preserving and improving health, as well as preventing a large number of CVDs [25–28]. Findings in our study point to the fact that physical inactivity is a much bigger issue among female adolescents than in male. This signalizes the fact that male subjects understand the importance of regular physical activity, and spend a lot of time in certain sport-recreational activities, i.e. compensatory physical activity.

According to the results of this research, it was established that IR in male graduate students correlated with higher values of SBP and DBP. However, the obtained values of BP are not yet in the cluster of "hypertensive". Also, it is observed that even in this age, obese adolescents are in a greater threat from CVDs. Considering the fact that RFs (IR, increased values of SBP and DBP) are more expressed in female graduate students in the examined population, it is assumed that they have a higher risk for developing CVDs. Additionally, the fact that female subjects who consume alcohol also smoke cigarettes in the majority of cases is rather interesting.

The obtained positive mutual dependence between age and RFs (SBP, WC, and cigarette smoking) points to a probability of development of CVDs. These findings in the adolescent school population enable appropriate and precise planning of sanitary and educational work in order to prevent cardiovascular illnesses.

Certain researches emphasize the fact that food habits, as well as other health habits and traditional customs in adolescent population, can present a danger to health [29–31]. For instance, in Peruvian subjects of both genders, a statistically significant relation of BMI and WC with SBP

and DBP was established [32]. Also, a linear correlation of BMI and HTN, i.e. reduced physical activity as a relevant indicator of obesity in adolescents in late adolescent age was defined in certain research [33–36].

Findings in our study showed that some standards risk factors for cardiovascular diseases are more expressed in male adolescents (increased BMI parameters, IR, regular cigarette smoking, alcohol consumption, and insufficient physical activity), while in female adolescents, RFs of everyday cigarette smoking and insufficient physical activity are particularly present, which is similar to results from the study performed on students from Niš [13].

Limitations in the conducted transverse research included financial problems, due to which laboratory testing of indicators of functional capability of cardiorespiratory system on a larger number of subjects were not applied, which would, for a margin of error $p \leq 0.01$, enable a more complete defining of risk factors for development of cardiovascular diseases. For these reasons, it is necessary that the upcoming longitudinal research include laboratory testing, with a greater number of subjects, so that, with a confidence interval of (99% CI) – a more complete identification of increased RFs for development of CVDs could be performed.

Conclusion

Findings in our study emphasize that in male graduate students, modifiable RFs are statistically significantly expressed, most notable being BMI values, abdominal obesity, cigarette smoking, alcohol consumption, and insufficient physical activity. In addition, RFs (smoking, and particularly insufficient physical activity) are present among female graduate students, generate the development of CVDs, and accompanying adverse effects. In addition, a statistically significant correlation between SBP and DBP, BMI, and WC was established, while age was in positive correlation with the variables SBP, WC, and cigarette smoking. In female students, SBP was correlated with DBP, BMI, and WC, while DBP was associated with BMI and physical inactivity, and cigarette smoking was linked with variables alcohol consumption and age.

From the obtained findings, it can be concluded that timely implementation of preventive measures (adoption of a healthy lifestyle – change of nutritional habits, cessation of smoking, increase of physical activity, regulation of BM and BP), as well as changing life habits, i.e. reduce RFs in the adolescent population, is essential in reducing the mortality and morbidity of CVDs.

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Original Article

ATRIAL FIBRILLATION DOUBLED IN-HOSPITAL MORTALITY IN 1379 ACUTE CARDIOGENIC PULMONARY EDEMA PATIENTS

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Abstract. *Medical significance of heart failure (HF) is obvious; it results from high prevalence, morbidity and mortality rate. Acute cardiogenic pulmonary edema (ACPE) is an emergency, the most severe retrograde left ventricular (LV) insufficiency. PubMed search revealed not a single paper with the objective to evaluate atrial fibrillation (AF) prevalence and prognostic significance in ACPE patients. Given the lack of information on the clinically very relevant topic, the aim of the study was to analyze prevalence, pathophysiologic consequences and possible prognostic significance of AF in ACPE. We studied homogenous group of 1397 ACPE patients, including those in cardiogenic shock, but without concomitant acute myocardial infarction (AMI). Prevalence of AF in ACPE was 29.74%. Intra-hospital mortality of ACPE patients with AF was 20.05% vs. 12.85% in patients without AF (p=0.00078). In conclusion, prevalence of AF is very high in the largest published homogenous acute cardiogenic pulmonary edema series (without AMI). Pathophysiologic mechanisms of AF-induced clinical course detrimental effects include impairment of left ventricle function (even critically), as well as induction / worsening of ischemia, etc. AF is associated with (almost) doubled mortality in acute cardiogenic pulmonary edema. AF was a better predictor of in-hospital mortality then LV ejection fraction, diabetes mellitus, and many others*.

Key words: *Acute cardiogenic pulmonary edema, heart failure, atrial fibrillation, pulse pressure, prognosis*

Introduction

Medical significance of heart failure (HF) is indisputable, resulting from high prevalence, morbidity and mortality. Prevalence of HF is believed to be 1–2% in developed countries [1]. One in five adults will have HF during lifetime, and average 1-year mortality rate is very high (23.4%) [2]. The estimation suggested 3-fold increase in HF hospitalizations from 1996 to 2050 [2]. Before 1990, the modern era of treatment, 60–70% of HF patients did not manage to survive first five years [1].

Acute cardiogenic pulmonary edema (ACPE) is an emergency, the most severe retrograde left ventricular (LV) insufficiency, associated with substantial mortality rate, both short- and long-term [3, 4]. Patients with ACPE show some differences in comparison with other acute HF patients, for example, higher hemoglobin level on admission and a more pronounced decrease during the first day of hospitalization [5].

Atrial fibrillation (AF) is the most common chronic arrhythmia, and it is associated with a 2-fold increased risk of mortality [6]. AF is also the most common arrhythmia in HF; the prevalence of AF in acute HF is >30%. AF does increase the thrombo-embolic risk (especially stroke) and it worsens HF symptoms [2]. AF can cause systolic HF ("tachycardiomyopathy") [2].

PubMed search conducted on 6/13/2015 for the terms "pulmonary edema atrial fibrillation patients" revealed 194 papers, none with the objective to evaluate AF prevalence and prognostic significance in pulmonary edema patients.

Given the lack of information on the clinically very relevant topic, the aim of the study was to analyze prevalence, pathophysiologic consequences and possible prognostic significance of AF in ACPE.

Material and Methods

We studied homogenous group of 1397 ACPE patients, including those in cardiogenic shock, but without concomitant acute myocardial infarction (AMI) [7].

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Patients had crackles in >50% of lung field, as well as oxygen saturation <95% and were hospitalized at the Department for Cardiovascular Diseases, Clinical Center of Niš, during the period 1993–2005 [7].

The average age was 69.98±9.48 years (23-94 years) and males were slightly predominant (50.9%). Coronary artery disease and arterial hypertension were the most important etiologic factors. Protocol consisted of 25 parameters. Statistical analysis was done by commercial program SPSS, Chicago, Illinois, version 19. P-values of <0.05 were considered significant.

Results

Prevalence of AF in ACPE was 29.74%. The average age was 72.3±9.1 years in patients with AF and 69.1±9.5 years in those without AF (p<0.000001). In-hospital mortality of ACPE patients with AF was 20.05% vs 12.85% in patients without AF (p=0.00078) (Fig. 1).

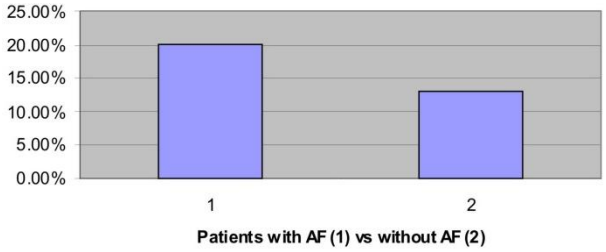

Fig. 1. In-hospital mortality of ACPE patients with vs without AF. ACPE, acute cardiogenic pulmonary edema; AF, atrial fibrillation

Pulse pressure (difference between systolic and diastolic blood pressure) was statistically significantly lower in ACPE patients with vs without AF (43.7±37.8 mmHg vs 49.0±37.3 mmHg; p=0.0334) (Fig. 2).

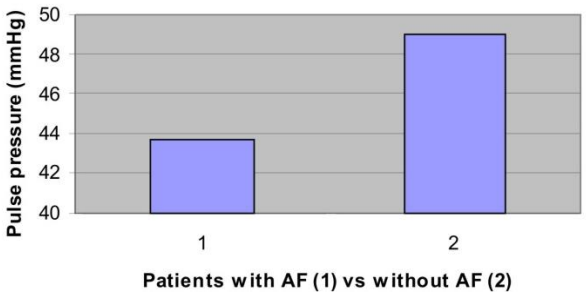

Fig. 2. Pulse pressure in ACPE patients with vs without AF. ACPE, acute cardiogenic pulmonary edema; AF, atrial fibrillation

The average heart rate on admission in ACPE patients with AF was 123.9±33.2 beats per minute (bpm), significantly higher as compared to patients without AF (107.6±26.2 bpm; p<0.000001) (Fig. 3).

Interventricular septum diastolic dimension was higher in patients with AF (12.8±2.2 mm) vs patients without AF (12.0±2.6 mm; p<0.05). No significant

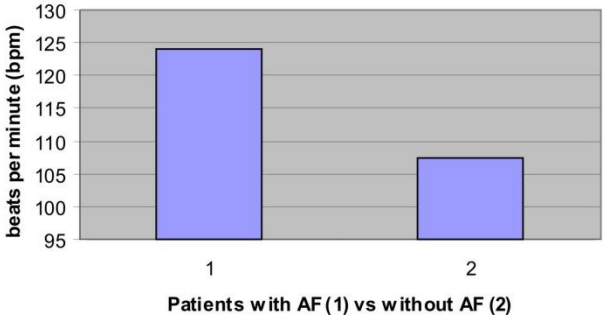

Fig. 3. Heart rate at admission in ACPE patients with vs without AF. ACPE, acute cardiogenic pulmonary edema; AF, atrial fibrillation

differences were found in: gender prevalence, prevalence of diabetes mellitus and of chronic obstructive lung disease, LV diastolic diameter, LV ejection fraction, prevalence of LV with preserved systolic function, systolic blood pressure (BP), diastolic BP, serum glucose level, white blood cell count, blood urea nitrogen and creatinine, as well as K^+ and Na^+ serum concentration.

Discussion

The prevalence of AF in ACPE was very high (29.74%), just as might be expected according to the medical literature. Acute and Chronic Heart Failure Guidelines of the European Society of Cardiology, published in 2012, cite the prevalence of AF in acute HF > 30% [1].

The average age was significantly higher (3.2 years; p<0.000001) in patients with AF compared to patients without AF. This was not surprising, as AF is predominantly the disease of aged population (AF is up to 90 times more prevalent in persons >80 years) [8]. AF was associated with almost doubled in-hospital mortality of our ACPE patients (20.05% vs 12.85%; p=0.00078; see Fig. 1). This is, to our knowledge, documented for the first time in such large homogenous series of ACPE patients without AMI.

As early as 1938, as cited by Gallagher and Camm [9], Brill observed that AF may cause HF without any other heart disease and following AF cease, recovery may be complete and long lasting. AF is a strong independent risk factor for HF [1]. Namely, AF is associated with a 3-fold increased risk of HF [6]. Vice versa, HF increases the chances for AF even 4.5 times (in men) to 5.9 times (in women) [10]. The higher the New York Heart Association (NYHA) class, the higher the AF prevalence in HF patients (from 4% in NYHA class I, to 40% in NYHA class IV) [1].

In our study, the average heart rate on admission in ACPE patients with AF was significantly higher than in patients without AF (16.3 bpm; p<0.000001) (see Fig. 3). It is an important and expected finding, because there is a clear association between uncontrolled heart rate and development of HF [1]. Moreover, there is a clear need to control high HR in acute HF, including ACPE. AF can worsen HF symptoms and worsened HF

can substantially increase heart rate in AF [1]. Patients with HF and preserved left ventricular ejection fraction (LVEF) are older and more often female and obese, less likely to have coronary artery disease and more likely to have AHT and AF than those with HF and reduced LVEF [1]. Underlying co-morbidities or subtle alterations (such as mild left atrial dilatation or low-normal LVEF), in the absence of overt heart disease, are baseline independent risk factors for incident HF during a long-term follow-up. Furthermore, incident HF is an independent predictor of adverse outcomes [11].

Conclusion

1. Prevalence of AF is very high (29.74%) in the largest published homogenous acute cardiogenic pulmonary edema series (without AMI).
2. Pathophysiologic mechanisms of AF-induced clinical course harmful effects include impairment of left ventricle function (even critically), as well as induction/ worsening of ischemia.
3. AF is associated with (almost) doubled mortality in acute cardiogenic pulmonary edema.
4. AF was the better predictor of in-hospital mortality then LVEF, diabetes mellitus, and many others.
5. Heart rate control/cardioversion are very important goals in therapy of acute cardiogenic pulmonary edema, with amiodarone and direct current cardioversion as first line therapy.

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Original Article

ASSOCIATION BETWEEN HYPERPROLACTINAEMIA AND OTHER CAUSES OF FEMALE INFERTILITY

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Abstract. *Hyperprolactinaemia is one of the major causes of reproductive axis disorders. Adequate treatment for hyperprolactinaemia is very successful in restoring ovulation, but there is still a proportion of patients unable to achieve pregnancy despite adequate control of hyperprolactinaemia. This prospective clinical trial included 104 hyperprolactinaemic patients in reproductive age: 78/104 (75%) suffered from infertility and the other 26 hyperprolactinaemic patients were still unmarried and not interested in pregnancy. Hyperpolactinaemia as the only reason for anovulation and infertility was diagnosed in 43/78 (55.12%) of our patients. In 35/78 (44.88%) patients, hyperprolactinaemia was associated with other causes of infertility: endometriosis, premature ovarian failure, PCO and insulin resistance, etc. After the appropriate treatment, mostly with bromocriptine (in 69/78 – 88.46%, alone or in combination with induction of ovulation), 35/78 (44.87%) patients achieved pregnancy. In the group of infertile patients with hyperolactinaemia as the only cause of infertility, 33/43 (76.74%) patients became pregnant, and in the group of patients who had combination of hyperprolactinaemia and other causes of infertility only 2/35 (5.71%) achieved pregnancy. The treatment of hyperprolactinaemia is obligatory in all patients with infertility. If adequate suppression of serum prolactin levels is achieved, but the pregnancy is still missing despite the fact that ovulatory cycles are established, the other causes of infertility should be searched for, and the clinician should not reject the possible existence of some unknown cause of infertility, so the patient should be referred to ART procedures which give more chances in such circumstances.*

Key words: *Hyperprolactinaemia, infertility, bromocriptine, assisted reproductive techniques*

Introduction

Hyperprolactinaemia is one of the major causes of reproductive axis disorders, being the major cause of hypogonadotropic anovulation and is one of the leading causes of infertility in women aged 25–34 [1–4]. Adequate treatment for hyperprolactinaemia is very successful in restoring ovulation. Nevertheless there is still a proportion of patients unable to achieve pregnancy despite adequate control of hyperpolactinaemia.

The aim of this article is to present the association between hyperprolactinaemia and other causes of female infertility, the combination which could be resistant to infertility treatment.

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Material and Methods

This prospective clinical trial included 104 hyperprolactinaemic patients in reproductive age. The diagnosis of hyperprolactinaemia was established by single measurements of serum prolactine levels in two separate occasions (at least two hours before or after sleeping). The serum was obtained without excessive venipuncture stress and a level higher than upper limit confirmed the diagnosis (> 530 mIU/l according to World Health Organization Standard 84/500), as it was previously described [3, 5, 6].

All hyperprolactinaemic patients referred to our Clinic were subjects of clinical investigation: anamnesis, clinical exam, pelvic ultrasound examination, urine and blood analyses (blood picture, biochemical parameters including parameters of hepatic and renal function, hormonal analysis). The patients with secondary hyperprolactinaemia (due to medicaments, hypothyreosis, renal or hepatic failure, etc.) were excluded from further investigation. The other 104 hyperprolactinaemic patients were included in this investigation. Transvaginal ultrasound (TVUS) measurements of follicle diameters were performed during menstrual cycle in patients with regular cycles. At day 2–4 of spontaneous menstrual cycle serum levels of follicle-stimulating hormone

(FSH), luteinizing hormone (LH), prolactin (PRL), oestradiol (Es), progesterone (Pr) and testosterone (Ts) were measured and in the middle of luteal phase (day 22) serum levels of Pr and PRL were measured as well. Ovulation was confirmed by adequate development of dominate follicle, appearance of corpus luteum on TVUS examination and serum progesterone levels > 5 ng/ml (16 nmol/l) in the middle of luteal phase (day 22), as it was described previously [7, 8]. Pituitary MR was performed in all hyperprolactinaemic patients with serum prolactin levels higher than 2000 mIU/l, as well in cases with disproportion of serum prolactin level and severity of clinical findings (e.g. prolactin < 2000 mIU/l and long lasting amenorrhoea). In patients with headaches and visual disturbances pituitary MR was also performed. Visus, perimetria and examination of *fundus oculi* were performed in patients with microprolatinomas and headaches.

Infertile patients were also subjects of infertility investigation: hysterosalpingography or sonohysterosalpyngography, analysis for related infections, laparoscopy and hysteroscopy where indicated, etc. Husband's semen analyses were performed too. The effects of therapy for hyperprolactinaemia were evaluated at first checkup, at the 45th day of the therapy and after 3, 6 and 12 months of therapy. If the pregnancy was missing after 6–9 months from the beginning of the therapy for hyperprolactinaemia and normalization of serum prolactin levels, induction of ovulation was started parallel with therapy for hyperprolactinaemia or patient was referred to ART (assisted reproductive technology) procedures (which had been already done in infertile couples with mechanical infertility or male factor and other indications for ART). Patients who achieved pregnancy were controlled and delivered at our Clinic.

Data were processed and statistical analyses were performed using commercial software. Statistical significance was tested with Student's t-test ($p<0.05$ was considered as statistically significant) and t-test for proportions for small independent samples with Cochran and Cox's corrective approximate method for small independent samples was performed where needed.

Results

Clinical characteristics of all patients included in this prospective clinical investigation are shown in Table 1.

Clinical characteristics of infertile hyperprolactinaemic patients (78/104 or 75%) are shown in Table 2. The other 26 hyperprolactinaemic patients were still unmarried and not interested in pregnancy, referred to our Clinic due to cycle irregularity, galactorrhoea or alopecia and hirsutism.

Serum prolactin levels were higher in amenorrhoeic infertile patients in comparison with serum prolactin levels in patients with oligomenorrhoea (1489.44± 388.19 mIU/l; p=0.025463). There were no significant differences regarding age and duration of infertility between hyperolactinaemic infertile patients with amenorrhoea, oligomenorrhoea and regular cycles, with exception of statistically significant younger age of oligomenorrhoeic patients in comparison with age of the patients with normal cycles (Table 3 and 4).

Table 1. Clinical characteristics of all hyperprolactinaemic patients (n=104).

Age (years)		29.96 ± 5.81
Cycle irregularity	60/104	(57.69%)
– amenorrhoea	30/104	(28.84%)
– oligomenorrhoea	30/104	(28.84%)
Regular cycle	44/104	(42.31%)
Galactorrhoea	12/104	(11.53%)
Infertility	78/104	(75.00%)
Hirsutism	13/104	(12.50%)
Alopecia	6/104	(5.76%)
Premature ovarian failure	3/104	(2.88%)
Macroprolactinoma	1/104	(0.96%)
Microprolactinoma	11/104	(10.57%)
Enlargement of sella turcica	1/104	(0.96%)
Anovulatory cycles	76/104	(73.07%)
Ovulatory cycles	28/104	(26.93%)
– inadequate luteal phase		11/28 (39.29%) or 11/104 (10.57%)
– adequate luteal phase		17/28 (60.71%) or 17/104 (16.35%)

Table 2. Clinical characteristics of hyperprolactinaemic patients with infertility (n=78)

Age (years)		30.55 ± 5.22
Duration of infertility (years)		4.56 ± 2.86
Primary infertility	67/78	(85.89%)
Secondary infertility	11/78	(14.11%)
Amenorrhoea	21/78	(26.92%)
Oligomenorrhoea	30/78	(38.46%)
Regular cycles	27/78	(34.61%)
Galactorrhoea	8/78	(10.25%)

Table 3. Age of hyperolactinaemic patients with infertility

	1. Patients with amenorrhoea n=21	2. Patients with oligomenorrhoea n=30	3. Patients with regular cycles n=27
Age (years) X ± SD	32.0 ± 5.61	28.06 ± 3.61	31.83 ± 3.79

t-test for 1 and 2 p=0.052944; t-test for 1 and 3 p=0.924765; t-test for 2 and 3 p=0.04001

Table 4. Duration of infertility in patients with hyperprolactinaemia

	1. Patients with amenorrhoea n=21	2. Patients with oligomenorrhoea n=30	3. Patients with regular cycles n=27
Duration of infertility (years) X ± SD	4.42 ± 3.35	3.33 ± 1.32	4.8 ± 2.39

t-test for 1 and 2 p=0.440426; t-test for 1 and 3 p=0.768643; t-test for 2 and 3 p=0.067

Hyperolactinaemia is relatively often associated with other possible causes of infertility — in 35/78 (44.88%) patients (Table 5).

Table 5. Association of hyperprolactinaemia and other causes of infertility in our patients

Male factor	6/78	(7.69%)
Mechanical factor	4/78	(5.12%)
Endometriosis	5/78	(6.41)
Premature ovarian failure	3/78	(3.85%)
Chlamydia	3/78	(3.85%)
Asherman's syndrome	1/78	(1.31%)
Endometrial polyp	4/78	(5.12%)
Myoma	7/78	(8.97%)
Insulin resistance	2/78	(2.56%)

Hyperpolactinaemia as the only reason for anovulation and infertility was diagnosed in 43/78 (55.12%) of our patients. This group was separately analyzed. Amenorrhoea was present in 20/43 (46.51%), oligomenorrhoea in 12 (23.53%), and regular cycles in 11/43 (29.96%). Anovulatory cycles were present in all patients with amenorrhoea and oligomenorrhoea and their serum prolactin levels were the highest (Table 6).

Table 6. Serum prolactin levels in patients with hyperrolactinaemia as the only reason for infertility

	Patients with amenorrhoea[1] n=20	Patients with oligomenorrhoea[2] n=12	Patients with regular cycles [3] n=11
Serum prolactin levels (mIU/l) X ± SD	3255.0 ± 1646.78	1665.5 ± 1140.32	1519.0 ± 427.53

t-test for 1 and 2 p=0.03475; t-test for 1 and 3 p=0.033315; t-test for 2 and 3 p=0.71

There were 11 patients with regular cycles and elevated serum levels of prolactin as the only diagnosed cause for infertility. Inadequate luteal phase was diagnosed in 6/11 (54.54%) of those patients according to transvaginal ultrasound measurements of follicle diameter during menstrual cycle and the mid-cycle serum progesterone levels. Serum prolactin levels in patients with inadequate luteal phase were higher in comparison to serum PRL levels in patients with adequate luteal phase (1624.33±369.0 mIU/l vs 1189.33 ±166.63 mIU/l; p=0.03853).

There were 35 pregnancies in the whole group of infertile patients with hyperprolactinaemia (44.87%). This proportion of achieved pregnancies is higher in the group of patients with hyperprolactinaemia as the only cause of infertility —33/43 or 76.74% (Table 7). Two patients among them became pregnant again after the first delivery with spontaneously normalized serum prolactin levels. Table 7 shows the therapy for infertility in patients who achieved pregnancy.

Table 7. Treatment of infertility in patients with hyperolactinaemia who achieved pregnancy

Pregnancy after spontaneous cycles	7/33	(21.21%)
Bromocriptine only therapy	16/33	(48.49%)
Bromocriptine + clomiphene	6/33	(18.18%)
Bromocriptine + clomiphene + HCG + IUI	1/33	(3.03%)
Quinagolide	2/33	(6.06%)
Bromocriptine + IVF	1/33	(3.03%)

HCG, human chorionic gonadotrophine; IUI, intrauterine insemination; IVF, in vitro fertilization

There were only 2/35 (5.71%) patients who achieved pregnancy in the group of infertile patients with hyperpolactinaemia associated with other causes of infertility, which is statistically significantly different compared to the group of infertile patients with hyperprolactinaemia as the only cause of infertility (t=6.27319; p<0.05).

Cycles in hyperprolactinaemic infertile patients treated with bromocriptine became regular after 12.75 ± 8.68 weeks of the therapy.

Galactorrhoea ceased after 6.05 ± 0.07 weeks, but did not totally disappear in all cases.

Hyperprolactinaemic patients successfully treated for infertility achieved pregnancy after 8.75 ± 3.89 months of the therapy for hyperprolactinaemia (range from 1.5 to 24 months).

Bromocriptine, alone or in combination with clomiphene, was administered in 69/78 (88.46%) hyperprolactinaemic infertile patients. In the group of infertile patients treated with bromocriptine once a day, pregnancy was achieved in 7/34 (20.58%), and if bromocriptine was administered 2 or 3 times a day, 17/35 (48.57%) patients became pregnant (t=2.439964; p<0.05). Between these two groups of hyperprolactinaemic patients there were no differences in age: (29.0±8.44) years in the group with bromocriptine once a day vs. 29.75±7.38 years in the group with 2 or 3 daily doses of bromocriptine (t-test - p=0.899264); nor in duration of infertility (5.75±2.87 years vs. 4.25 ±2.5 years; t-test – p=0.408262).

Bromocriptine therapy was stopped in two patients due to visual disturbances. The first patient had visual hallucinations ("fire from the electric cooker") and the second patient experienced scintillations. Another three patients switched to quinagolide due to intolerance to bromocriptine. In most cases, initial intolerance was easily overcome with taking the first dose of bromocriptine immediately before sleeping or with gradually increasing the bromocriptine dose.

Outcome of the pregnancies was as follows: 19/35 were delivered *per vias naturalis*, with only one preterm delivery. Caesarean section was performed in 8/35 (22.86%) pregnancies. All children were vital and born at term, with one exception, born in 34th week, vital. After the treatment for hyperprolactinaemia, there were 5/35 (14.28%) spontaneous abortions, and 3/35 (8.57%) missed abortions.

Discussion

In most cases of hyperprolactinaemic infertile patients, treatments with control serum prolactin levels can easily restore ovulation and the great majority of such patients become pregnant. The problem exists in the proportion of hyperprolactinaemic patients with combination of hyperprolactinaemia and some other causes of infertility.

Combination of hyperprolactinaemia and endometriosis in infertile patient is especially difficult for treatment. There are many reports about hyperprolactinaemia in patients with endometriosis [9–11], as well as reports about positive correlation of serum prolactin levels and the stage of endometriosis [12–15]. There is also evidence that patients with endometriosis have at least occult hyperprolactinaemia, according to TRH (thyrotropin-releasing hormone) stimulation, with higher serum prolactin levels in patients who had not achieved pregnancy during the treatment for endometriosis [12, 16]. On the other hand, the impact of minimal and mild endometriosis to infertility is still unclear [7], even though the minimal and mild endometriosis have been found during laparoscopy in many infertile patients. The infertility in those patients was considered as idiopathic until laparoscopy was performed. Unfortunately laparoscopy is not a part of routine investigation of infertility in some countries [17]. Human decidua produces prolactin, and prolactin is considered to be a better endometrial marker than prostanoid or CA 125, because decidua and endometriotic implants are the only sources for prolactin in abdomen, which is not the case with CA 125, moreover receptors for prolactin are found in endometriotic tissue [18]. There is a hypothesis that the content of prolactin in peritoneal fluid depends only on the activity of endometriotic implants, but there are also opposite opinions that the prolactin secretion from those implants is negligible, without impact on infertility in these patients [19]. It was speculated that prolactin from endometriotic implants could be a reason for local ovarian dysfunction and inadequate luteal phase which is followed by spontaneous abortions. Some studies supported this hypothesis [20], and the other authors conclude that the endometriosis is associated with inadequate luteal phase, but aberrant prolactin secretion by endometriosis implants has nothing to do with that [21].

Prolactin has immunomodulatory role as up-regulator of immune processes, and hyperorlactinaemia is often present in autoimmune diseases [22]. It is possible that immunomodulator characteristics of prolactin are connected with association of hyperprolactinaemia and endometriosis.

Nocturnal prolactin peak is exaggerated and prolonged in patients with endometriosis [23]. Authors of the study concluded that disturbances of nocturnal prolactin secretion could contribute to occurrence of infertility in patients with endometriosis, and this is the part of pathophysiology of that disease. The question is which one is the primary: hyperprolactinaemic environment which makes individual susceptible to development of endometriosis or endometriotic implants that can secrete enough amounts of prolactin to cause hyperprolactinaemia and subsequent infertility [18].

Clinical experience showed that the treatment of patients with associated hyperprolactinaemia and endometriosis is complicated, and if the success is absent, the couple should be referred to IVF as soon as possible.

The other causes of infertility that could be associated with hyperprolactinaemia are premature ovarian failure (in 5.12% of our patients) and insulin resistance in hyperorlactinaemic anovulation (in 2.56% of our patients). Even though the proportion is small, those patients still deserve attention. Hyperprolactinaemia and polycystic ovarian syndrome are different conditions, but insulin resistance could be associated with both of them. The association of prolactinoma and polycystic ovarian syndrome is possible, which has already been reported [24]. This is important during the infertility treatment of those patients: if the treatment with bromocriptine improves insulin resistance, the connection of hyperprlactinaemia and insulin resistance is obvious. This was the case with both of our hyperprolactinaemic patients with insulin resistance, but the small sample precludes us from definitive conclusions.

The relation of hyperprolactinaemia and psychological stress due to infertility is a specific question. It is well known that elevated prolactin levels are physiological correlates of psychosocial stress response. The levels of prolactin are higher in emotional than in manipulative tears [25]. There are no clinical reports about the impact of psychosocial stress caused by infertility to serum prolactin levels in hyperprolactinaemic patients, but clinical experience showed that empathy, compassion and improvement of overall quality of life could improve the success of infertility treatment.

The possible causes of unexplained infertility are abnormal function of sperm and oocyte, disorders of fertilization, implantation and embryo development during early stages. Hyperprolactinaemia could exist parallel to such functional disorders, which should be kept in mind in cases when the pregnancy was not achieved despite of the successful treatment of hyperprolactinaemia, so patient should be referred to ART procedures. Yet, there is no evidence that hyperprolactinaemia is associated with the mentioned abnormalities, possible causes of idiopathic infertility.

The majority of our hyperprolactinaemic patients are treated with bromocriptine. In the beginning of the therapy, about one half of the patients had nausea and vertigo, but these side effects disappeared when the medication was taken immediately before going to sleep or with gradually increased the doses of bromocriptine. Total daily dose of bromocriptine could be divided in two or three smaller doses, which offers better control of circadian variations of prolactin serum levels, as well as better control of nocturnal prolactin levels. The majority of our infertile patients with hyperprolactinaemic anovulation achieved pregnancy with divided daily bromocriptine dose. Visual hallucinations that happened

with two of our patients during bromocriptine treatment could be explained by the fact that the molecule of bromocriptine is similar to molecule of LSD [7]. The patients should be warned that their concentration could decrease during the bromocriptine treatment, which is important for some jobs or during car driving. For patients that could not stand side effects of bromocriptine or in whom bromocriptine treatment failed the best choice is quinagolide [26].

Quinagolide is equally successful in the treatment of hyperprolactinaemia as bromocriptine [27], but there are also reports that quinagolide is superior to bromocriptine in the treatment of hyperpolactinaemia associated infertility [28, 29]. It is better to avoid cabergoline in early pregnancy, even though there are reports about its safety, we state that patients who desire pregnancy, should switch to bromocriptine or quinagolide. Among all dopamine agonists, cabergoline has the longest half life (65 hours), so it is possible to be administered once or twice a week, but also there is a chance for early pregnancy to be exposed to the effects of cabergoline. The biggest study reported till now has included over 300 cases and the incidence of foetal anomalies was not elevated [30]. Anyway, further clinical trials are still needed for definitive conclusions [31]. Taking into account the effects of cabergoline on immunological system and macrophages, possible development of cardiac valvulopathy and related disorders (pericarditis and pericardial effusion) [29, 32], it seems reasonable to avoid this drug in early pregnancy, especially that safety of bromocriptine and quinagolide in pregnancy is already proven.

Bromocriptine or quinagolide should be administered in hyperprolactinaemic patients who desire the pregnancy as long as needed for patient to achieve the pregnancy. In our patients with adequate prolactin suppression pregnancy was achieved after 8.75±3.89 months of therapy (range from 1.5 to 24 months). Bromocriptine is used from 1971 and till now there were no reported harmful effects on early pregnancy and it is considered safe.

About one fifth of our patients achieved pregnancy without the therapy for hyperprolactinaemia which could be explained by macroprolactinaemia: hyperolactinaemia due to excess macroprolactin with normal concetrations of bioactive monomeric prolactin [33]. Macroprolactin is composed of macromolecules — isoformes of prolactin (dimeric or trimeric molecules; big- and big-big prolactin) with little if any biological activity, but readily measured by standard assays. It was stated that the screening for macroprolactin should be a part of investigation in all hyperprolactinaemic patients because it could be a significant cause of misdiagnosis and inappropriate treatment [33, 34,].

Spontaneous abortions were noted as outcome in 8/35 (22.85%) patients who became pregnant after the therapy with bromocriptine, but this proportion was similar to the proportion of spontaneous abortions in general population. One half of our hyperprolactinaemic patients with secondary infertility experienced missed abortion before the treatment for hyperprolactinaemia, which allows us to make a hypothesis that elevated prolactin levels could be a reason, probably not only due to inadequate luteal phase or aberrant endometrial receptivity, but also due to some still unknown way.

If the pregnancy passes successfully through the first trimester, the outcome is usually the delivery of term and viable infant. The other studies have also reported that after successfully treating hyperprolactinaemia the incidences of spontaneous abortions, ectopic gravidities, preterm deliveries and other complications of pregnancy were not elevated [35].

During the lactation in patients with prolactinomas, there were no further growths of tumours [7, 35].

Spontaneously restored ovulatory cycles have already been reported after the delivery of successfully treated hyperprolactinaemic patients [7, 35–38]. Similar situation has also been noted in our patients: two of them became pregnant again without the therapy, year and a half and two years after the first delivery. In both of them serum prolactin levels were spontaneously normalized, which could be explained by pituitary infarcts developed during the shrinkage of microprolactinoma in pregnancy or spontaneous recovery of hypothalamic dysfunction responsible for lactotroph hyperplasia [7].

Conclusion

In one half of the infertile patients with hyperprolactinaemia, this is the only cause of infertility and in other half hyperprolactinaemia is associated with some other causes of female infertility.

The treatment of hyperprolactinaemia is obligatory in all patients with infertility. In our series, bromocriptine was successfully used in the majority of patients with infertility, with better effects when used in divided doses during all day.

If adequate suppression of serum prolactin levels is achieved, but the pregnancy is still missing despite the fact that ovulatory cycles are established, other causes of infertility should be searched for, and the clinician should not reject the possibility of existence of some unknown infertility factor, so the patient should be referred to assisted reproductive technology procedures which provide more chances in such circumstances.

The treated hyperprolactinaemia has no influence on pregnancy outcome.

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Case Report

A LIVEBORN INFANT WITH TRIPLOIDY 69,XXX: CASE REPORT

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Abstract. *Since liveborn babies with triploidy are quite rare, we report here a new case of a liveborn female baby, with a karyotype 69,XXX. Ultrasound examination of the fetus, in the 37th week (9th month) of uncontrolled pregnancy, discovered severe intrauterine growth restriction and olygoamnion. A sample of fetal blood was taken by cordocentesis, in order to analyze fetal chromosomes. Two days later, the liveborn child was delivered by Cesarean section and died the same day, 7 hours and 55 minutes later, due to respiratory insufficiency. Autopsy revealed deformity of the joints, ectrodactyly of feet, deformity of the face (large, low positioned ears, hypotelorism and hypoplastic mandibula), with irregular position of both hands, hypoplastic lungs, kidneys, suprarenal glands, gallbladder and thymus agenesis. Chromosome analysis performed from fetal blood lymphocytes taken by cordocentesis showed karyotype 69,XXX. We would like to emphasize the significance of a health education of pregnant women, in order to establish regular examinations, and thus improve diagnostic and disease management possibilities.*

Key words: *Triploidy, multiple anomalies, cordocentesis*

Introduction

Triploidy presents a chromosome abnormality which is characterized by an extra-haploid set of chromosomes that could be inherited either from the father or from the mother. Data that have been obtained so far, point to the fact that triploidy could be present even in 2 per cent of the human fertilization and such pregnancies are usually ended with spontaneous abortion in the period from the seventh to the seventeenth week of pregnancy [1, 2]. Liveborn babies with triploidy are very rare, therefore, in this report we present a case of a female born baby, with karyotype 69,XXX, that lived for 7 hours and 55 minutes.

Case Report

A thirty-eight-year-old patient in the 37th (9th month) week of gestation, in her fourth pregnancy, was referred to our clinic for advice about delivery. She had three healthy children, so she decided not to control her pregnancy regularly. She had one ultrasound examination in the 8th week of pregnancy and had never been biochemically screened prenatally. Maternal-fetal physicians performed ultrasound examination of the fetus, and discovered severe intrauterine growth restriction and olygoamnion. With a suspicion on trisomy 18, they immediately took a sample of fetal blood by cordocentesis, in order to analyze fetal chromosomes.

The patient was held in the clinic, and two days later, she gave birth to a liveborn child by Cesarean section. The newborn had symmetric restriction of growth, it was 900g heavy and 35 cm long (under the third percentile), hypothrophic, with deformities of face and limbs. The baby died that same day, 7 hours and 55 minutes later, due to respiratory insufficiency.

Autopsy revealed deformity of the joints, ectrodactyly of feet, deformity of the face (large, low positioned ears, hypotelorism and hypoplastic mandibula), with irregular position of both hands, hypoplastic lungs, kidneys, suprarenal glands, gallbladder and thymus agenesis (Figs 1–3).

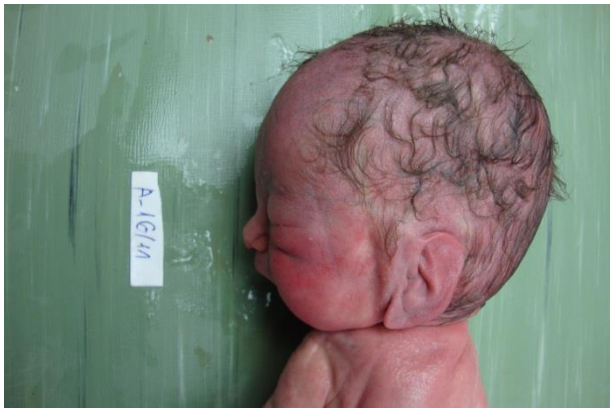

Fig. 1. Deformities of the face and head

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Fig. 2. Ectrodactyly of feet

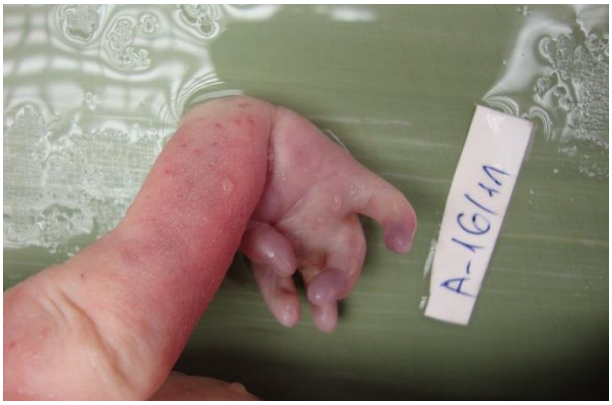

Fig. 3. Hand deformities

Chromosome analysis performed from fetal blood lymphocytes taken by cordocentesis showed karyotype 69,XXX**.** Triploidy was detected in 50 metaphase cells after G-banding with trypsin-Giemsa (GTG).

Discussion

Triploidy is the third most frequent case of chromosome abnormality and could be the cause of 15 to 18 per cent of all spontaneous miscarriages**.** It appears in 1:10 000 of liveborn children (out of that number 51 to 69 percent are male babies) [2, 3]. The frequency of triploidy in fetuses is 1:2000 [4].

Three possible mechanisms of triploidy appearance are described hereby:

1) nondisjunction in meiosis I or meiosis II of spermatogenesis (sperm formation), resulting in an extra set of paternal chromosomes (diandry)

2) nondisjunction in meiosis I or meiosis II of oogenesis (egg formation), resulting in an extra set of maternal chromosomes (digyny)

3) double fertilization of a normal egg, resulting in an extra set of paternal chromosomes (dispermy)

It has been reported that mechanism 1 accounted for 23.6% of triploidy cases, mechanism 2 for 10%, and mechanism 3 for 66.4% [5].

Most cases of triploidy result from dispermy [6–8]. Several studies have reported that the majority (62–77%) of cases of triploidy of maternal origin result from nondisjunction in meiosis II, although another investigation found nondisjunction to be evenly distributed between meiosis I and meiosis II [6, 7, 9].

Fetal nuchal translucency thickness (the sonographic appearance of a subcutaneous collection of fluid behind the fetal neck) in the first trimester is frequently increased for fetuses with triploidy [10–12]. Triploidy associates minor facial anomalies (facial asymmetry, low set ears), mild ventriculomegaly, multiple major structural defects of the internal organs, intrauterine growth retardation (asymmetric most frequently) and sindactily (of third and forth fingers most frequently). Other possible ultrasound findings in triploidy are: hypertelorism and microphtalmus, micrognatia, major facial anomalies (cleft), agenesis of corpus callosum, cardiac malformations, septal defects, single umbilical artery, omphalocele, renal anomalies, holoprosencephaly [4].

Unusual findings for triploidy in the presented case were hypotelorism, ectrodactyly and thymus agenesis.

It has been mentioned in the literature that the fetuses, whose haploid set is maternal in origin have a better chance to be born. Further, infants with triploid/diploid mosaicism will have longer survival than those with true triploidy [13].

Conclusion

In the presented case, the baby with triploidy was born due to uncontrolled pregnancy. In most cases, fetal chromosomal aberrations are presented with ultrasonographically detectable anomalies. That is the reason why thorough anatomical survey is a necessary part of fetal screening.

We would like to emphasize the significance of health education of pregnant women, in order to establish regular examinations, so we would have better diagnostic and disease management possibilities.

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Case Report

UNUSUAL ARTERIAL ANASTOMOSES ON THE ANTERIOR SIDE OF THE MEDULLA OBLONGATA: A CASE REPORT

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Abstract. *The cerebral arterial circle is a constant carotid-basilar anastomosis on the brain base. However, some transitory primitive intercarotid or carotid-vertebral or carotid-basilar or lateral basilo-vertebral anastomoses can persist and change the common angioarchitecture of the brain. One of these transitory persistent anastomoses was found in a 72-year-old male, autopsied at the Institute for Forensic Medicine of Niš, after a fatal cranial fracture. We discovered persistent lateral basilovertebral anastomosis that originated from the right side of the basilar artery, immediately below the beginning of the right anterior inferior cerebellar artery, which was connected with the left anterior spinal artery (ASA). In addition, there were two transversal anastomoses between both vertebral arteries. Although the discovered arterial anastomoses on the ventral side of the medulla oblongata persisted in the human adult, pathologic changes of this artery and other cerebral arteries were not found. The rarity of these vascular variants in the vertebrobasilar system deserves a description in this article and future scientific attention.*

Key words: *Human brain, lateral basilo-vertebral anastomosis, anterior spinal artery, intervertebral anastomoses*

Introduction

The vertebral artery (VA) is formed in the embryo between the 32nd and 40th day of gestation. Vascular anastomoses developing between the proatlantal intersegmental and successive six cervical intersegmental arteries lead to the formation of a primitive VA on each side from the subclavian artery [1]. Primitive arterial anastomoses appear transiently, while the basilar artery (BA) is formed by a pair of longitudinal neural arteries (LNAs) [2–5].

Morphologically, VA course in the neck has three topographical segments—prevertebral, cervical and atlantic parts, whereas its fourth topographical segment—intracranial or V4 part starts after VA piercing the dura and arachnoid mater at the level of the foramen magnum entering the posterior cranial fossa. V4 segment of the VA usually extends to the junction with the opposite one at the level of bulbopontine sulcus into the unpaired BA [6].

The VA distributes the greatest number of the branches in V4 part that are officially marked as anterior and posterior spinal arteries, inferior posterior cerebellar artery, lateral and medial medullary, meningeal and cerebellar tonsillar branches and choroidal branch to fourth ventricle [7]. These arteries supply corresponding structures of grey and white substances of the spinal cord, myelencephalon or medulla oblongata and cerebellum, as well as the meninges of the posterior cranial fossa, and participate in choroid plexus of the central cavity of the rhombencephalon [6].

The anterior spinal artery (ASA), as one of previous branches, merges bilaterally as a delicate short VA branch that joins with the opposite branch into single ASA that descends along the anterior median fissure of the spinal cord. Along its course, it is reinforced by other spinal branches of ascending and deep cervical, intercostal, subcostal, lumbar, iliolumbar and lateral sacral arteries, which enter the vertebral canal via corresponding intervertebral foramina [6, 8]. ASA has a considerable functional significance because of its penetrating branches that feed the anterior two thirds of the spinal cord [9].

In this article we want to describe an incidental finding of a persistent lateral basilo-vertebral anastomosis (LBVA) and its involvement in the formation of ASA, as well as a presence of two transversal channels between the two VAs on the anterior side of the medulla oblongata in a human adult cadaver.

Material and Methods

The investigation of the carotid and vertebrobasilar (VBS) systems of 377 cadaveric specimens, routinely autopsied at the Institute for Forensic Medicine of Niš, was performed during co-author's (MT) undergraduate and postgraduate studies. The latest study was approved by the Research Ethics Committee Faculty of Medicine

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Niš (No. 01-206-1). The focus of our investigation was morphological status of cerebral arteries on the brain base. The arteries were dissected in the subarachnoid space and documented in the notebook and by photos. With the help of the ruler immediately positioned to the cerebral arteries, outer diameters (ODs) of arteries were calculated on digital images by the ImageJ program (http://rsb.info.nih.gov/ij/index.html).

A unique case of vascular variations of the VBS was discovered in 72-year-old male, routinely autopsied at the Institute for Forensic Medicine of Niš, after a fatal cranial fracture.

Marking of the constant arteries in this case was in accordance with the official Terminologia Anatomica [7], whereas the marking of the primitive vessels was in accordance with the corresponding descriptions the papers published earlier [3, 10].

Case Report

We inspected the images and schemes of a dissected human brain base, with vascular components of the carotid and vertebrobasilar systems, in a 72-year old male. Except for the islands of the atheromatous plaques and the fetal origin of both posterior cerebral arteries, other morphological and/or pathological changes of the arteries of the carotid system on the brain base were not found. We found small atheromatous plaques, but also some vascular variants of the arteries of the VBS. The left VA was dominant (OD=4.19 mm), whereas the right VA was hypoplastic (OD=2.81 mm); their convergent junction was at the level of bulbopontine sulcus. The trunk of BA runs along the basilar sulcus and bifurcates in the interpeduncular fossa.

Among other variations of VBS, there were also segmental duplication of the left superior cerebellar artery (SCA), early bifurcation of the right SCA and the presence of the LBVA, which gives off from the right side of the BA, immediately below ipsilateral anterior inferior cerebellar artery (AICA). This LBVA coursed parallel with AICA along a part of its course and then it descended in front of the right V4 and joined with the left ASA, below the level of the pyramid of the medulla oblongata. Single ASA descended to the anterior median fissure of the spinal cord. Another intervertebral anastomosis, relatively long, positioned bellow the junction of the left ASA and LBVA in the single ASA, was also found. Rostral intervertebral anastomosis was relatively short (5.51 mm) and large (OD=0.45 mm), whereas caudal intervertebral anastomosis was longer (24.76 mm) and thinner (0.38 mm) (Figs. 1–2).

Discussion

The presence of LBVA and two intervertebral transversal anastomoses in this case can be explained by embryological data [11]. Namely, anomalous blood vessels may be due to the persistence of vessels which are normally obliterated by fusion and absorption of the parts which are usually distinct.

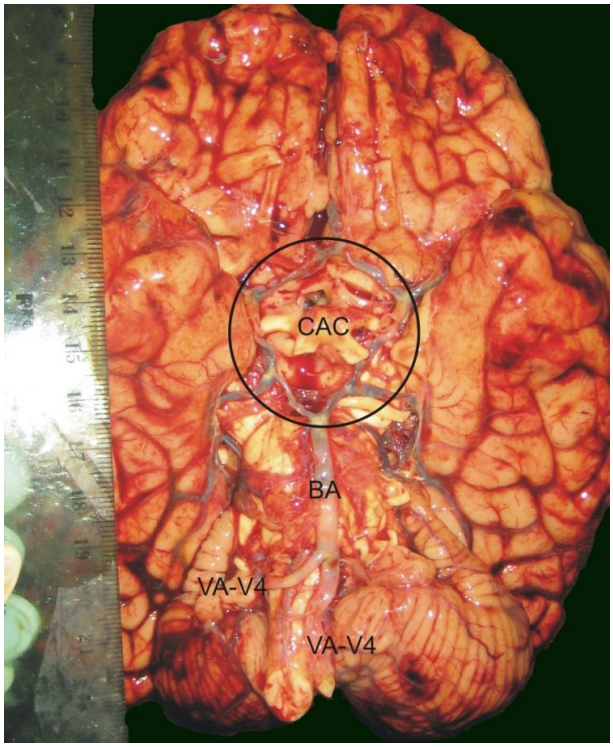
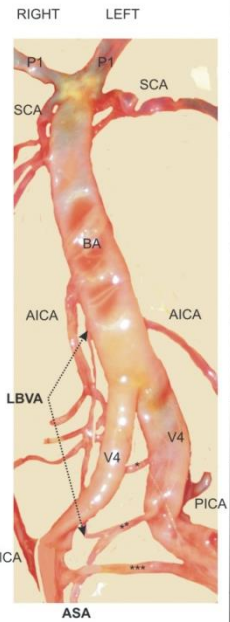


Fig. 1. Arteries in the human brain base of presented case. Vascular components of the cerebral arterial circle are encircled.
VA–V4, vertebral artery-intracranial part (on both sides); BA, basilar artery.



Arteries of the vertebrobasilar system	Outer diameter		Length	
	Left	Right	Left	Right
Posterior cerebral artery–pre-communicating part (P1)	1.79	1.29		
Superior cerebellar artery (SCA)	0.96	0.96		
Basilar artery (BA)	4.61		31.19	
Anterior inferior cerebellar artery (AICA)	0.49	0.81		
Lateral basilo-vertebral anastomosis (LBVA)		0.38		
Vertebral artery-intracranial part (V4)	4.19	2.81		
Rostral intervertebral anastomosis (*)	0.38		5.51	
Left anterior spinal artery** (ASA)	0.62			
Caudal intervertebral anastomosis (***)	0.45		24.76	
Anterior spinal artery (ASA)	0.62			

Fig. 2. Combination of the picture of the separated arteries of the vertebrobasilar system and the Table with calculated quantitative values of vessels' outer diameters and lengths.
Abbreviations in the picture are explained in the Table.

The posterior cerebral circulation initially consists of two parallel longitudinal neural arteries (LNAs), which later fuse forming the BA over the midline of developing pons. Lateral to each LNA is the primitive LBVA of Padget, which gives off many vessels which form a plexiform network with the LNA [2]. Prior to the complete development of the VA, the posterior circulation is supplied by transitory carotid-vertebral and carotid-basilar channels—caudal division of the internal carotid artery, the trigeminal, otic, hypoglossal and proatlantal intersegmental arteries [1–5]. If the embryo has an inappropriate development of the VA or inappropriate fusion between the VA and BA, blood circulation of the posterior brain is supplied mainly by the primitive LBVA, through which the VA and BA communicate with each other.

Among primitive carotid-vertebral anastomoses, the proatlantal intersegmental artery (PIA) has a branching pattern that closely resembles the typical distribution of spinal radicular arteries [12]. It gives off a dorsospinal vessel that further divides into ventral and dorsal branches. The ventral branch supplies the developing BA and eventually becomes incorporated into the definitive VA. In addition, the ventral branch gives off ascending and descending branches that later fuse with their opposite counterparts to give ASA. The spinal branch of PIA and its ventral radicular component remain prominent in the adult and can form the V4 segment.

We presented that right LBVA and left ASA participated in the formation of single ASA, whereas Tuccar et al. [13] described unilaterally origin of the left ASA from the hypoplastic left VA. Similar LBVA on the right side was also found in the human fetus [3].

One century ago, Stopford [14] cited that the right ASA was found to be absent in 9 %, the left ASA in 3%, and that the ASA arose by one stem from the angle formed by the junction of the two VAs in 3% of cases. This author also noted that the origin of the right and left branches remained separate in 6%, but there were one or more transverse channels between them, or they were fused forming one median vessel; these two alternatives occurred in equal proportion (47%). In a study by Zhao et al. [15] the incidence of the ASA scanned by multi-detector computed tomography was 52%.

Presented transversal intervertebral anastomoses could be compared with a case (n. 28) described by Stopford [14]. An intervertebral transversal anastomosis and ASA which originated from it, were presented in one fetal case [3], and one adult case [10]. Yonas et al. [10] noted that a group of small vessels, which later joined to form the ASA, arose from the aberrant crossing channel between the two V4 parts, whereas other authors [3, 5] were of opinion that it could be partially persistent PIA.

We measured OD of the right ASA and single ASA and it was 0.62 mm, although the caliber can range from 0.34 to 1.02 mm [16].

The clinical importance of the persistent LBVA and intervertebral anastomoses is yet unclear, although Yonas et al. [10] revealed ruptured large aneurysm located on the junction of the right VA and the aberrant crossing vessel from which ASA gives off. However, a thorough knowledge of vertebrobasilar variations may improve the outcome of head and neck operations, as well as the interpretation of angiography findings [17].

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