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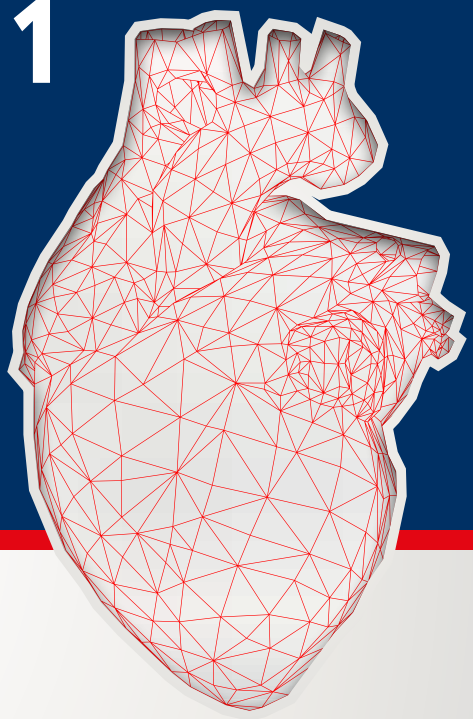

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Detection of pulmonary embolism on CT-angiography using contrast attenuation of pulmonary veins

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Abstract

Introduction: *In areas of pulmonary embolism (PE), the enhancement of pulmonary veins on computed tomography pulmonary angiography (CTPA) should be decreased due to reduced arterial perfusion.*
The purpose of this study was to investigate the accuracy of contrast density measurements (differences) in all pulmonary veins and the left atrium for the prediction of PE.

Material and methods: *Seventy-five patients with PE and 22 patients without PE on CTPA were included. Four readers measured the enhancement of the blood in the pulmonary vein immediately before the entrance to the left atrium, right after the aperture, in the center of the left atrium, in the pulmonary trunk and in the aorta. Enhancement of the pulmonary veins with and without upstream PE, and ROC curves with HU thresholds for optimal sensitivity and specificity for PE were calculated.*

Results: *More PEs were found in the right and lower lobes. PE-affected lobes demonstrated 13.8 ± 45 HU less enhancement in the pulmonary vein, compared to a paired non-affected pulmonary vein of the same patient ($P < 0.0001$). On average, non-affected pulmonary veins demonstrated no difference in enhancement compared to each other: 0.2 ± 21 HU. The optimal cutoff level in the ROC curve analysis for PE affection proved to be decreasing enhancement in the pulmonary vein of more than 10 HU compared to the atrium.*

Conclusion: *Decreasing enhancement in the pulmonary vein of more than 10 HU compared to the atrium could provide additional information and confidence in the diagnosis of PE.*

Key words: pulmonary embolism detection, CT-pulmonary angiography, enhancement and perfusion of pulmonary veins

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Introduction

Pulmonary embolism (PE) is a common disease with a potentially poor patient outcome. A thrombus occluding the pulmonary artery causes obstruction of lung circulation and can result in cardiogenic shock and death. Often, PE is not clinically recognized because the symptoms can be very unspecific and therefore can have low diagnostic value [1, 2]. Symptoms by themselves do not make it possible to exclude PE or to confirm it [1, 2]. To decide on diagnostic steps and additional therapy, risk stratification is crucial [1]. Established clinical

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scores, such as the Wells score [3, 4] or the Geneva score [5, 6], classify patients into low-, intermediate- and high-risk categories. These scores include patients' risk factors for PE, symptoms and clinical signs [3–6].

Correct and immediate diagnosis, as well as management and initiation of treatment, is important for patient outcomes [7].

In intermediate- and high-risk patients, multidetector row computed tomography pulmonary angiography (CTPA) is the procedure of choice and has become the gold standard when PE is suspected [2, 8–11]. The overriding characteristics of PE in CTPA are an occlusive or non-occlusive filling defect inside a pulmonary artery [12, 13]. When the vessel is fully occluded, it can appear expanded, and the thrombus can form an acute angle with the artery wall [12–14]. A partial filling defect, in which the thrombus is surrounded by a contrasting agent, is called a "polo mint sign", occurring on images perpendicular to the long axis of the vessel [12]. On longitudinal images of the vessels, it is called the "railway track sign" [12].

Secondary findings in CTPA, such as an enlarged diameter of the pulmonary artery ("Pallas Sign"), atelectasis, pulmonary infarction ("Hamptons hump"), pleural effusion and oligemia ("Westmark sign") can provide additional proof of PE in cases of uncertainty, but they are unspecific [13, 15–17]. Furthermore, the signs of pulmonary hypertension and cardiac congestion — such as right ventricular dilation, horizontalization or deviation of the interventricular septum and contrast reflux into liver veins — can facilitate detecting or confirming the PE diagnosis. The PE sensitivity of these right ventricular congestion signs was reported as being as high as 78% [2]. Filling defects in pulmonary veins adjacent to PE was recently described by Souza et al [18]. This "Pulmonary Vein Sign" was defined as presence of homogeneous filling defect in a pulmonary vein in the last 2 cm from the left atrium. This visual sign only reached a PE sensitivity of 36% by radiologists.

The purpose of this study was to investigate the accuracy of contrast density measurements (differences) in all pulmonary veins and the left atrium for the prediction of pulmonary embolism since the contrast in pulmonary veins should be decreased due to reduced arterial perfusion in areas of PE.

Material and methods

IRB approval was waived due to the retrospective nature of the study with irreversible anonymization.

Inclusion/exclusion of patients

Our Radiology Information System (Centricity RIS-i 6, General Electric Company, GE Healthcare, Chicago, IL, USA) was searched for the diagnosis of PE. Over a time period of 2 years (2016 and 2017), 82 consecutive patients with pulmonary embolisms were submitted to CTPA at our institution. Two senior radiologists with 10 and 12 years of experience in chest imaging reviewed the images for diagnosis confirmation and mapping of the PE (see ground truth below). In 3 patients, the diagnosis of PE could not be verified on CTPA, and these patients were excluded (low contrast or beam hardening artifacts). Of the remaining 79 patients, 4 had to be excluded due to lobectomy or severe motion artifacts. Twenty-three patients demonstrated embolisms in the drainage locations of all four pulmonary veins and were used for PE distribution and arterial enhancement statistics, but were excluded from the work-up of different enhancement in the pulmonary veins (Fig. 1). Twenty-two age- and sex-matched patients with normal CTPA exams and without PE findings were added as a control group.

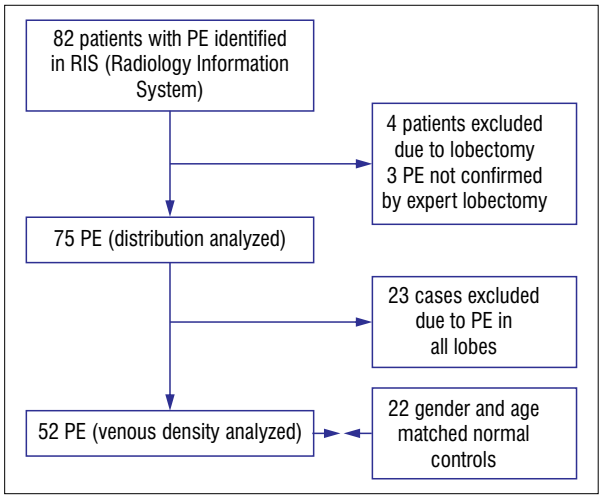

Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) with the inclusion of 82 patients and exclusion of 7 and 23 patients

CT imaging

CT images were acquired by two CT scanners (both by Siemens Healthcare, Erlangen, Germany): a SOMATOM Definition Flash (128 × 0.6 mm, pitch 0.6, slice thickness 1 mm) and a SOMATOM Definition Edge (128 × 0.6 mm, pitch 0.6, slice thickness 1 mm). A CT tube voltage of 100 kVp and a reference CT current time product of 100 mA were used. Standard contrast medium with 300 mg/mL iodine concentration was used at a flow rate of 4 mL/s (Xenetix 300; Guerbet, Aulnay-sous-Bois, France). A region of interest (ROI) was placed in the pulmonary trunk. Image acquisition started 4 seconds after the threshold of 100 Hounsfield units (HU) was reached in the ROI. Iterative recon-

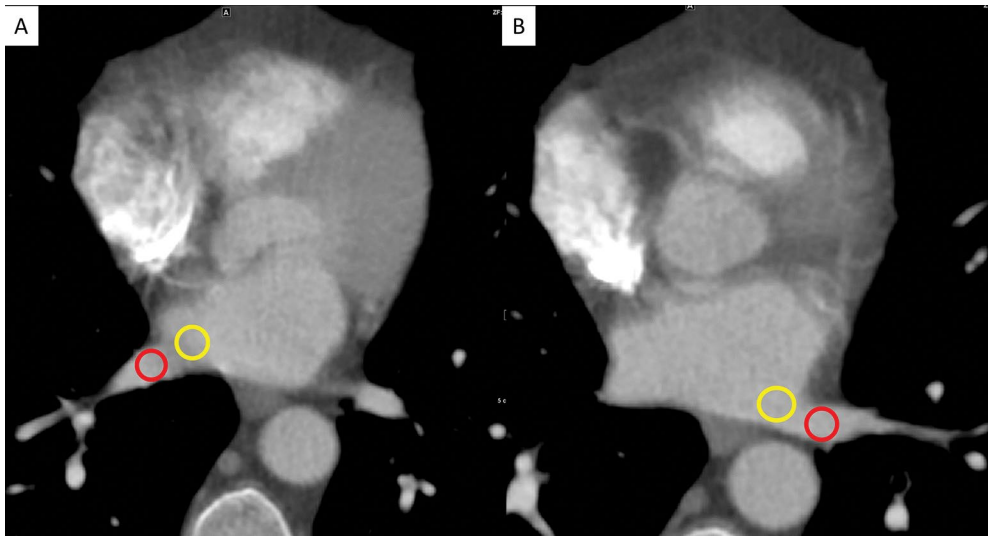

Figure 2. Density measurement in: **A** — the right inferior pulmonary vein; and **B** — the left inferior pulmonary vein. The readers in group 1 placed the ROI (region of interest, red circle) in the vein immediately before the entrance into the left atrium, and the readers in group 2 set the ROI in the atrium, as close as possible to the venous aperture (yellow circle)

struction (SAFIRE, level 3) was performed using kernels I26f and I70f.

Ground truth

In the remaining 75 cases, the mapping of the PE was reported in consensus by two senior radiologists with 10 and 12 years of experience in chest imaging. The PEs were classified as follows: central (involving the right or left main pulmonary artery), lobar, segmental or subsegmental PEs in the upper or lower lobe on the right or left side. Every embolus was counted separately and was noted with the most proximal affection of the pulmonary artery. Since the middle lobe and the lingula drain into the upper pulmonary veins, they counted as the upper lobes. In case of an additional lingular or middle lobe vein (normal variants), the mean densities of the upper lobe vein and the additional vein were calculated. Any aforementioned location of PE counted as a positive lobar result.

CT image analysis

The readouts were generated using a Picture Archiving and Communication System (PACS Philips, Amsterdam, Netherlands and Sectra, Linköping, Sweden). Group 1 consisted of two readers with 10 and 3 years of chest imaging experience, and group 2 consisted of two radiologists with 8 and 1 year(s) of chest imaging experience; both groups measured the 4 pulmonary veins in 97 cases (388 ROIs). The readers from group 1 placed the ROI (region of interest) into the vein immediately before the entrance into the left atrium, and the readers in group 2 set the ROI in the atrium, as close as possible to the venous aperture (Fig. 2). In addition, the readers also measured the density of the blood in the center of the left atrium, in the pulmonary trunk and in the middle of the aortic arc. After 4 weeks, the two groups remeasured the 4 pulmonary veins in half of the cases (n = 50) for intra-reader variability.

Statistics

Any form of embolism, even an isolated subsegmental PE, counted as affected pulmonary vein with an upstream PE. The mean enhancement of the pulmonary veins with and without upstream PE was calculated and compared to each other using Wilcoxon's unpaired rank sum test. In addition, the paired enhancement of the 1 to 3 normal veins and the 1 to 3 embolism-affected veins per patient were analyzed using Wilcoxon's paired rank sum test. Additionally, the average density difference of the veins within the same patient and the difference in the density to the atrium were calculated and analyzed by Wilcoxon's test. The results of both readers in the groups counted separately for the reader correlation, and the mean of their results was used for Wilcoxon's test. For the determination of the best cutoff level for (1) enhancement differences between atrium and pulmonary veins and (2) enhancement differences of the veins (normal vs. upstream embolism) receiver operator characteristic curves (ROC) were generated to find the area under the curve (AUC) and the optimal sensitivity and specificity (confidence interval included).

Table 1. Distribution of pulmonary emboli (total emboli load)

PE		R	L	R+L
Central*		14	10	24
Lobar	UL	11	7	
	LL	14	11	
	UL+LL	25	18	43
Segmental	UL	11	8	
	LL	17	17	
	UL+LL	28	25	53
Subsegmental	UL	4	8	
	LL	14	21	
	UL+LL	18	29	47
Total UL				73
Total LL				94
Total	UL+LL	85	82	
			Number of patients	
1 lobe PE (1 drainage vein)			21	
2 lobes PE (2 drainage veins)			22	
3 lobe PE (3 drainage veins)			9	
4 lobes PE (all drainage veins)			23	

*pulmonary trunk or main pulmonary artery
UL: upper lobe; LL lower lobe; R: right; L: left; PE: pulmonary embolism

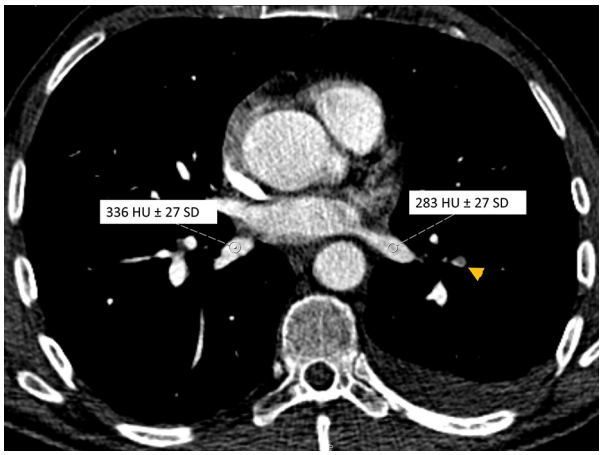

Figure 3. A 57-year-old male patient with a segmental pulmonary embolism in the anterior-lateral artery of the left lower lobe (orange arrow). The left pulmonary vein of the lower lobe demonstrated less enhancement than the right side

Intra- and inter-reader correlations were determined with Pearson's correlation coefficient.

All tests of significance were two-tailed, and a P-value of < 0.05 was considered to indicate statistical significance. Calculations were performed with MedCalc® software, version 16.4.3 (MedCalc Software, Ostend, Belgium).

Results

Seventy-five patients with pulmonary embolism (male:female = 40:37, mean age = 61.6 ± 16.2 years old) and 22 normal control patients (m:f = 11:11, mean age 60.2 ± 16.2 years old) were included. The emboli were classified as follows: 24 central, 43 lobar, 53 segmental and 47 subsegmental (Table 1). More PEs were found in the right and lower lobes, and more isolated subsegmental PEs were found on the left side (Table 1). In 21, 22, 9 and 23 patients one, two, three or four lobes, respectively, were affected by PEs.

Group 1: on average, the pulmonary vein of a PE-affected lobe was 13.8 ± 45 HU less enhanced than a paired non-affected pulmonary vein of the same patient ($P < 0.0001$, Fig. 3). Group 2: these paired measurements did not demonstrate significant differences (mean difference = 7.8 ± 48 HU, $P = 0.336$).

In group 1, the mean and median enhancement differences from an *affected* vein to the atrium (HUatrium-HUpv) were 5.1 ± 3.8 and 8.5 (CI: –4.2 to 15.0), respectively; meanwhile the mean and median enhancement differences from an *unaffected* vein to the atrium (HUatrium-HUpv) were –3.1 ± 2.1 HU and –2 HU (CI: –7.9 to 1.0), respectively. These enhancement differences were significant (affected vs. unaffected: $P = 0.0052$).

The optimal cutoff level in the ROC analysis for PE affection proved to be decreasing enhancement in the pulmonary vein of more than 10 HU, compared to the atrium (Fig. 4). The AUC for this ROC curve was 0.57 (CI: 0.51 to 0.63) with sensitivity of 47.8% (37.3–58.5%) and specificity of 74.7% (67.4–81.1%). Group 2, who measured in the left atrium closest to the venous aperture did not score significantly different enhancements between veins with or without upstream PEs ($P = 0.31$). Figure 5 demonstrates the venous enhancement differences (HUatrium-HUpv) depending on the number of embolism-affected lobes with the largest distinction found between patients without PE and with one PE. A specific ROC curve analysis (Fig. 6) of these patient selections found an AUC of 0.785 (CI: 0.70 to 0.86) with the best sensitivity of 85.7% (63.6–96.8%) and specificity of 63.5% (53.1–73.1%) using the criterion of > 3 HU (difference in HU between atrium and pulmonary vein). Again, no significant differences were found for group 2.

Generally, the blood density in the pulmonary trunk (PT) was higher than that in the left atrium (LA), and it was higher in the LA than in the aorta in both groups (Table 2). In patients with pulmonary embolisms, the

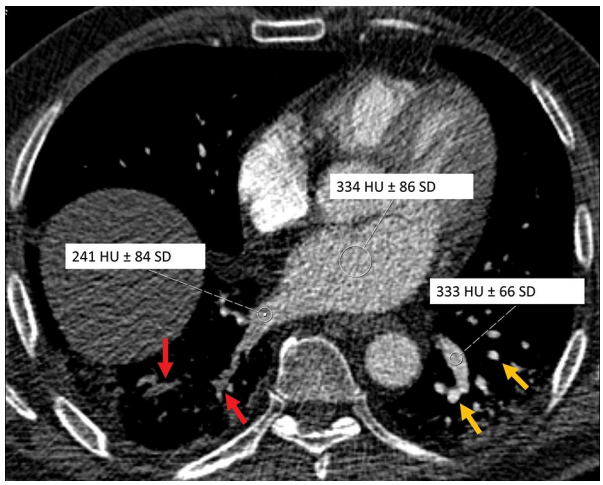

Figure 4. A 63-year-old male patient suffering from lobar and segmental pulmonary embolisms in the right lower lobe (red arrows). The right lower pulmonary vein demonstrated less enhancement than the normal left lower pulmonary vein and the atrium. Note the regular enhancement/perfusion of the segmental arteries of the left lower lobe (yellow arrows)

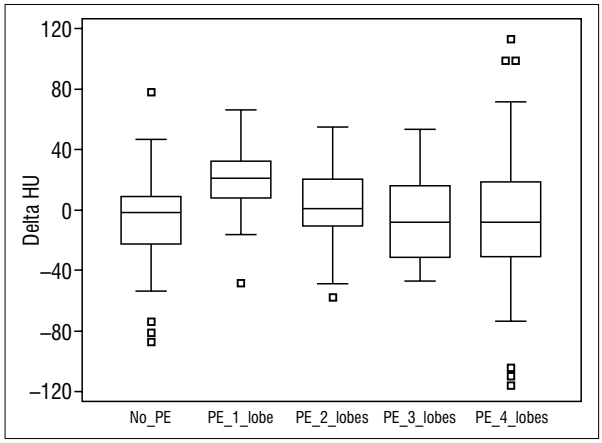

Figure 5. Box-and-whisker plot of the enhancement difference from an affected vein to the left atrium (HUatrium-HUpv) in patients without PE and patients with 1 to 4 affected lobes

density along this track was at each point higher than in the patients without embolisms ($P = 0.046$ for all 3 measurements in the PT, LA and aorta in both groups combined).

There was no significant difference in the mean absolute pulmonary vein density (non-paired), whether in cases with or without pulmonary embolisms ($P > 0.1742$). The means and medians of the pulmonary vein density in groups 1 and 2 for the different embolism categories are indicated in Table 3.

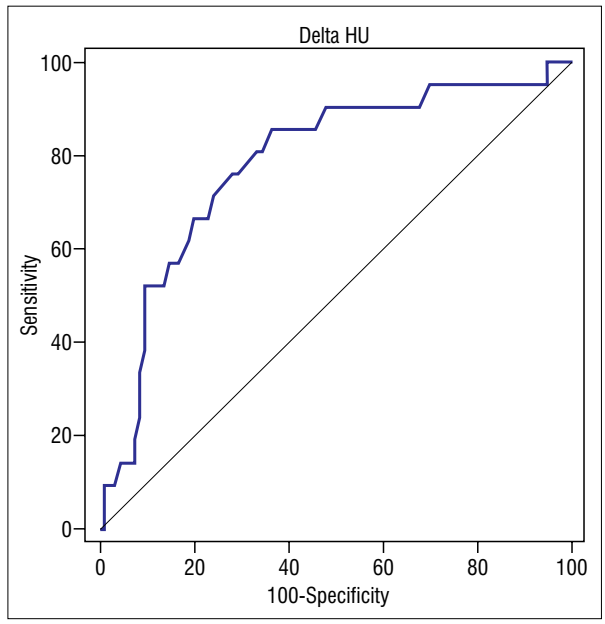

Figure 6. Patients with PE affecting only one lobe: ROC curve analysis of enhancement differences between the left atrium and pulmonary vein (HUatrium-HUpv). Best sensitivity and specificity of 85.7% and 63.5%, respectively, were found for a threshold of a > 3 HU difference

Both the inter- and intra-reader correlations were very high: the intra-reader correlations of the 4 readers were ≥ 0.93 (CI: 0.91 to 0.95). The inter-reader correlations in the groups and between the groups were ≥ 0.92 (CI: 0.91 to 0.94), although the ROIs were set slightly differently.

Discussion

In this study, we found that the veins in the drainage area of the PEs had, on average, 14 HU less enhancement than the veins of unclogged areas ($P < 0.0001$). For practical reasons, we also provided results for the measurement differences between the atrium and pulmonary veins (when comparing veins, one never knows whether the vein compared is free of embolisms). An attenuation difference of +10 HU indicates PE when applying this technique, with the strength clearly lying in the 75% specificity. Especially difficult to find are solitary PEs for radiologists, and for these embolisms, the accuracy increased to a sensitivity of 86% (threshold: HUatrium-HUpv > 3 HU). Our results indicate up to 50% higher sensitivities than the "Pulmonary Vein Sign". There could be different reasons for that: First, Souza et al. [18] set the ROI into the left atrium to trigger the CT exam, in our study the pulmonary trunk was used as trigger reference leading to an earlier CT phase.

Table 2. Central vascular enhancement dependent on PE

	HU (aorta)			HU (pulmonary trunk)			HU (atrium)		
	Mean ± SD	Median	(min to max)	Mean ± SD	Median	(min to max)	Mean ± SD	Median	(min to max)
PE (all 4 PV with upstream PE)	284 ± 82	293	438 to 144	407 ± 100	398	597 to 190	332 ± 75	324	476 to 211
PE (1 to 3 PV with upstream PE)	303 ± 84	294	608 to 142	392 ± 105	372	673 to 154	325 ± 85	315	597 to 132
Patients without PE	277 ± 92	268	527 to 128	380 ± 132	352	633 to 135	310 ± 99	288	527 to 125

PE: pulmonary embolism; PV: pulmonary veins; SD: standard deviation; HU: Hounsfield Units

Second, we measured HU differences between veins and atrium and computed the best cut-off levels for PE, while Souza et al. used a visual sign with probably rather large enhancement differences that could have led to a shift from sensitivity toward specificity.

As mentioned in the introduction, CTPA is the method of choice when detecting PE. It has very high sensitivity (90%) and specificity (94%) [14, 19–23]. In CTPA, PE is diagnosed by detecting a partial or fully occluded artery. Generally, the vessel density before (pulmonary trunk) and after the PE (left atrium) was higher, compared to the non-embolic cases. Pulmonary embolisms increase the pulmonary arterial resistance and pressure and can lead to a certain delay in circulation, which in turn can lead to accumulation of contrast media in the heart/lung. Therefore, one could expect high pulmonary vessel density in patients with PE. However, the clogged lobes are prone to lesser perfusion with less intravascular contrast media, which might be why the absolute vein density did not differ between any of the clogged and non-clogged lobes. The difference could only be found by comparing the veins in the same patient. In cases in which all four lobs are affected, there should be no HU difference. However, in these patients the diagnosis of PE requires no further sign for confidence boosting since all of the lobes are affected, and PE can usually be found easily.

More isolated subsegmental PEs were found on the left side (Table 1), likely because, on the right side, the subsegments were already occupied by larger segmental or lobar PEs.

Group 2 demonstrated a larger SD of the focal density measurement in the region of interest (ROI), indicating that the ROI was set larger due to larger space within the atrium (compared to the measurement within the veins for group 1); therefore, there was more noise and a larger SD.

Secondary findings can help in evaluation, especially in cases of uncertainty, and they have been described as predictors of severity and outcome [24]. However, there is disagreement in the literature in regard to their value in detecting PE, as well as predicting severity and outcome. They can distract from and interfere with the diagnosis of PE, thus presenting a potential pitfall [24]. Engelke et al. described sporadic secondary findings in cases of PE diagnosis that did not contribute to its detection [24]. They found PE burden to have the highest value for detection. However, they excluded pleural effusion from their study, which is more closely associated with PE. Similarly, contrast density differences between the pulmonary veins could be used to detect PE, especially, when there is doubt.

Other parameters can be utilized for the prediction of PE severity and outcome. Blood clot burden

Table 3. Enhancement of pulmonary veins dependent on upstream embolism

GROUP 1		Pulmonary veins (HU)		
		Mean ± SD	Median	(min to max)
PE (all 4 PV with upstream PE)		335 ± 79	331	(169 to 536)
PE (1 to 3 PV with upstream PE)	**Affected PV**	312 ± 75	310	(125 to 564)
	Non-affected PV	326 ± 85	326	(110 to 586)
Patients without PE		315 ± 103	303	(111 to 554)
GROUP 2		**Mean ± SD**	**Median**	**(min to max)**
PE (all 4 PV with upstream PE)		336 ± 79	329	(214 to 534)
PE (1 to 3 PV with upstream PE)	**Affected PV**	321 ± 82	313	(135 to 605)
	Non-affected PV	328 ± 89	315	(132 to 598)
Patients without PE		310 ± 106	291	(115 to 554)

PE: pulmonary embolism; PV: pulmonary veins; SD: standard deviation; HU: Hounsfield Units

was described as a predictor of severity by Ghaye et al. [25] and Araoz et al. [26], yet it cannot predict clinical outcomes. Another predictor of severity but not outcome is right ventricular failure [26]. Previous studies have found cardiac parameters to be superior in predicting the patient's clinical outcomes [26]. According to Bilj et al., the best predictor of clinical illness-specific outcomes is the right to left ventricular ratio [27]; nevertheless, the sample size in this study was very small. The vein enhancement measurements applied in this study could also be used in the future to help predict severity and outcome.

There are some limitations in our study: No classifications according to PE severity, secondary cardiopulmonary diseases or patient outcome were made. Anatomical anomalies of pulmonary vessels, such as the normal variants of pulmonary veins (e.g., additional veins), bronchopulmonary sequester, lung transplantation, dystelectasis, and structural lung disease, for example fibrosis, COPD or tissue scars, could perhaps account for the reduction in contrast density and are potential reasons for wrong density values. These pitfalls can be easily detected with CT and must be considered when interpreting contrast density reductions in pulmonary veins.

Additionally, CT-tube voltage plays a role in the absorption fraction and the density measurements of contrast media and must be kept constant. For example, low-dose CTPA for pregnant women can detect different venous enhancement due to lower CT-tube voltage and different blood volumes [28–34]. Enhancement of the pulmonary veins is highly dependent on the delay phase of the scan; therefore, the mean density did not prove to be useful, but the differences in enhancement within the same patent kept this variable out of the equation. All of these factors must be considered before utilizing this technique since they can distort density values and affect measurements.

In conclusion, decreasing enhancement in the pulmonary vein can provide additional information and confidence in the diagnosis of PE.

It is important to measure the blood density within the pulmonary veins right before the aperture and not after the aperture into the left atrium; and subtract it from the blood density in the center of the left atrium. An attenuation difference of >10 HU indicates PE when applying this technique, with the strength clearly lying in the 75% specificity.

Conflict of interest

None.

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Knowledge of pregnant women about venous thromboembolism

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Abstract

Introduction: *Venous thromboembolism occurs ten times more often among pregnant women compared to non-pregnant ones. Pulmonary embolism remains the leading cause of death in pregnancy and puerperium. The aim of the study was to investigate knowledge of pregnant or puerperal women about venous thromboembolism.*

Material and methods: *The study was conducted from October 2017 to January 2018 in a group of 204 women. The diagnostic survey method was applied with the use of a self-designed questionnaire. The survey was conducted using Google Form.*

Results: *Knowledge of venous thromboembolism was confirmed by less than 40.0% [CI 33.7, 47.0] of respondents. Less than a quarter of them received the information about the risk of pregnancy-related VTE from medical personnel, about 30% — from the Internet. Over 20% [CI 15.2, 26.1] admitted that they did not know any symptoms of this disease.*

Conclusions: *The survey showed marked deficiencies in knowledge concerning symptoms, risk factors and prevention of VTE among pregnant women. Therefore a special emphasis should be placed on education provided by medical staff in this group of patients.*

Key words: venous thromboembolism, thrombosis in pregnancy

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Introduction

Pulmonary embolism is the leading cause of death among pregnant and puerperal women [1–5]. The incidence of venous thromboembolic disease (VTE) among pregnant women is much higher than in a comparable non-pregnant age group [1–7].

The risk of VTE covers the whole period of pregnancy; however, 40% of episodes occur in the first trimester, especially in the case of in vitro fertilization [6–10]. The risk of pulmonary embolism is also increased in the postpartum period, especially after caesarean section [2, 5, 11]. Despite the decrease in the number of thromboembolic complications resulting from the fast mobilization of women after childbirth and their early return home, pulmonary embolism remains the main cause of death of women during pregnancy and confinement in developing countries [1–6].

The most common symptoms suggestive of deep vein thrombosis include [5, 12–14]: pain, swelling of the lower leg with a difference in their circumferences above 2 cm, tenderness or pain in the limb, excessive limb warm-up, redness of the skin, widespread superficial veins, subfebrile state, and — less frequently — fever.

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Pulmonary embolism should be suspected if there is: dyspnoea, tachypnoea, pleural chest pain (worsening during inspiration), coronary pain, haemoptysis or fainting [5, 12–14].

Nevertheless, the disease may be asymptomatic or oligosymptomatic in up to 70% of patients. Moreover, in the case of pregnant women, the diagnosis of VTE is more difficult, because symptoms such as calf oedema and dyspnoea may also occur in the course of normal pregnancy [5, 12–14].

Each woman planning or being at an early stage of pregnancy should be assessed for VTE risk factors [2, 11] (Table 1) and then qualified for one of three risk groups for the disease: high, moderate or low (Table 2).

Appropriate preventive measures should be used depending on the predicted risk of VTE [2, 11].

Prophylaxis of venous thromboembolism may be primary – before the occurrence of a VTE episode, or secondary – after diagnosis of VTE in the past. Apart from early start-up, the other modes of prevention, such as mechanical methods (graded pressure stockings, intermittent pneumatic pressure) [2, 5, 11, 15–16] as well as pharmacological ones (low molecular weight heparins — LMWH) are recommended.

The choice of the method to prevent thromboembolic complications should be considered individually depending on the risk of thrombotic complications (Table 2).

Prophylactic treatment should be considered both after giving birth in a natural way and after caesarean delivery. It is particularly important in women with thrombophilia and in patients who have already experienced an episode of VTE. If there are at least two risk factors, such as obesity or age over 35 years,

Table 1. Risk factors for venous thromboembolism

Pre-existing risk factors
Recurrent episodes of VTE in the past
VTE with no obvious cause or history of use estrogen
VTE related to the catchy cause
Family history of VTE
Known thrombophilia
Comorbidities, e.g. heart or lung diseases, systemic lupus, cancer, inflammatory diseases, nephritic syndrome, sickle cell disease, use of intravenous drug
Age > 35 years
Obesity BMI > 30 kg/m^2
Pluriparity ≥ 3 pregnancies
Smoking tobacco
Significant varicose veins
Obstetric risk factors
Preeclampsia
Dehydration/excessive vomiting/ovarian hyperstimulation syndrome
Multiple pregnancy or assisted reproduction
Urgent caesarean section
Efficient caesarean section
Tick delivery
Prolonged delivery > 24 hours
Perinatal haemorrhage > 1 l or the need for transfusion
Transient risk factors
General infection
Immobilization
Surgery during pregnancy or < 6th week of confinement

Table 2. Risk groups depending on risk factors

Risk groups	Definition	Preventive actions
High risk	Recurrent episodes of VTE in an interview (> 1 episode) = VTE with no obvious cause or related to use estrogen Single episode + thrombophilia or family history	Recommended LMWH prevention during pregnancy and in childbirth Stockings of graduated pressure in pregnancy and after childbirth
Moderate risk	≥ 3 risk factors other than those listed under the high risk category ≥ 2 risk factors other than those listed in the high risk category if the patient is hospitalized	LMHH prophylaxis should be considered Prophylaxis should be given after delivery for at least 7 days Graded compression stockings should be considered during pregnancy and confinement
Low risk	< 3 risk factors	Early commissioning is recommended Avoiding dehydration is recommended

anticoagulant prophylaxis and/or graded compression stockings should be considered for at least the duration of hospital stay [3, 5, 11]. If multiple risk factors coexist, prophylaxis should also be considered after the patient has been discharged [3, 5, 11].

Preventive measures in women after natural childbirth and after caesarean section, which are not burdened with additional risk factors, should be limited to early start-up and proper hydration [5, 11].

It is also important to avoid long-term travel in a seated position. The preventive methods of VTE during the journey should include frequent activities such as stretching the lower leg muscles, and whole body stretching exercises, wearing loose clothing, avoiding dehydration. If the journey lasts for more than 8 hours, it is recommended to use knee-high socks with gradual pressure, providing 15–30 mm Hg compression at the level of the ankle [5, 11].

The knowledge of pregnant women concerning risk and symptoms of VTE is very important, as it may help them to seek medical help quickly, and encourage them to take appropriate preventive measures.

Thus the goal of the present study was to investigate knowledge of pregnant or puerperal women about venous thromboembolism.

Material and methods

The method chosen for the study was the one of the diagnostic survey, the technique of polling with the use of a self-designed questionnaire, consisting of 20 closed questions, of which 13 concerned the topic of deep vein thrombosis (Fig. 1). The remaining six questions referred to the age, place of residence, education, week of pregnancy, the number of pregnancies/lay-ups, constancy of gynaecologist's care. Questions 1, 2, 8, 10, 11, 12 and 13 use the conjunctive cafeteria method. In questions 4, 5, 6, 7, 8, 14 it was possible to choose only one answer (disjunctive cafeteria). In the third question of the questionnaire, a five-point Likert scale was used.

The study was conducted within four months (from October 2017 to January 2018).

A mini pilot study was carried out among ten women during pregnancy and puerperium. The women surveyed did not make any comments, the questions were understandable.

The survey was conducted using Google Form, by providing a questionnaire on the Facebook social network website. The assumed average time of answering the questions was about 5 minutes. The selection of a random group was used in the work.

Two hundred and four questionnaires were qualified for the analysis.

Results

Demographic data

The most numerous age groups were respondents in the range of 26–35 years (63% [CI 56.4, 69.6]) and 18–25 years (31% [CI 24.9, 37.5]).

The highest percentage of respondents were women with higher education (71% [CI 64.5, 76.9]) and secondary education (26% [CI 20.4, 32.4]). The lowest (3% [CI 1.44, 6.3]) — women with primary education.

The majority of women were in their first pregnancy or their first parturition (56% [CI 49.0, 62.5]). For 34% [CI 27.7, 40.6] of the respondents it was the second pregnancy or puerperium.

Almost all of the examined women (98% [CI 95.1, 99.2]) were under the constant care of a gynaecologist during pregnancy.

Assessment of the knowledge of venous thromboembolism among the studied women

The surveyed women were asked about the knowledge of diseases that may occur and are characteristic of pregnancy. Knowledge of venous thromboembolism was confirmed by less than 40.0% [CI 33.7, 47.0] of respondents.

Women's knowledge about diseases that may occur during pregnancy did not come from medical personnel. When asked about "what possible diseases in pregnancy were you informed about by a gynaecologist/midwife/nurse?", the women listed: maternal gestational diabetes TORCH and Rh incompatibility. Only 23.0% [CI 17.8, 29.3] of the respondents received information about VTE. Worrying is the fact that a quarter of women declared that they did not receive information from medical staff about any of the diseases mentioned above.

Women were also asked a question about the most common cause of pregnancy-related deaths. Almost 39% [CI 32.8, 46.1] of women did not have knowledge on this subject, only about 36% [CI 29.5, 42.6] of respondents correctly pointed to pulmonary embolism.

Unfortunately, only less than a quarter of women surveyed received the information about the risk of pregnant VTE from medical personnel.

Half of the women surveyed (50.0% [CI 43.2, 56.8]) declared that they were familiar with the specific term "venous thromboembolism". About 30% of respondents learned about VTE from the Internet. Other sources of information were studies (16.7% [CI 12.2, 22.4]), doctor (13.7% [CI 9.7, 19.1]) and friends/family (12.7% [CI 8.8, 18.0]). Only about 11% [CI 7.2, 15.8] of the respondents obtained knowledge about VTE from a nurse or midwife (Fig. 1).

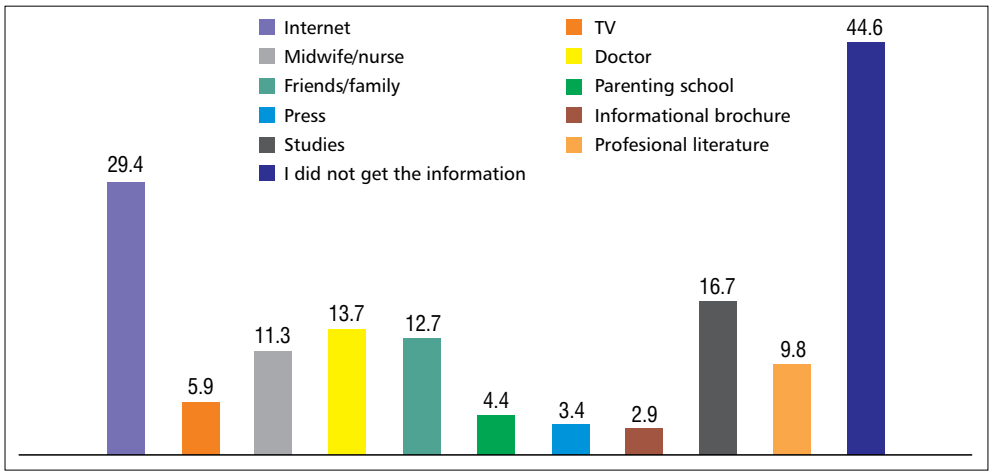

Figure 1. Sources of the respondents' knowledge about venous thromboembolism (%). *Percentages do not add up because the respondents had the opportunity to choose several answers

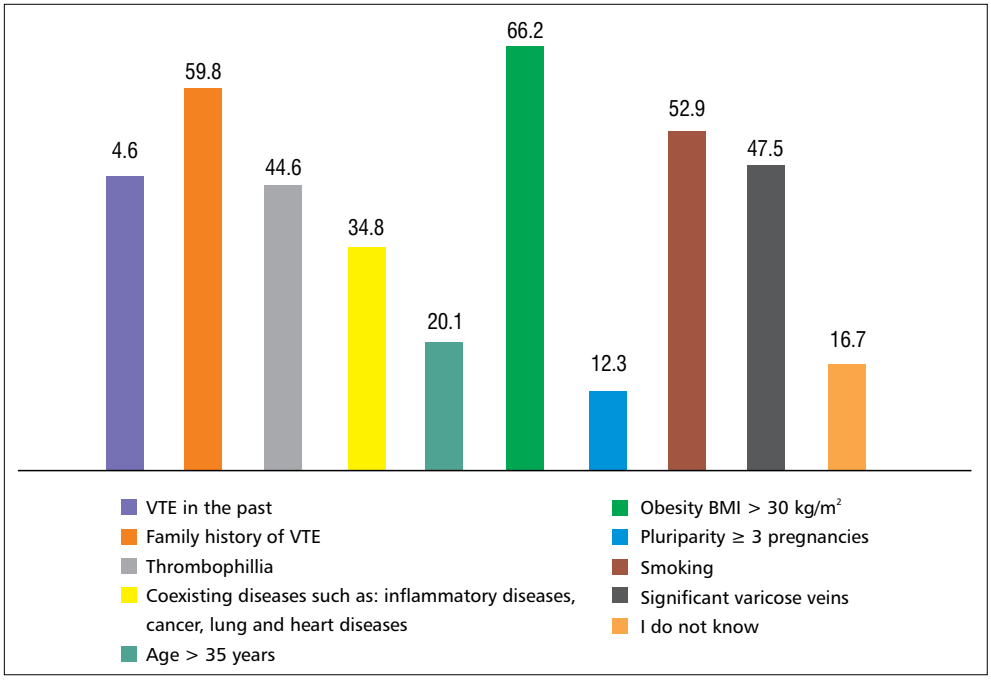

Figure 2. Knowledge about risk factors for venous thromboembolism among the studied women (%). *Percentages do not add up because the respondents had the opportunity to choose several answers

Assessment of knowledge of risk factors for venous thromboembolism among the studied women

Over 60% [CI 53.0, 66.3] of respondents correctly answered that pregnancy and puerperium increase the risk of VTE. However, 36% [CI 29.5, 42.6] of women were unable to indicate the right answer to this question.

Almost 17% [CI 12.6, 22.9] of respondents admitted that they did not know any risk factor for VTE (Fig. 2).

Respondents asked about obstetric risk factors for venous thromboembolic disease most frequently indicated immobilisation (47.5% [CI 40.8, 54.4]. Slightly fewer respondents indicated surgery (24.5% [CI 19.1, 30.8]) or caesarean section (27% [CI 21.3, 33.4]). Al-

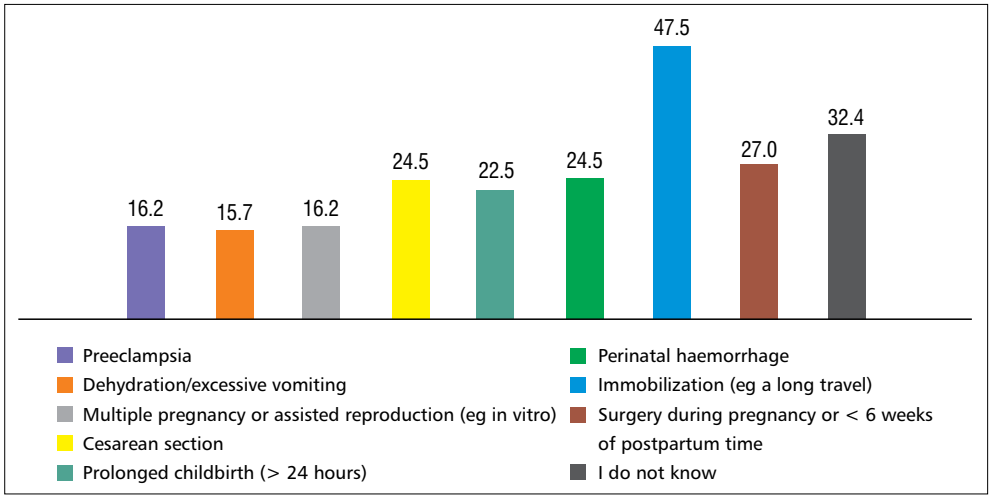

Figure 3. Knowledge of respondents about pregnancy and puerperal related risk of VTE (%). * Percentages do not add up because the respondents had the opportunity to choose several answers

most 1/3 of surveyed women didn't know any obstetric VTE risk factors (32.4% [CI 26.3, 39.0]) (Fig. 3).

Assessment of knowledge about the symptoms of venous thromboembolism among the studied women

Due to the change in the colour of the skin of one leg, medical assistance would be sought by ¾ women (rather yes — 21.6% [CI 16.5, 27.7], definitely yes — 53.9% [CI 47.1, 60.6]). A swelling of one leg would induce half of the women surveyed to report to the doctor and calf pain only about 13% [CI 9.3, 18.6]. Dyspnoea and cough for just over half of the respondents would be disturbing enough to go to the doctor immediately.

More than 70% [CI 63.5, 76.0] of respondents correctly indicated that pain, swelling, redness of one limb are symptoms that may signal deep vein thrombosis. Less than 50% [CI 43.2, 56.8] of the respondents indicated tenderness or painfulness of the limb. Only about one third of the surveyed women pointed to limb warming (33.3% [CI 27.2, 40.1]) and enlargement of superficial veins of the limb (30.4% [CI 24.5, 37.0]). Almost half of the respondents incorrectly identified pain and swelling of both legs with deep vein thrombosis. Just over 20% [CI 15.2, 26.1] of respondents admitted that they did not know any symptoms of this disease (Fig. 4).

Symptoms indicative of pulmonary embolism include dyspnoea, tachypnoea, chest pain increasing during inspiration, cough, haemoptysis and collapse. Over 70% of respondents correctly indicated dyspnoea (72.5% [CI 66.1, 78.2]) and pleural pain, increasing during inspiration (73.5% [CI 67.1, 79.1]). Worrying is that to a much lesser extent women indicated other equally important symptoms of pulmonary embolism, such as tachypnoea (41.7% [CI 35.1, 48.5]) or haemoptysis (12.3% [CI 8.4, 17.5]) (Fig. 5).

Assessment of knowledge on the principles of prevention of venous thromboembolism among the studied women

Most women (95% [CI 91.2, 97.3]) correctly identified the need for proper hydration. Women often chose answers such as tobacco abstinence (94.5% [CI 90.6, 97.0]) or maintaining normal body mass (90.7% [CI 85.9, 94.0]). It is astonishing to note that definitely fewer respondents indicated relaxing of calf muscles (64.2% [CI 57.4, 70.5]), wearing graduated bracing knee socks (50% [CI 43.2, 56.8]) or heparin injection (56% [CI 49.0, 62.5]). Unfortunately, 11% [CI 7.2, 15.8] of pregnant or puerperium women think they should consume alcohol in moderate amounts to prevent VTE.

Discussion

In the course of our study, women`s knowledge regarding venous thromboembolism during pregnancy and confinement was analysed. Unfortunately only half of the women surveyed reported that they were familiar with the term "venous thromboembolism". The importance of our findings is reflected in potential consequences of those knowledge deficits, because pulmonary embolism is still the leading cause of death among pregnant women and puerperium [1–5] and the incidence of venous thromboembolic disease among pregnant women is much higher than in a comparable non-pregnant age group [1–7].

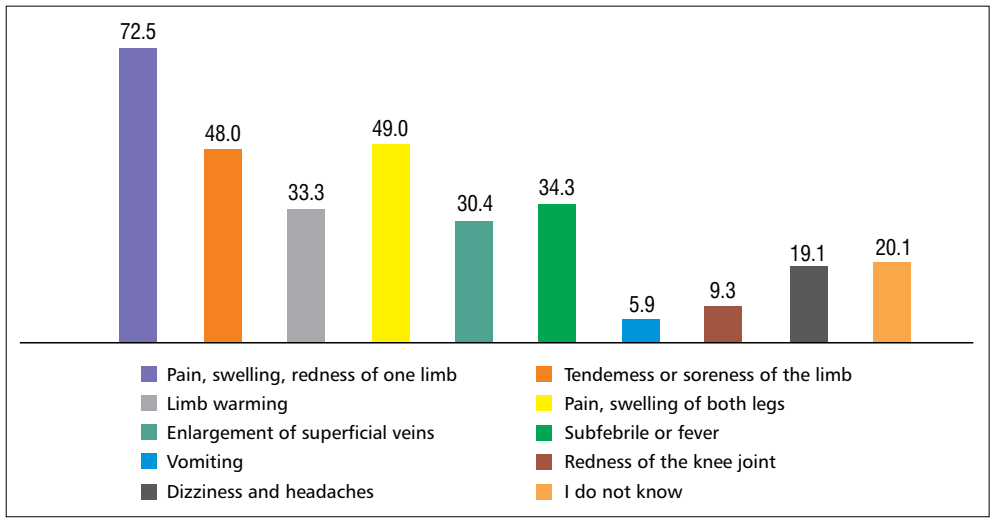

Figure 4. Symptoms of deep vein thrombosis in the respondents' opinion (%). * Percentages do not add up because the respondents had the opportunity to choose several answers

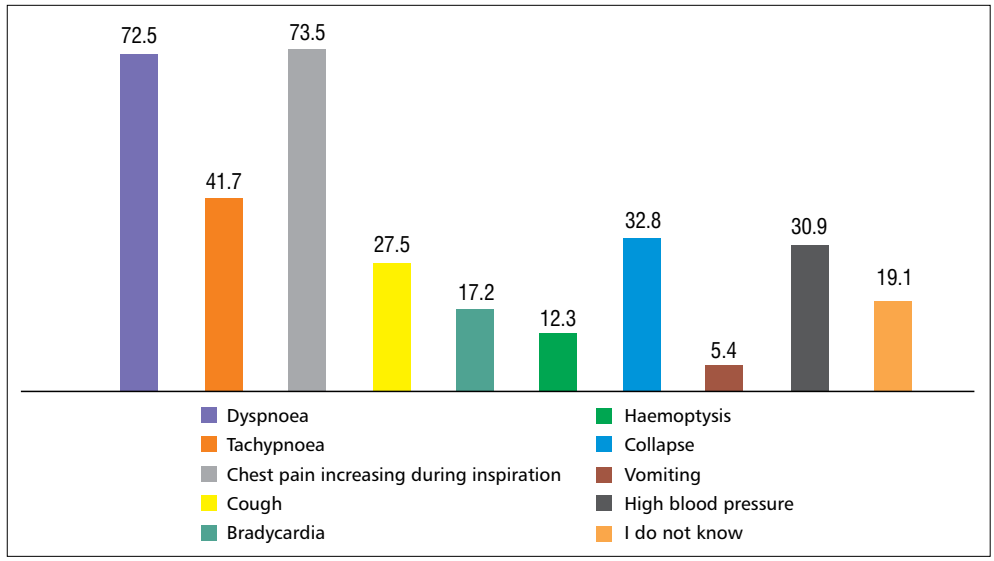

Figure 5. Symptoms of pulmonary embolism in the respondents' opinion (%). *Percentages do not add up because the respondents had the opportunity to choose several answers

Although 63% of respondents correctly answered that pregnancy and puerperium increase the risk of VTE, less than half of women could point to specific pregnancy and puerperium situations that increase the risk of disease.

The results of our study were similar to those obtained in the study by Mellon et al. who investigated awareness of pregnancy-associated health risks among pregnant women and male partners and showed significant knowledge deficiencies concerning common and serious health hazards associated with pregnancy [17].

Because of great deficiencies in knowledge of symptoms, risk factors and methods of prevention of venous thromboembolism, a special emphasis in education should be placed on these issues.

Public health campaigns could help increase awareness about the wide range of pregnancy-associated health conditions among pregnant woman and puerperium. It is worrying that only about 11% of the respondents obtained knowledge about VTE from a nurse or midwife, who are trained to educate patients.

Given the fact, that currently the Internet is the basic source of knowledge, especially for young people, it is worth paying attention to the reliability of information contained therein. At the same time, the Internet, due to its availability, should be used by professionals to improve knowledge not only about VTE but also other diseases of great epidemiological importance.

Conclusions

The incidence of venous thromboembolic disease among pregnant women is much higher than in a comparable non-pregnant age group and pulmonary embolism is the leading cause of death among pregnant women and puerperium.

Unfortunately, women's knowledge of venous thromboembolism was insufficient and currently the most common source of information not only for pregnant women is the Internet.

Conflict of interest

None.

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ORIGINAL PAPER

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Primary patency rates of endovascular interventions in hemodialysis patients with central venous stenosis and occlusions

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Abstract

Introduction: *The purpose of this study was to determine the primary patency rate of endovascular interventions in hemodialysis patients who had central venous stenosis or occlusion.*

Material and methods: *Twenty-seven hemodialysis patients, who underwent endovascular intervention between January 2013 and January 2018 for central venous stenosis or total obstruction, were included in the study. Endovascular interventions consisted of percutaneous transluminal angioplasty (PTA) or stent implantation. Primary patency rate of endovascular intervention at the sixth and twelfth months were evaluated.*

Results: *Stent implantation and PTA were used in 5 patients and 22 patients, respectively. Fourteen patients had stenosis and 13 patients had occlusion. The total procedural success rate was 81%, 86% in stenosis and 77% in occlusion. There was no procedure-related complication. The primary patency for PTA at 6 and 12 months were 40% and 10%, respectively. For stent implantation, primary patency rate at 6 and 12 months was 70% and 30%, respectively.*

Conclusion: *Endovascular interventions for central venous stenosis and occlusion are safe, with low rates of technical failure and they can be first-line treatment for central venous stenosis or occlusion in hemodialysis patients.*

Key words: central venous stenosis, central venous occlusion, endovascular intervention, percutaneous transluminal angioplasty, stent implantation

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Introduction

Central (superior vena cava, brachiocephalic, or subclavian) vein stenosis and occlusion are an important complication in hemodialysis patients. Central venous stenosis or occlusion usually occurs as a complication of central venous catheterization and significantly complicates dialysis. Clinically, central venous stenosis or occlusion manifests as ipsilateral arm or neck swelling and failure of hemodialysis access.

Surgical and endovascular treatments are available for the treatment of central venous stenosis or occlusion. Surgical treatment is often difficult and may not always be successful. Surgical approaches require general anesthesia and have high surgical morbidity in patients with end-stage renal disease. However, percutaneous treatment for central venous stenosis is feasible and efficient. Surowiec et al. [1] showed that transvenous angioplasty was helpful for hemodialysis patients with central venous stenosis and helped maintain functional access in the affected limb. Endovascular treatment options include percutaneous transluminal angioplasty (PTA) or stent implantation. The optimal endovascular treatment remains unclear; the superiority of stent placement compared with PTA has not been fully established [1–3]. The National Kidney Foundation Disease Outcomes Quality Initiative guidelines have recommended angioplasty as initial treatment; stenting is indicated in case of central vein stenosis recurring within 3 months [4, 5].

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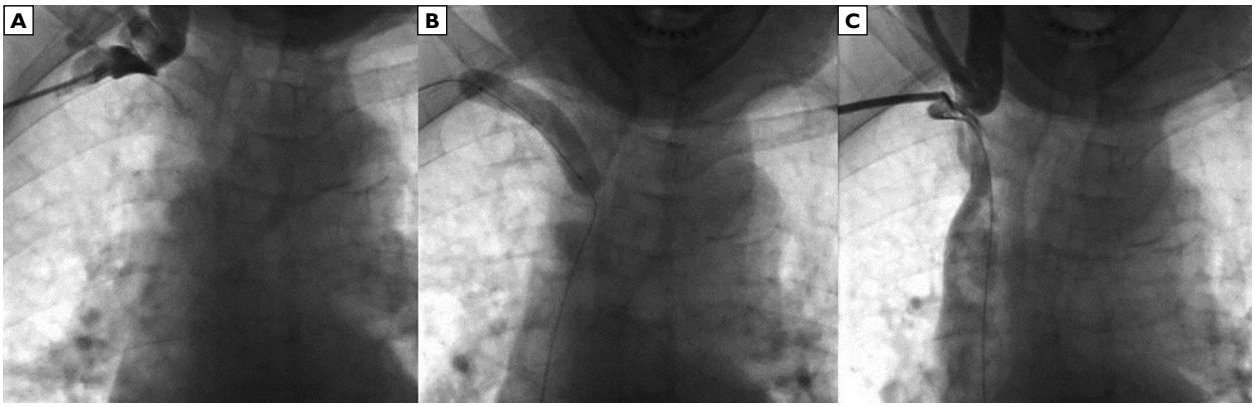

Figure 1. A 58-year-old patient with a history of 10-year hemodialysis. **A** — initial diagnostic venogram showed complete occlusion of right subclavian vein; **B** — the lesion was crossed anterogradely using guide wire, and PTA was performed; **C** — post PTA venogram showed normal filling of right subclavian vein. During follow-up, the patient had not any recurrence at 12 months

The aim of the study was to determine 6-month and 12-month primary patency of percutaneous balloon angioplasty and stent implantation in hemodialysis patients who had central venous stenosis or occlusion.

Material and methods

This study was a retrospective, single-center study based on collected data of endovascular interventions which were PTA or stent implantation for central venous stenosis or occlusion. Data were collected from the interventional radiology department database from January 2013 to January 2018. The study was approved by the ethics committee. Written informed consent was obtained from all the patients.

PTA or stent implantation was performed in end-stage renal failure patients on hemodialysis who had clinical signs of central venous stenosis or occlusion. All patients had a history of central hemodialysis catheter placement. Clinical signs in these patients were prolonged post-hemodialysis hemorrhage, increased venous pressure, ipsilateral arm or neck swelling and decreased blood flow during dialysis sessions. Patients who had previous PTA or stent implantation and previous surgical treatment for the same lesion were excluded from the study. In all patients, the location and length of the stenosis or occlusion were evaluated by diagnostic venography before the intervention.

Endovascular interventions were started with antegrade puncture with an 18-G needle into the proximal stenotic/occlusive vein and a 7-French vascular sheath was inserted via this vein. Antegrade venous access through the common femoral vein was added to the procedure in difficult cases. A total dose of 3000 IU heparin was injected via the vascular sheath to prevent thrombus formation. The stenotic site was traversed using a 0.035-inch hydrophilic guidewire (Terumo, NJ, USA). For some hard lesions, different guidewires, such as stiff guidewire or 0.018-inch guidewire or microcatheter, were also used for passing the stenosis/ /occlusion. PTA or stent implantation was performed after traversing the lesion. Depending on the size of the vessels, PTAs were 1 mm larger (ranging from 10 to 14 mm) than the normal size of the venous segment, and the length of the balloons ranged from 2 to 8 cm (Fig. 1). Stenting was performed if a residual stenosis of greater than 50% was present after PTA. Only bare self-expanding metal stents (Wallstent, Boston Scientific, Natick, MA, USA) were used and the diameter of the stent was chosen nearly the same as the adjacent normal vein (Fig. 2). Stent diameters ranged from 10 to 14 mm, with length ranging from 4 to 6 cm. Post-dilatation with a balloon often was performed after stent deployment to improve stent expansion. A final angiogram was performed to evaluate residual stenosis and technical failure was defined as inability to cross the stenotic or occlusive segment and residual stenosis > 30%.

The primary patency was defined as patency in the patent central vein without recurrent stenosis or occlusion. Assisted primary or secondary patency was defined as a patent central vein that underwent further intervention to improve patency.

Statistical analysis

Statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) 17.0 statistical software for Windows (SPSS Inc., Chicago, IL, USA). The chi-square test and Kaplan-Meier analysis were used to calculate primary patency of the PTA and stent implantation in the groups (Fig. 3).

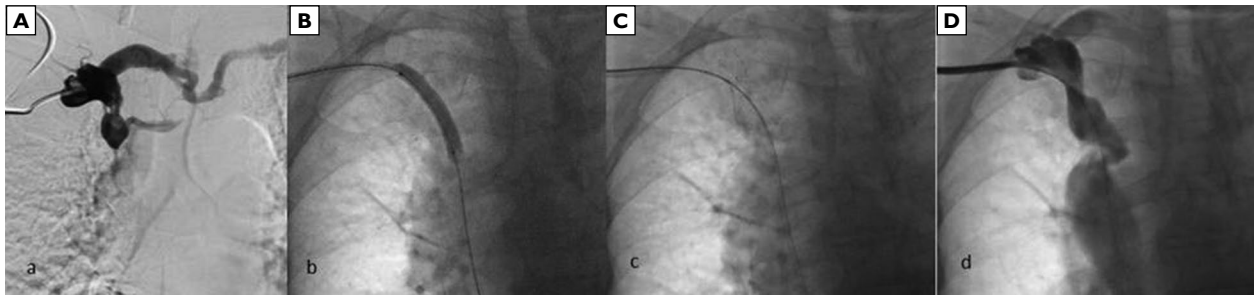

Figure 2. A 66-year-old patient with a history of 8-year hemodialysis. **A** — initial diagnostic venogram showed serious stenosis of superior vena cava. **B, C** — predilatation and stent implantation was performed. **D** — post procedure venogram showed normal filling of superior vena cava. At follow-up, restenosis was seen at 8 months

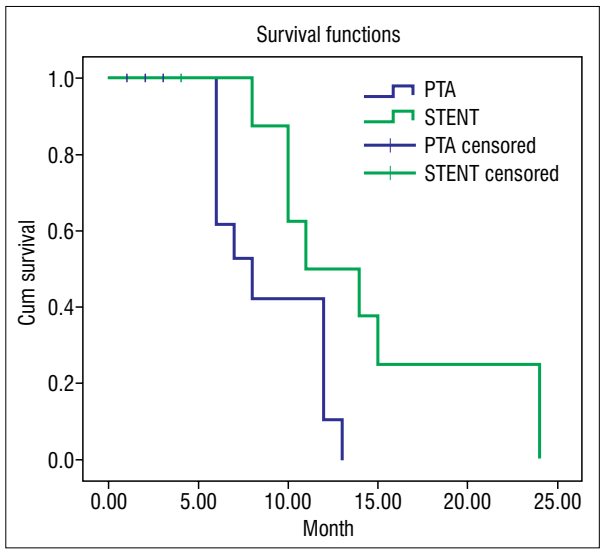

Figure 3. Kaplan-Meier graphs: a comparison of 12-month primary patency rates between PTA and stent implantation

Results

Endovascular procedures were performed in 27 hemodialysis patients with central venous stenosis or occlusion. There were 14 (52%) males and 13 (48%) females. The mean age of the patients was 62.2 ± 14 years (range, 35−87 years). Stent implantation was used for 5 patients and PTA for 22 patients. Before endovascular treatment, 14 patients had stenosis and 13 had occlusion. Only PTA was performed in 86% of 14 patients with venous stenosis and 77% of 13 patients with occlusion, while other patients underwent stent angioplasty. The sites of central vein stenosis or occlusion were the superior vena cava in 11 cases, brachiocephalic vein in 15 cases and the subclavian vein in 1 case. Demographic characteristics of the patients are summarized in Table 1. The overall procedural success rate for PTA and stent implantation was 83%; 100% in stenosis and 70% and 100% in occlusion. After balloon angioplasty, residual stenosis greater than 30%

Table 1. Demographic data and procedural details of patients

Mean age of patients	66 ± 14 years
Sex (female)	13 (48%)
Mean duration of hemodialysis	8 years
Type of lesions	
Stenosis	14 (52%)
Occlusion	13 (48%)
Site of lesions	
Superior vena cava	11 (40%)
Brachiocephalic vein	15 (55%)
Subclavian vein	1 (3%)
Mean length of the lesions	
Stenosis	36.2 ± 6.2 mm
Occlusion	28.5 ± 4.3 mm
Endovascular therapy	
Percutaneous balloon angioplasty	22 (81%)
Stent implantation	5 (19%)
Size of balloons used	
Superior vena cava (8 patient)	12*40 mm (x 4), 12*60 mm (x 2), 14*40 mm (x 2)
Brachiocephalic vein(13 patient)	12*40 mm (x 6), 10*40 mm (x 3), 10*60 mm (x 4)
Subclavian vein (1 patient)	8*40 mm (x 1)
Size of stents used	
Superior vena cava (3 patient)	12*40 mm (x 2), 14*40 mm (x 1)
Brachiocephalic vein (2 patient)	12*40 mm (x 2)

Balloons and stents are expressed as diameter * length in mm

was detected in the control angiograms in 2 patients who had stenosis and 3 patients who had occlusion, which were considered as technical failure. The total success rate for all procedures was 81%. There were no procedure-related complications and all patients underwent hemodialysis after the initial procedure.

The primary patency for PTA at 6 and 12 months was 40% and 10%, respectively. For stent implantation, primary patency at 6 and 12 months was 70% and 30%, respectively. The mean reintervention time was 7 months for PTA and 11 months for stent implantation. The mean reintervention time was 11 months in patients with stenosis and 6 months in patients with occlusion. There was no statistically significant difference between balloon angioplasty and stent implantation groups according to the chi-square test and Kaplan-Meier analysis ($p > 0.05$).

In the PTA group, 20 (91%) initial PTAs required secondary intervention during the 12-month follow-up period due to loss of primary patency. Secondary PTA was used in 18 patients and 2 patients underwent stent implantation. In the stent implantation group, 3 (70%) patients required secondary intervention and PTA was applied to these patients. Total reinterventions in both groups were required 23 (85%) patients during the 12-month follow-up period, but only 8 patients were followed up 6 month after second intervention and secondary patency was seen 75% at 6 months.

Discussion

The number of patients with chronic renal failure requiring hemodialysis is increasing and a smooth vascular structure is required for successful dialysis. Vascular complications are one of the main causes associated with an increase in morbidity and mortality in hemodialysis patients. Central venous stenosis and occlusion are a major concern in patients receiving prolonged hemodialysis. There are various surgical approaches to management of central venous stenosis or occlusion such as interposition grafting to the internal jugular vein, and direct patch angioplasty of axillo-subclavian stenosis which include jugular venous turndown. The results of surgical reconstruction of the central veins are better than those of endovascular therapy with primary patency rates of 80% to 90% at one year [6]. However, these surgical approaches are difficult to perform in hemodialysis patients with numerous comorbidities. Central veins are generally obscured by the bony skeleton and these major surgeries often require clavicular division or sternotomy along with general anesthesia. Endovascular treatments are less invasive and therefore preferred over surgical treatment in many centers. Exceptionally, subclavian vein stenoses adjacent to the costoclavicular junction respond poorly to treatment with endovascular therapy because of extrinsic compression at the thoracic outlet. The optimal treatment of access-related venous stenosis at this location must include a transaxillary first rib resection and mobilizing the subclavian vein to the jugular confluence [7]. Endovascular therapy is not usable only for benign central venous stenosis and occlusion but also for malignant processes. Also, surgical resection and reconstruction of the superior vena cava in selected patients with malignant mediastinal tumors may be very beneficial [8].

One of the negative consequences of endovascular treatment is acceleration of occlusion formation. Recurrent lesions after angioplasty have more aggressive neointimal hyperplasia than the primary lesion because the mechanism of angioplasty involves cracking and fissuring of the vessel intima which can increase neointimal hyperplasia [9]. The endovascular therapy options include balloon angioplasty and stent implantation. Although, transluminal angioplasty is the preferred treatment for central venous stenosis or occlusion [4], optimal endovascular management strategy is unclear in many centers.

In this study, the total procedural success rate was found to be 81%; it ranges between 70% and 90% in the literature [1, 2, 10–12]. The primary patency for PTA at 6 and 12 months was 40% and 10%, respectively. For stent implantation, primary patency at 6 and 12 months was 70% and 30%, respectively. Previous studies showed that primary patency rates for PTA ranged between 23% and 55% at 6 months and 12% and 50% at 12 months and primary patency rates for stent implantation ranged from 42% to 89% at 6 months, and from 14% to 73% at 12 months [1–3, 11, 13–16]. Our results were correlated with these studies. In our study, secondary or assisted primary patency rate was 75% during the 6-month follow-up.

As we know, stent implantation has some late complications such as stent fracture and migration of the distal stent fragment to the inferior vena cava or stent compression distortion. In our cases, there were no stent-related late complications and all patients underwent hemodialysis after the initial procedure. In our study cohort, only bare self-expanding metal stents were used. The bare self-expanding metal stent (Wallstent) excels as a conduit, rarely fracturing or failing primarily through the main body of the stent. The stent maintains strength via both radial force and compression resistance. Although the bare self-expanding metal stent has proven advantageous, there remain two critical shortcomings. First, the edges of the stent are weaker than the main body, making it prone to collapse. And he second is the lack of deployment accuracy and precision, making it prone to stent forshortening. In our

cases, there were no collapse and significant shortening of stent after procedure. New generation nitinol venous stents design is advantageous for improved precision and accuracy during deployment without significant stent forshortening. Studies comparing PTA and stenting in central venous lesions reported that the patency rates in central lesions were equal at 12 months [2, 3]. Restenosis is common after PTA or stent implantation, therefore, cost effectiveness is now being questioned in many centers. Stent implantation in our country is 3–4 times more expensive than PTA. So, we prefer PTA firstly in hemodialysis patients with initial stenosis and occlusion. However, in patients with residual stenosis greater than 50% after PTA, stent implantation was performed.

Mid-term primary patency rate of endovascular intervention and surgical treatment are similar in central stenosis or occlusion, with a significant incidence of secondary interventions [17]. It would be beneficial to choose endovascular intervention as a first-line treatment because of its less invasiveness and cost-effectiveness.

Our study has certain limitations. First, our sample size was small. It was necessary to collect data over a long time period to have a sufficient number of cases for statistical power. Additional limitations were retrospective nature of the study, availability of only limited width bare self-expanding metal stents and absence of surgically treated cases.

Conclusion

Although long-term patency rates of endovascular interventions in central venous stenosis and occlusion in hemodialysis patients are not satisfactory, because of less invasive nature and high technical success rate, it can be chosen as a first-line treatment method.

Conflict of interest

None.

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REVIEW

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The role of selected metalloproteinases and some genetic factors in the pathogenesis of abdominal aortic aneurysm

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Abstract

Aortic aneurysm is defined as a pathologically dilated segment of the main artery. There are three main types of aortic aneurysms: real, pseudo and dissecting. The most common aneurysms are abdominal aortic aneurysms defined as vasodilatation equal to or above 30 mm. Abdominal aortic aneurysm development is usually asymptomatic. Many various risk factors have been linked to AAA development. The pathophysiology of AAA is associated with inflammation, smooth muscle cells apoptosis and matrix degradation. The changes always result from imbalance between active matrix metalloproteinases (MMPs) and their inhibitors — TIMPs. Abdominal aorta is the most common location for the aneurysm. The risk of developing AAA increases with age. It is more common in men. Its rupture is associated with a high risk of death. The pathogenesis of AAA is complex and still not fully understood. In pathophysiological processes, aortic wall degeneration and atherosclerosis dominate. The factors involved in the pathogenesis of AAA and TAA are not quite the same. Important factors involved in the formation of AAA and increasing the risk of its rupture are MMPs. Also, polymorphisms of numerous genes have been associated with the risk of developing AAA. The two groups of factors related to AAA formation and development are presented and discussed in this work.

Key words: abdominal aortic aneurysm pathogenesis; metalloproteinases; risk factors

Acta Angiol 2021; 27, 1: 22–31

Introduction

Aortic aneurysm is defined as pathologically dilated segment of the main artery with loss of parallelism in its wall layers and at least 50% wider diameter of the affected artery than expected in persons of the same age and same sex [1, 2]. The correct dimensions of the aorta in adults, measured from the outer edge of the contour, are listed in Table 1.

The first description of the abdominal aortic aneurysm has been provided already in the 16th century by Vesalius [3]. In the first half of the 20th century, unsuccessful attempts were made to treat AAAs by various surgical methods. The first successful surgery of AAA with aortic reconstruction using corpse vessels was carried out by Dubost in 1951 [4]. In 1965, Cooley and DeBakey introduced surgery for ascending aortic aneurysms, while in 1986 Volodos was the first who implanted a stentgraft in to the abdominal aorta [5, 6].

The classification of aortic aneurysms is based on different criteria. There are three main types of aortic aneurysms: real aneurysm, pseudoaneurism and dissecting aneurysm. In terms of histological structure, aortic aneurysms can be divided into two major groups baggy and fusiform. Both are true aneurysms and include all layers of the aortic wall. Fusiform aneurysms are more common. They are manifested by symmetrical widening covering the entire aortic circumference. Baggy aneurysms are less common. They are characterized by local bulge. The clinical division of aortic aneurysms is based on their location – thoracic aortic aneurysm (TAA) and abdominal aortic aneurysm (AAA). This division is important because these aneurysms are treated by

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Table 1. Normal aortic dimensions in adult [2]

Aortic segment	Diameter (mm)	Test method
Aortic valve ring	W: 23 ± 2	USG (transthoracic)
	M: 26 ± 3	
Bay of Valsalva	W: 30 ± 3	USG (transthoracic)
	M: 34 ± 3	
Pad of the aorta	< 37	USG (transthoracic)
Ascending aorta (proximal part)	W: 26 ± 3	USG (transesophageal)
	M: 29 ± 3	
Ascending aorta	14–21/m^2 body surface	USG (transesophageal)
	25–38	TK
Descending aorta	10–16/m2 body surface	USG (transesophageal)
	17–28	TK
Abdominal aorta	14–21	USG, presentation B

W – woman; M – men; USG – ultrasound examination

various medical specialties [7]. The division and classification of aortic aneurysms is presented in Table 2.

The most common aneurysms are abdominal aortic aneurysms, which are defined as vasodilatation equal or above 30 mm. Infrarenal aneurysms make up 90% of all aortic aneurysms. The incidence of AAA is gender-specific. Men are more likely to suffer from AAA. It is estimated that 3 to 9% of men over 50 years of age develop AAA, while the percentage for women over 55 years of age is 1 to 2%. The epidemiological data indicate that the incidence of AAA increases with age. The AAA is rare in people under the age of 50; however, 12.5% of men and 5.2% of women aged 74 to 84 do develop AAA [8–10].

Abdominal aortic aneurysm is usually not accompanied by any specific symptoms. If any, the most common symptoms are permanent, crushing pains in the lower abdomen or lumbar region. Possible are pains that resemble spinal root pains, but the movement does not affect the intensity of the pain. AAA with a diameter above 5 cm may be palpated for physical examination. Often, such an aneurysm is tender, especially when it increases rapidly. However, no relationship between palpation and increased risk of AAA rupture has been associated. In auscultation, murmurs over the abdominal aorta can be heard [7]. The scant clinical manifestations of AAA result in high mortality in this disease. In addition, 78% of patients with AAA rupture die of this before reaching the hospital [11]. Before reaching the hospital [11]. Currently, the basic diagnostic methods for AAA detection are ultrasonography (USG) and computed tomography (CT) of the abdominal cavity.

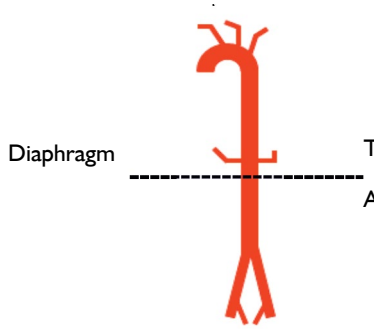
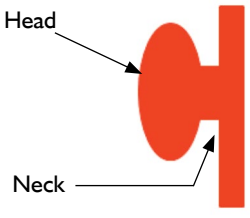
Conservative treatment of AAA includes periodic ultrasound check-ups of the aneurysm, adequate control of blood pressure and lipid profile. The results of experimental studies have shown that the administration of β-blockers favorably affects the metabolism and hemodynamics of connective tissue and the durability of the aortic wall [11]. The main method of treating AAA is surgery. Every year, approximately 4.000 surgical procedures are performed in Poland for abdominal aortic aneurysm [12].

Abdominal aortic aneurysms increase their diameter at different rates. AAAs with a diameter of 40 mm increase their diameter by about 2.6 mm/year, while those with a diameter of 60 mm by 6.5 mm/year. This is related to Laplace law. The risk of AAA rupture depends on its diameter [7, 8, 13] (Table 3).

AAA rupture is associated with a high risk of death of 65 to 90% [14]. It accounts for approximately 11,000 deaths each year in the United States, with mortality rates from ruptured AAAs reaching up to 90% [13]. Moreover 2% of all deaths are AAA-related [10]. Smoking is a serious factor not only modulating AAA formation, but also affecting the expansion and rupture of the aneurysm. Smokers had a higher rate of annual increase in aneurysm diameter than former smokers and non-smokers. This is because the concentration of proteases, such as elastase, degrading elastin that is naturally present in the aortic wall increases [14, 15].

Numerous risk factors which can lead to AAA development have been identified. Three most important ones are age (> 65 years), sex (males) and cigarette smoking [16, 17]. Researches proved a positive association between development of AAA and increasing years of smoking and a negative association with smoking cessation [17]. Other risk factors include a family history of abdominal aortic aneurysm, coronary artery disease, arterial hypertension, hypercholesterolemia, peripheral artery disease (e.g., Takayasu inflammation), and previous myocardial infarction and other cardio-

Table 2. Division and classification of aortic aneurysm

Division criteria	Characteristics			
Type of aortic aneurysms	 Real aortic aneurysm	 Aortic pseudoaneurysm	 Aortic dissecting aneurysm	
Localization of aortic aneurysms (clinical division)	 Diaphragm — Thoracic aortic aneurysms — Abdominal aortic aneurysms			
Histological structure of the aortic aneurysms	 Head, Neck — Baggy aortic aneurysm		 Fusiform aortic aneurysm	
Location of the abdominal aortic aneurysm	 Infrarenal	 Juxtarenal	 Pararenal	 Suprarenal
Etiology	Atherosclerosis aneurysm	Degenerative aneurysm	Inflamminatory aneurysm	Post traumatic aneurysm

vascular diseases [18–20]. Moreover, excess weight was associated with increased risk, whereas, exercise and consumption of nuts, vegetables, and fruits were associated with reduced risk of AAA [17]. Risk factors of AAA are summarized in Figure 1.

Structure of the abdominal aorta wall

The aorta is an elastic artery, which divides into three main parts: the ascending aorta, the arch of aorta and the descending aorta. The abdominal aorta is a part of the descending aorta, and it develops from splanchnic mesoderm [21, 22]. It starts at the aortic hiatus of the diaphragm and ends in aortic bifurcation.

The aortic wall consists of three layers: outer adventitia, media, and inner intima (Fig. 2).

The intima has direct contact with blood. It is a single layer of endothelial cells upon loose connective tissue. It also has part called internal elastic lamina which consists of collagen and elastic fibers and a small amount of fibroblasts and smooth myocytes. The media is the widest layer; it consists of smooth muscle cells embed-

Table 3. Relationship between the risk of rupture of the abdominal aortic aneurysm on its diameter [7, 8, 13]

AAA diameter	Risk of cracking during the year (%)
< 4 cm	0
4–5 cm	0.5–5
5–6 cm	3–15
6–7 cm	10–20
7–8 cm	20–40
> 8 cm	30–50

An increase in AAA diameter by 5 mm in half a year increases the risk of rupture by 2 times

ded in a dense matrix of fibrillar structural proteins. The adventitia is made of connective tissue proper with a large number of collagen fibers, and fewer elastic fibers and smooth muscle cells. It also has ganglion cells and vasa vasorum — small blood vessels that supply the wall in nutrients. Their branches reach up to the border with tunica media [23, 24].

The aortic media provides viscoelasticity through concentric bands of elastin filaments with associated collagen fibers and smooth muscle cells (SMCs), which are termed lamellar units. The media of the abdominal aorta usually consists of 28 to 32 lamellar units and it is avascular – smooth muscle cells survival depends of transintimal nutrition and oxygen delivery from the plasma [25].

Pathogenesis of the abdominal aortic aneurysm

The pathophysiology of AAA is accompanied by inflammation, SMC apoptosis and matrix degradation. Once considered a consequence of advanced atherosclerosis, evidence accumulated indicating that AAA is a focal representation of systemic cardiovascular disease [10]. Degenerative etiology dominates the pathogenesis of AAA, partly related to the atherosclerotic process [26]. In both AAA and TAA, the amount of elastin, collagen and glycosaminoglycans are reduced compared to normal aortas. Imbalance between the amount of active MMPs and their inhibitors – TIMPs – are responsible for the majority of the above listed pathological changes [27, 28]. MMPs are members of the metzincin group of proteases, which are named due to the zinc ion and the conserved Met residue at the active site [29]. The main inhibitor of MMPs is glycoprotein — TIMP-1. The second TIMP is non-glycosylated protein, produced by fibroblasts and endothelial cells and called TIMP-2. TIMP-1 expression is regulated by interleukin 1 (IL-1) and tumor necrosis factor alpha (TNF-α). No effect of cytokines on TIMP-2 has been demonstrated [30]. Metalloproteinases in a healthy aorta are produced by endothelial cells, SMCs and fibroblasts. Additional sources of these enzymes were observed in AAA, which led to an imbalance in ratio of MMP to TIMP [31]. Different MMPs play a major role in the pathogenesis of TAA and AAA (Fig. 3).

In addition to the MMP/TIMP system, immune cells, the renin-angiotensin-aldosterone system, the inflammatory process and oxygen free radicals play an important role in the pathogenesis of AAA [31].

The role of MMP-1 in the pathogenesis of AAA

Metalloproteinase 1 (collagenase 1; MMP-1) is an enzyme involved in the digestion of collagen fibers. Increased MMP-1 gene expression was found in patients with AAA while the level of its inhibitors was reduced [32]. Inflammatory cells are a small source of MMP-1 [33].

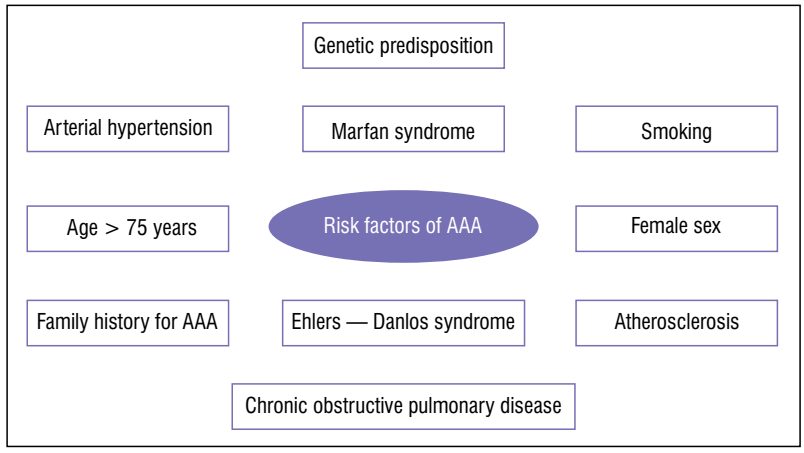


Figure 1. Risk factors for abdominal aortic aneurysm (AAA) [13, 21]

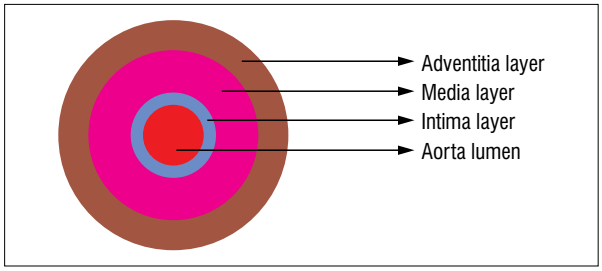


Figure 2. Schematic structure of the abdominal aorta wall

It has been shown that the presence of elevated MMP-1 concentration in the aortic wall is associated with elevated risk of rupture [34].

The role of MMP-2 in the pathogenesis of AAA

The main role of MMP-2 in human tissue is degradation of both type IV collagen, which is an important component of basal membranes, and denatured collagen [35]. MMP-2's role in abdominal aorta aneurysm relies on degradation of the intercellular substance of the aortic wall, which can lead to its rupture. Under normal conditions, the process of changes in vascular tissue is controlled by the balance between the action of MMP and their inhibition, which involves TIMPs.

Increased expression of MMP-2 has been observed not only in the blood of patients suffering from AAA but also in the AAA tissue [16], which further increased the likelihood of AAA wall rapture.

The role of MMP-3 in the pathogenesis of AAA

MMP-3 (stromelysin 1) is responsible for digesting collagen and several other extracellular matrix proteins, which are important in maintaining the structural integrity of the aortic wall and pericellular activation of proMMPs. For example it is necessary for transformation of the proMPP-1 zymogen into fully active MMP-1. Immunohistochemical studies have previously revealed the expression of stromelysin-1 in abdominal aortic aneurysm in relation to macrophages present within the aortic wall. Thus, this additionally supported the idea that aneurysm expansion is due to a chronic inflammatory process [36].

Upregulation of stromelysin-1 and TIMP-3 expression may play a significant role in the expansion of an atherosclerotic aorta to form an aneurysm. It seems plausible that excessive production of stromelysin-1 in an atherosclerotic aorta weakens the aortic wall and causes additional proteolysis by activating other latent, constitutively expressed metalloproteinases [37]. MMP-3 contributes to plaque destabilization and promotes TAA formation by degrading the elastic lamina, and therefore plays an important role in aneurysm formation. MMP-3 was shown to degrade type IV collagen, fibronectin, laminin, proteoglycan core protein, and type IX collagen [38].

Results of genetic study revealed that the 5A allele in the promoter region of the MMP-3 gene occurs more frequently in AAA patients. This study also showed a link between the 5A/5A genotype and intensity of MMP-3 gene expression. The aortic aneurysmal wall of patients, who were homozygous for the 5A-allele, contained larger quantities (> 45%) of MMP-3 protein than the wall from 5A/6A heterozygotes; suggesting that the 5A-allele causes increase in MMP-3 production in these patients [39]. Meta-analysis of genes or putative AAA-related genes showed their positive correlation between MMP-3 rs3025058 polymorphism and a higher risk of AAA development [40].

The role of MMP-9 in the pathogenesis of AAA

MMP-9, also, called gelatinase B or type IV collagenase, is the metalloproteinase, which has three repeats of a type II fibronectin domain inserted in the catalytic domain through which the proteinase interacts with gelatin, collagens, and laminins [36]. Numerous cytokines are able to regulate MMP-9 expression, but the major role in it has TNF-α. At the transcriptional level an important positive regulator is nuclear factor-κB (NF-κB) [40]. ECM proteins which are proteolytically processed by MMP-9 include collagen, elastin, fibronectin, and laminin [41].

MMP-9 is responsible for degradation of ECM proteins at the aortic wall. In the pathogenesis of AAA, a major role has inflammatory response in the endothelial, medial, and adventitial layers. Besides monocytes, other cells secreting MMP-9, such as macrophages and neutrophils, participate in this process. The activity of monocytes is modulated by proinflammatory cytokines, for example TNF-α, which can promote the secretion of MMPs via MAPK pathway [41]. Increased angiogenesis was also detected in the aneurysm wall [42] as a result of MMP-9-stimulated release of VEGF [43], the factor which stimulates angiogenesis.

Activation of TGF–β may be one of the ways in which MMP-2 and MMP-9 work together. Although it is generally believed that the activation of the TGF-βsignaling pathway offers protection against AAA development, it also has important roles in enhancing Type I and III collagen production, and increasing expression of protease inhibitors, plasminogen activator inhibitor-1 (PAI-1) and TIMP-1 [44].

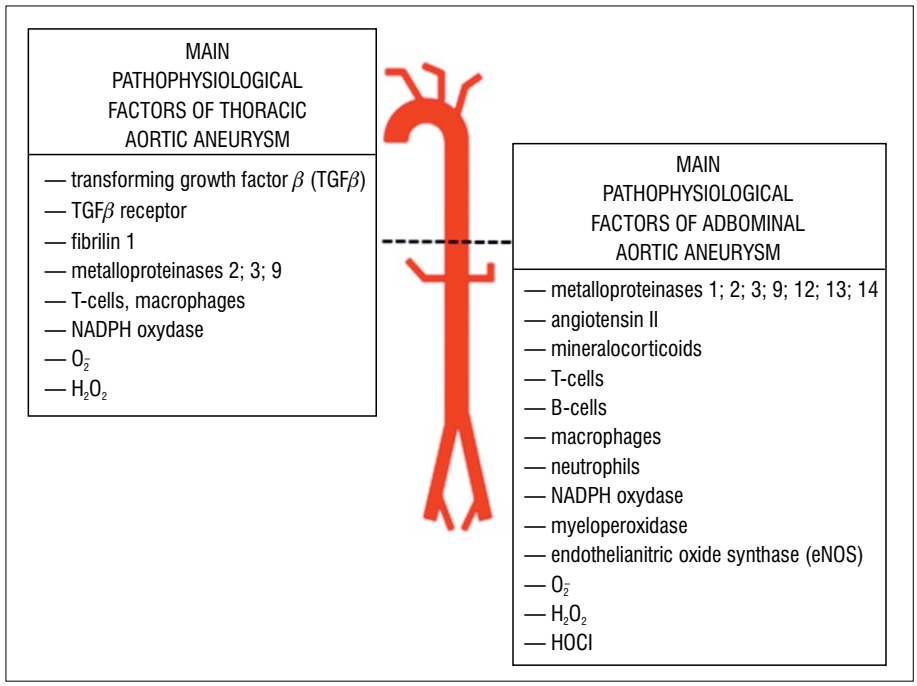


Figure 3. Factors affecting the pathophysiology of thoracic aortic aneurysm (TAA) and abdominal aortic aneurysm (AAA). Based on [31]

Correlation of MMP-9 concentration with maximum aortic diameter was considered a clinical marker of AAA growth. MMP-9 activity varies depending on the diameter of the aorta. Its expression is increased in aneurysms with a diameter of 5 to 6 or even 9 cm [45, 46].

The role of MMP-12 in the pathogenesis of AAA

The main source of MMP-12 (metalloelastase) in the aortic wall are macrophages [47]. However, the role of this metalloproteinase in the pathogenesis of AAA is not completely understood. Results of experimental studies have shown that MMP-12 knockout (KO) mice have developed AAA. Interestingly, mice with KO of *MMP-12* and *MMP-9* and KO of *MMP-9* alone did not develop AAA [48]. It is currently indicated that MMP-12 cannot be directly involved in the pathogenesis of AAA but apparently helps other MMPs in extracellular matrix degradation [31].

The role of MMP-13 in the pathogenesis of AAA

The main source of MMP-13 (collagenase 3) are SMCs in the aortic wall. MMP-13 expression is increased in AAA people, especially in symptomatic AAA and in AAA with a high risk of rupture [49, 50] In genetic studies it has been shown that polymorphism (−77A/G) is a significant independent risk factor for AAA formation. These results indicated that MMP-13 plays an important role in the pathogenesis of AAA [31, 32].

The role of MMP-14 in the pathogenesis of AAA

MMP-14 (membrane type 1 MMP) is produced by macrophages and SMCs in the aortic wall. Clinical studies have shown that patients with AAA showed elevated *MMP-14* gene expression [51]. Experimental studies have also shown that in mice with $CaCl_2$-induced AAA MMP-14 derived from macrophages played a key role in direct degradation of the extracellular matrix, which led to the development of AAA. It was found that MMP-14 directly regulated the elastolytic activity of macrophages [52].

Selected genetic-related factors associated with AAA

First reports on possible genetic background of AAA were published in 1977 when the article about three brothers, surgically treated for ruptured, previously symptomless AAA, was published [53].

In 2016 Bradley and colleagues performed a meta-analysis and systematic review of the available literature to show which factors are genuine and which may

be caused by type I errors, biases, and differences in study design [54]. The most important genetic variants are described briefly as follow:

1. 9p21 rs10757278 — one of several polymorphism clustered together in a region of chromosome 9 that has been linked to increased risk of heart disease, abdominal obesity, dyslipidemia, hypertension and, potentially, diabetes. The overall estimate of heart disease cases that may involve this SNV (or related ones nearby) is said to be 20–30% [55]. Genome-wide association studies (GWAS) have identified a 9p21 as a major risk locus for coronary artery disease and myocardial infarction. All of the listed factors can lead to development of AAA [56].

2. *SORT1* rs599839 — *SORT1* gene on chromosome 1, carries information about protein called sortilin. Sortilin is a transmembrane protein primarily found in brain tissue. It is recognized as a major player in different processes of atherogenesis. Research results suggest that sortilin has a significant role in the pathogenesis of vascular and metabolic disorders through contributions to inflammation and calcification of arterial wall. Moreover, sortilin might play role in dysregulation of lipoprotein metabolism and type II diabetes mellitus [57].

3. *LRP1* rs1466535 — association between the rs1466535 SNV in the gene of low density lipoprotein receptor-related protein 1 (*LRP1*) and abdominal aortic aneurysm was showed by GWAS conducted by Bown et al. [58]. Later this association was also confirmed by a group of Italian scientists led by Silvia Galora and Claudia Saracini [59]. Despite the evidence provided by the two reports, it is not certain if the association is specific for aneurysmal disease or the atherosclerotic process [60].

4. *MMP3* rs3025058 — SNV rs3025058 was first described in 1995 as a variant located upstream of *MMP3* and influencing the regulation of this gene expression. The role of MMP3 proteinase was presented in previous sections of this review.

5. *AGTR1* rs5186 — rs5186, a SNV, also, known as +1166A/C or A1166C is located in the 3' untranslated region of AGTR1 mRNA. It is among the most studied of over 50 SNVs in *AGTR1* [61]. AGTR1 is a part of the renin-angiotensin system. Its physiological role is regulation of blood pressure and the balance of fluids and salts in the body. Angiotensin II (created in renin-angiotensin cascade) binds to the AT1 receptor in the blood vessels and stimulates them to constrict what results in increased blood pressure. Binding of angiotensin II to the AT1 receptor also stimulates production of aldosterone, a hormone that triggers the absorption of water and salt in the kidneys. The increased amount of fluid in the body also increases blood pressure [62]. As listed previously, elevated blood pressure is a risk factor of AAA development.

6. *ACE* rs4646994 — rs4646994 is one of four SNVs representing perhaps the best studied *ACE* SNV. It is actually not a single nucleotide variant at all; instead, it is an insertion/deletion of an Alu repetitive element in an intron of the *ACE* gene. Alleles containing the insertion are called "I" alleles, and "D" alleles lack the repetitive element [63]. Function of angiotensin-converting enzyme (ACE) is catalysis of the cleavage of the angiotensin I into the active octamer the angiotensin II, which contributes to hypertension by inducing smooth muscle in the vessels to constriction and renal tubule sodium reabsorption [64].

7. *APOA1* rs964184 — The rs964184 (G;G) genotype is associated with hypertriglyceridemia [65]. The *APOA1* encodes a protein called apolipoprotein A-I (apoA-I). It is a component of high-density lipoprotein (HDL). HDL is a molecule that transports cholesterol and phospholipids through the bloodstream from the body's tissues to the liver. Once in the liver, cholesterol and phospholipids are redistributed to other tissues or removed from the body. ApoA-I attaches to cell membranes and promotes the movement of cholesterol and phospholipids from inside the cell to the outer surface. Once outside the cell, these substances combine with ApoA-I to form HDL. ApoA-I also triggers a reaction called cholesterol esterification that converts cholesterol to a form that can be fully integrated into HDL and transported through the bloodstream. Hypertriglyceridemia, which can develop easier in a group of patients with this gene variant, is a one of many causes of atherosclerosis [65].

Summary and conclusions

1. The abdominal aortic aneurysm is the most common location for this condition.
   A) The risk of developing AAA increases with age.
   B) It is more common in men. AAA rupture is associated with a high risk of death.
2. Abdominal aortic aneurysm most often is asymptomatic, which hinders its early detection and treatment.
3. The pathogenesis of AAA is complex and still not fully understood. The most important processes in the pathophysiology of AAA are degeneration and atherosclerosis of the arterial wall.
4. The factors involved in the pathogenesis of AAA and TAA are not quite the same.
5. Important compounds involved in the formation of AAA and increasing the risk of its rupture are some of the extracellular matrix metalloproteinases.
6. Genetic variants of numerous genes are associated with the risk of developing AAA.

7. More research is needed into the pathogenesis of AAA and identification of biomarkers that would enable early detection of this disease.

Conflict of interest:

None.

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The influence of compression therapy on the levels of inflammatory biomarkers in patients with chronic venous disease

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Abstract

Chronic venous disease (CVD) is defined as any morphological and functional abnormalities of long duration manifested either by symptoms and/or signs indicating the need for investigation and/or care. The pathophysiological mechanism of CVD can be characterized by reflux, obstruction, or a combination of both, which leads to increased venous pressure.

Compression therapy remains the gold standard of the conservative treatment of CVD in all stages. The possible forms of compression therapy are elastic stocking, non-elastic and elastic bandages, and intermittent pneumatic compression. Compression bandages have been proven to improve the healing of venous ulcers, in comparison with standard care without compression therapy.

In the last years, inflammation has been shown to play an important role in the pathophysiology of CVD. The influence of the altered shear stress on the endothelial cells (EC) causes EC to release inflammatory molecules, chemokines, vasoactive agents, express selectins, and prothrombotic precursors such as ICAM-1, MCP-1, MIP 1β, VCAM, L-selectin, E-selectin, IL-1β, IL-4, IL-6, IL-8, IL-12p40, IL-13, G-CSF, GM-CSF, IFN-γ, TNF-α, and MIP-1α.

Several studies have been performed to investigate the influence of compression therapy on the level of various inflammatory biomarkers in patients with CVD. In these studies level of the most inflammatory molecules, such as IL-1β, IL-6, IL-8, IL-12p40, G-CSF, GM-CSF, IFN-γ, TNF-α, VEGF, MMP 3, 8, 9 and TIMP-1 decreased after the therapy.

Key words: inflammatory biomarkers, compression therapy, chronic venous disease, inflammation

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Introduction

Chronic venous disease (CVD) is defined as any morphological and functional abnormalities of long duration manifested either by symptoms and/or signs indicating the need for investigation and/or care [1]. The prevalence of CVD has been previously investigated in many epidemiological studies that have been carried all around the world. The reported incidence of CVD ranges between 20% and 60%, depending on the region where the research was conducted, different criteria for patient selection, disease definition, different imaging techniques used, and exposure to risk factors [2]. The reported prevalence of CVD was higher in the western populations of developed regions that are exposed to various risk factors such as sedentary lifestyle, low fiber diet, or constipation [3]. More advanced stages of CVD (C3–C6 in the CEAP classification) affect about 5% of the population, and the end stages (C5–C6) of the CVD – about 1–2% [4]. The presence of CVD may be associated with lower quality of life — almost 30% of patients present with symptoms of depression [5].

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Pathophysiology of CVD

The pathophysiological mechanism of CVD can be characterized by reflux, obstruction, or a combination of both. Both lead to increased ambulatory venous pressure. Other factors may be e.g. failure of the calf and foot muscle pomp (in neuromuscular problems) [5]. The most frequent cause of venous hypertension is valvular incompetence (70–80% of cases), while isolated outflow obstruction is found in ca. 2 %. Valvular incompetence may be secondary to deep vein thrombosis in 18–25%, or due to congenital anomaly in 1–3% [6]

The role of inflammation in a CVD

In the last years, inflammation has been shown to play an important role in the pathophysiology of CVD [7]. Venous hypertension in the lower limbs leads to a vicious circle of vascular and inflammatory phenomena that increases hypertension even more. High venous pressure in the lower extremities leads to leukocyte accumulation due to leukocyte adhesion to the endothelium and migration through the endothelium of small vessels [8]. It also results in a reduction of shear stress (SS) the main regulator of endothelial activation state that promotes pathological changes of venous valves and vein wall [9]. Low SS leads to local inflammation, through the activation of endothelial cells (ECs) and leukocytes, that release vasoactive agents, express selectins, inflammatory molecules, chemokines, and prothrombotic precursors, and through the infiltration of inflammatory cells into venous walls and leaflets [10, 11]. Changes in EC signaling result in increased production of inflammatory biomarkers, e.g. chemokines, cytokines, growth factors, proteases, and others, that cause worsening of the inflammatory process [12]. Many studies report an increased expression of inflammatory markers in vitro, in pre-clinical studies, and in patients with CVD, which confirms the role of inflammation in CVD [13].

Compression therapy — a gold standard in a treatment of CVD

Compression therapy remains the gold standard of the conservative treatment of CVD in all stages, because of its non-invasive nature, ease of use, and efficacy of reducing venous hypertension which is a main pathophysiological mechanism of CVD. The possible forms of compression therapy are elastic stocking, non-elastic and elastic bandages, and intermittent pneumatic compression [5].

In the last decades, elastic stockings have been the cornerstone of conservative treatment of C0–C4 CVD. Despite their popularity, evidence of the efficacy for this type of compression remains unclear and is based on the lack of randomized controlled trials for both primary and post-thrombotic CVD [14, 15]. However, there is some evidence, based on non-RCTs and clinical experience supporting their use to improve patients' symptoms [15] and quality of life [16].

Compression bandages have been proven to improve the healing of venous ulcers, in comparison with standard care without compression therapy [17]. Types of bandages include traditional systems with elastic components and non-elastic compression systems [18]. High compression systems with a sustained compression of at least 40 mm Hg with a four-layer bandage have been shown to be more effective than the lower grades of compression [19]. Compression bandages are recommended as the initial treatment in patients with venous leg ulcers [5].

Inflammatory biomarkers in patients with CVD

In the last years, many studies confirmed an increased level of proinflammatory molecules in patients with CVD. The influence of the altered shear stress on the endothelial cells (EC) causes EC to release inflammatory molecules, chemokines, vasoactive agents, express selectins, and prothrombotic precursors [20]. ICAM-1 is a molecule responsible for the detection of changes in mechanical stress forces and SS, promoting leukocyte recruitment, adhesion, and transmigration [21]. Overexpression of ICAM-1 in EC has been shown in several studies [22, 23]. MCP-1, macrophage inflammatory protein 1β, vascular cell adhesion molecule (VCAM), as well as L-selectin, E-selectin, and ICAM-1 enhance leukocyte rolling, adhesion, and migration through the endothelium of vein wall and valve [21]. Plasma levels of VCAM-1, angiotensin-converting enzyme, endothelial leukocyte adhesion molecule, and L-Selectin are also increased in varicose veins [24, 25].

The endothelial glycocalyx (GCX) — structure responsible for the prevention of leukocyte adhesion, thrombosis, and inflammation in CVD is injured by the altered shear stress and mechanical forces on the wall of the vein, which leads to loss of GCX [26]. In the vein wall of varicose veins, there is an increased level of degraded, sulfated glycosaminoglycans, which confirms the GCX disruption [27].

Matrix metalloproteinases — proteolytic enzymes identified in many tissues and organs including the venous system, play a crucial role in tissue remodeling

and turnover of the collagen, elastin, and other proteins [28]. Overexpression of MMPs and cytokines has an important effect on the venous wall and valves causing tissue destruction with skin changes and formation of the ulcer [29, 30]. In vein samples from the patients with CVD, have been found a variety of MMPs such as: MMP-1, -2, -3, -8, -9, -12, and -13 [31]. Their role includes degradation of adventitial extracellular matrix, as well as collagen bundles and elastin in the medial layer, having also potential early effect on venous dilation [32]

Cytokines were proven to play an important role at different stages of CVD. The majority of pro-inflammatory cytokines (IL-1β, IL-4, IL-6, IL-8, IL-12p40, IL-13, G-CSF, GM-CSF, MCP-1, IFN-γ, TNF-α, MIP-1α, and MIP-1β) were found to be elevated in ulcer tissue from patients with CVD [33].

Levels of inflammatory biomarkers in patients undergoing compression therapy

Several studies were performed to investigate the influence of compression therapy on the levels of various inflammatory biomarkers in patients with CVD.

The interesting study held by Beidler et al. investigated changes in inflammatory cytokine levels in ulcer tissue from patients with CVD treated with a high-grade 3- or 4-layer compression bandage system for 4 weeks. The study group consisted of 30 limbs with untreated CVD and leg ulceration. Tissue samples were obtained using biopsy from healthy and ulcerated tissue before and after therapy. Cytokine levels were measured using a multiplexed protein assay. The majority of pro-inflammatory cytokine levels (IL-1β, IL-6, IL-8, IL-12p40, IL-13, G-CSF, GM-CSF, MCP-1, IFN-γ, TNF-α, MIP-1α, MIP-1β) were elevated in ulcer tissue, in comparison with controls. Most of the investigated molecule levels (IL-1β, IL-6, IL-8, IL-12p40, G-CSF, GM-CSF, IFN-γ, TNF-α) significantly decreased after the compression therapy. On the other hand, the level of an anti-inflammatory cytokine, IL-1Ra, increased after 4 weeks of treatment. Ulcers with a higher level of IL-1α, IL-1β, IFN-γ, IL-12p40, and GM-CSF were more likely to heal rapidly [33].

In an earlier study, Murphy et al. investigated serum levels of VEGF and TNF-α in a group of 8 patients undergoing 4 weeks of treatment with 4-layered, graduated compression therapy. Serum samples were taken from the superficial veins of the lower limb before and after the treatment. Serum from the arms of the same patients was used as a control. The level of VEGF and TNF-α were measured with ELISA assay. All patients had elevated cytokine levels before the treatment compared with the control. In each case, the reduction to below control values in the levels of VEGF and TNF-α was observed [34].

Another study, held by Gohel et al. [35], comprised 80 patients with chronic leg ulceration treated with multilayer compression bandaging. Inflammatory biomarkers were measured in the wound fluid and in the venous blood taken from the antecubital vein at recruitment and after 5 weeks as well as the size of ulceration. Levels of proinflammatory molecules were measured using the ELISA technique. Median ulcer size reduced from 4.4 cm^2 to 2.2 cm^2 after the treatment. The volume of wound fluid strongly correlated with the size of an ulcer. Among all of the investigated cytokines and factors (TNFα, IL1β, bFGF, VEGF, TGFβ 1, MMP2, MMP9) only bFGF showed a significant positive correlation between its concentration in wound fluid and an ulcer size. Changes in wound fluid TGFβ 1 concentrations inversely correlated with changes in ulcer size. Other factors did not show significant correlations with ulcer healing. Also, the correlation between the wound fluid and serum cytokine concentrations was poor [35].

In a 2008 study, Beidler et al. [36] investigated levels of matrix metalloproteinases (MMPs) in a leg ulcer tissue of patients with CVD before and after 4 weeks of high-strength compression therapy. The study group included 29 patients with untreated CVD and leg ulceration. Tissue samples were obtained by biopsies from healthy tissues and from ulcerated tissue before and after therapy. MMPs were measured using a multiplexed protein assay. MMP1, 2, 3, 8, 9, 12, and 13 levels were elevated in ulcer tissue comparing with healthy tissue. Levels of MMP3, 8, and 9 significantly decreased after the compression therapy. A decrease in MMP1, 2 and 3 levels was linked with significantly higher rates of ulcer healing at the end of treatment [36].

A more recent study, performed by Caimi et al. investigated plasma concentration levels of gelatinases (MMP-2 and MMP-9) and their inhibitors (TIMP-1 and TIMP-2) in a group of 36 patients with CVD and venous leg ulcers, before and after the treatment with a multi-layer bandaging system. The levels of gelatinases and their inhibitors were measured in fasting venous blood using an ELISA kit. A significantly higher level of gelatinases and their inhibitors was observed in patients with leg ulcers, comparing with normal controls. Healing of the ulcers after the therapy was associated with a decrease in MMP-9 and TIMP-1 levels and in MMP-2/TIMP-2 ratio compared to the baseline values. However, even after the therapy, the levels of all examined parameters were higher than in the control group [37].

Conclusions

In the last years, inflammation has been proven to play an important role in the pathophysiology of chronic venous disease.

Compression therapy remains the gold standard of the conservative treatment of CVD in all stages, and has been proven to improve the healing of venous ulcers.

Many studies reported an increased expression of inflammatory markers in vitro, in pre-clinical studies, and in patients with CVD.

Several inflammatory molecules, chemokines, vasoactive agents, selectins, and prothrombotic precursors, such as ICAM-1, MCP-1, macrophage inflammatory protein 1β, VCAM, L-selectin, E-selectin, IL-1β, IL-4, IL-6, IL-8, IL-12p40, IL-13, G-CSF, GM-CSF, IFN-γ, TNF-α, MIP-1α, as well as matrix metalloproteinases MMP-1, -2, -3, -8, -9, -12, and -13 were identified in patients with CVD.

Several studies were performed to investigate the influence of compression therapy on the level of various inflammatory biomarkers in patients with CVD.

Presented studies showed a reduction in levels of inflammatory biomarkers such as IL 1β, IL-6, IL-8, IL-12p40, G-CSF, GM-CSF, IFN-γ, TNF-α, VEGF, MMP 3, 8, 9 and TIMP-1 after the therapy.

Not all biomolecular mechanisms of the healing effect of compression therapy on venous leg ulcers have been well understood, so further studies regarding this topic may be needed.

Conflict of the interest

None

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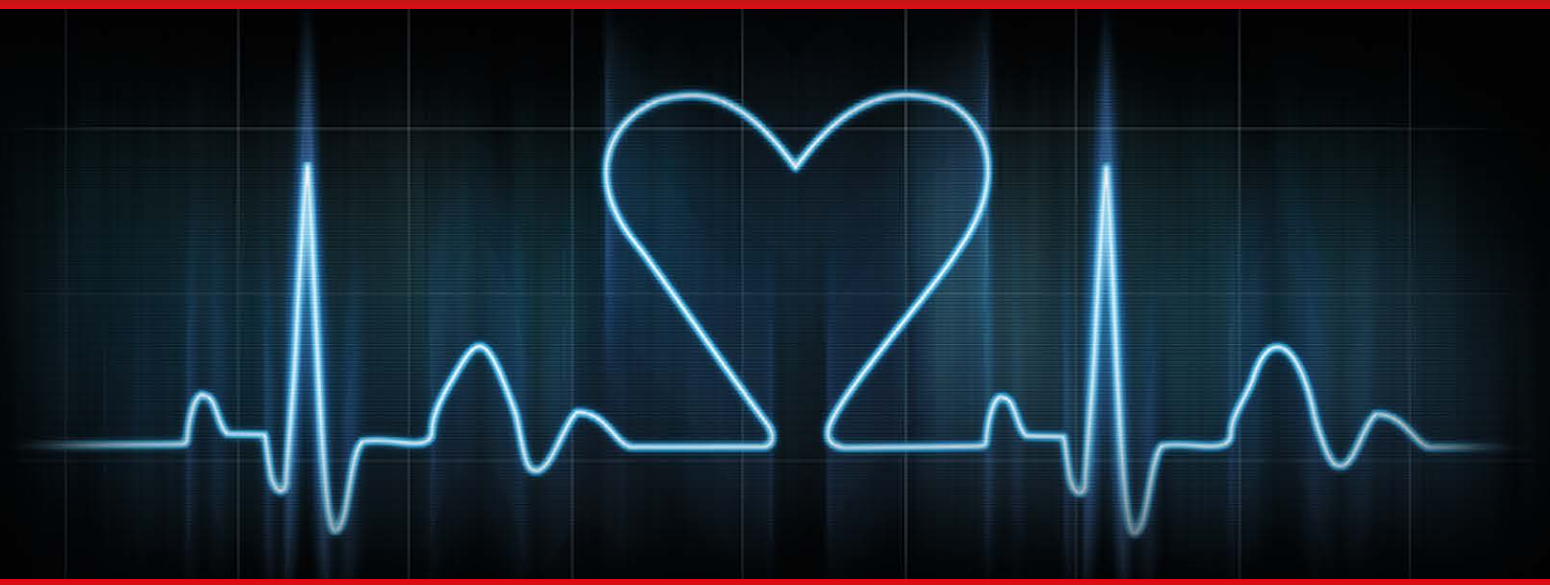
X Zaawansowany kurs hipertensjologii dla specjalistów

Kurs w formie hybrydowej



Kołobrzeg, 27–29 sierpnia 2021 roku

Szczegółowe informacje oraz rejestracja:

www.zaawansowanykurs.viamedica.pl

ORGANIZATOR

VIA MEDICA

PATRONAT MEDIALNY

tvmed

PARTNER

ikamed.pl internetowa księgarnia medyczna

21-0287.001.011

Konferencja jest skierowana do wszystkich osób zainteresowanych tematyką. Sesje satelitarne firm farmaceutycznych, sesje firm farmaceutycznych oraz wystawy firm farmaceutycznych są skierowane tylko do osób uprawnionych do wystawiania recept lub osób prowadzących obrót produktami leczniczymi — podstawa prawna: Ustawa z dnia 6 września 2001 r. Prawo farmaceutyczne (Dz. U. z 2017 r. poz. 2211., z późn. zm.)

VIRTUAL MEETING

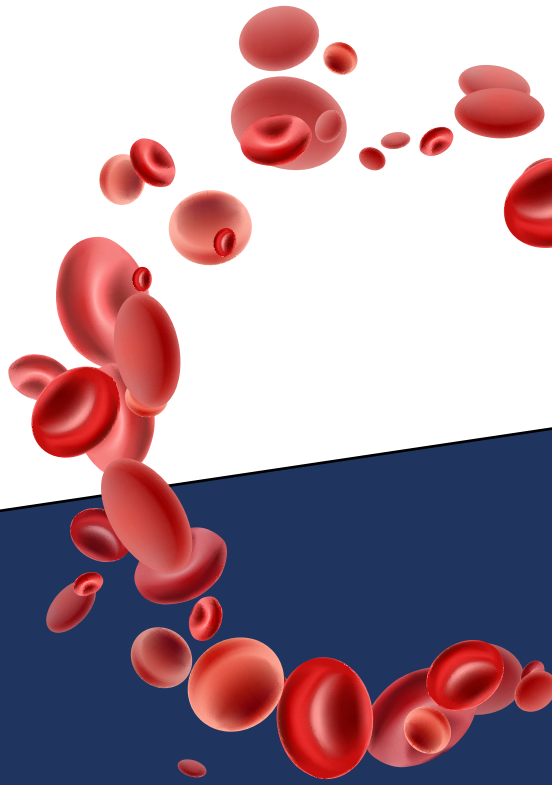
WORLD THROMBOSIS DAY
OCTOBER 13

POLSKIE TOWARZYSTWO FLEBOLOGICZNE 1992 1992 POLISH PHLEBOLOGICAL SOCIETY

Światowy Dzień Zakrzepicy pod patronatem Polskiego Towarzystwa Flebologicznego

Środa, 13 października 2021
17:30–20:00

PRZEWODNICZĄCY KOMITETU NAUKOWEGO
prof. dr hab. n. med. Zbigniew Krasiński



21-0162.001.002

Szczegółowe informacje i bezpłatna rejestracja na:

www.zakrzepica.viamedica.pl

ORGANIZATOR
VIA MEDICA

Virtual Meeting jest skierowany do osób uprawnionych do wystawiania recept lub osób prowadzących obrót produktami leczniczymi — podstawa prawna: Ustawa z dnia 6 września 2001 r. Prawo farmaceutyczne (Dz. U. z 2017 r. poz. 2211. z późn. zm.).