ISSN 1234–950X

ACTA ANGIOLOGICA

2020, Vol. 26, No. 2

POLISH JOURNAL OF VASCULAR DISEASES

JOURNAL OF POLISH SOCIETY FOR VASCULAR SURGERY

JOURNAL OF POLISH ANGIOLOGICAL SOCIETY

VIA MEDICA

www.journals.viamedica.pl/acta_angiologica

MULTIMEDIALNA PLATFORMA WIEDZY MEDYCZNEJ

tvmed

- **Ponad 5000 wyemitowanych nagrań**
- **Ponad 300 transmitowanych konferencji**
- **Ponad 2000 współpracujących z nami specjalistów**
- **Ponad 1600 godzin materiałów wideo**

Dostęp do najlepszej wiedzy medycznej w ramach jednej prostej opłaty. Warto skorzystać już dziś!

www.tvmed.pl

VIRTUAL MEETING

SOCIETAS MEDICINAE INTERNAE POLONA
1906

Konferencja pod patronatem
Łódzkiego Oddziału
Towarzystwa Internistów Polskich

28 listopada 2020 roku

FORUM INTERNISTÓW 2020

Szczegółowe informacje oraz bezpłatna rejestracja:

www.foruminternistow.viamedica.pl

ORGANIZATOR

VIA MEDICA

PATRONAT MEDIALNY

tvmed

PARTNER

ikamed.pl
internetowa księgarnia medyczna

19-0345.001.011

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.)

XVII Zjazd Polskiego Towarzystwa Nadciśnienia Tętniczego

Ryzyko sercowo-naczyniowe: nadciśnienie tętnicze, hipercholesterolemia, hiperglikemia i inne ważne czynniki ryzyka sercowo-naczyniowego

Gdańsk, 24–26 czerwca 2021 roku

Polska Filharmonia Bałtycka im. Fryderyka Chopina
ul. Ołowianka 1

www.zjazd.ptnt.pl

17zjazdptnt@viamedica.pl

58 320 94 94

ORGANIZATOR

VIA MEDICA

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

19-0290.001.011

ACTA ANGIOLOGICA

www.journals.viamedica.pl/acta_angiologica

JOURNAL OF POLISH SOCIETY FOR VASCULAR SURGERY

JOURNAL OF POLISH ANGIOLOGICAL SOCIETY

Acta Angiologica (ISSN 1234–950X) is published by VM Media sp. z o.o. VM Group sp. k., Świętokrzyska 73, 80–180 Gdańsk, Poland, tel: (+48 58) 320 94 94, fax: (+48 58) 320 94 60, e-mail: viamedica@viamedica.pl, https://journals.viamedica.pl/

Editorial Address: Department of Vascular Surgery and Angiology, Medical University of Lublin, S. Staszica 11, 20–081 Lublin, Poland

Advertising: For details on media opportunities within this journal please contact the advertising sales department, Świętokrzyska 73, 80–180 Gdańsk, Poland, tel.: (+48 58) 320 94 94; e-mail: dsk@viamedica.pl

19-0178.002.001

Acta Angiologica is indexed at: Thomson Reuters (Emerging Sources Citation Index), Index Copernicus (113,15), Scopus, EMBASE, EBSCO, Google Scholar, CrossRef, Ulrich's Periodicals Directory, Ministry of Education (20) and Polish Medical Bibliography (GBL). Website www.journals.viamedica.pl/acta_angiologica is certified by Health On the Net Foundation (www.hon.ch)

V Konferencja *online* czasopisma

FOLIA CARDIOLOGICA

27 listopada 2020 roku

Przewodnicząca Komitetów Naukowego i Organizacyjnego
prof. dr hab. n. med. Beata Wożakowska–Kapłon
Redaktor Naczelna czasopisma „Folia Cardiologica"

VIRTUAL MEETING

CZASOPISMU „FOLIA CARDIOLOGICA" PATRONUJĄ
SEKCJE POLSKIEGO TOWARZYSTWA KARDIOLOGICZNEGO:

CHORÓB SERCA U KOBIET, ECHOKARDIOGRAFII, ELEKTROKARDIOLOGII NIEINWAZYJNEJ I TELEMEDYCYNY, KARDIOLOGII DZIECIĘCEJ, KARDIOLOGII EKSPERYMENTALNEJ, INTERWENCJI SERCOWO-NACZYNIOWYCH, NIEWYDOLNOŚCI SERCA, REHABILITACJI KARDIOLOGICZNEJ I FIZJOLOGII WYSIŁKU, INTENSYWNEJ TERAPII KARDIOLOGICZNEJ I RESUSCYTACJI, RYTMU SERCA, WAD ZASTAWKOWYCH SERCA ORAZ FARMAKOTERAPII SERCOWO-NACZYNIOWEJ

Rejestracja oraz szczegółowe informacje na stronie internetowej:

www.cardiologica.viamedica.pl

Sekcja Farmakoterapii Sercowo-Naczyniowej PTK

ORGANIZATOR
VIA MEDICA

PATRONAT MEDIALNY
tvmed

PARTNER
ikamed.pl internetowa księgarnia medyczna

19-0298.001.011

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.)

ACTA
ANGIOLOGICA

2020, Vol. 26, No. 2

www.journals.viamedica.pl/acta_angiologica

Contents

VIA MEDICA

EDITORIAL

Acta Angiol
Vol. 26, No. 2, pp. 47–50
Doi: 10.5603/AA.a2020.0007

ISSN 1234–950X
www.journals.viamedica.pl/acta_angiologica

What should a surgeon know about COVID-19?

Aleksandra Krasińska[1], Małgorzata Wichrowska[1], Zbigniew Krasiński[2]

[1]Department of Ophthalmology, Poznań University of Medical Sciences, Poland

[2]Department of Vascular, Endovascular Surgery, Angiology And Phlebology, Poznań University of Medical Sciences, Poland

At the beginning of 2020, the world was informed about an outbreak caused by the new coronavirus in China. The fear of infection results mainly from the scope of the pandemic and high virulence of the pathogen, but it is also associated with ignorance and insufficient information for society and the medical community, especially those who do not deal with infectious diseases in their daily practice. Based on knowledge from previous coronavirus epidemics (SARS 2002–2003 and MERS 2012), it was difficult to predict the extent of the new pathogen and its potential infectivity, pathogenicity and mortality. As health care professionals, we should know not only how to help our infected patients, but also how to protect ourselves when we provide health services to SARS-CoV-2- positive patients and to those who need our help, regardless of the epidemic situation. This letter provides brief information for the thoracic, cardiac, and vascular surgeons' community about principles that, according to various scientific societies, can rationalize the treatment of our patients, whether infected or not.

The COVID-19 pandemic was announced by the World Health Organization (WHO) on March 11, 2020. COVID-19 (Coronavirus Disease 19) is an infectious disease caused by SARS- CoV- 2 (severe acute respiratory syndrome coronavirus 2), originally named 2019-nCoV (2019-Novel Coronavirus). The first cases were observed in Wuhan (China) in December 2019. They were described by local doctors as pneumonia of unclear etiology. On January 7, 2020, the pathogen was isolated and identified in China. SARS- CoV-2 belongs to the family of coronaviruses (*Coronaviridae*) and is classified as a beta-type coronavirus. It is an enveloped, single-stranded RNA virus, one of the largest cytopathic RNA viruses. Coronaviruses are a family of pathogenic viruses which are widespread around the world and attack both humans and animals. In humans, they mainly cause respiratory infections, which are usually mild. The concerns surrounding the new SARS-CoV-2 virus stem from the fact that, like the SARS-CoV and MERS viruses, they can cause severe respiratory distress syndromes and multi-organ failure with a potentially fatal course.

It has been speculated that the source of the primary human infection could be animals sold at a fish market in Wuhan, China, suggesting that SARS-CoV-2 is a zoonotic pathogen. The first cases of COVID-19 are patients who confirmed their presence at the said market. Currently, the droplet route is considered the main route of human-to-human transmission. However, the way of acquiring the infection is not entirely clear. From a practical point of view, it is important for surgeons that the RNA of the virus has been identified in almost all body fluids (sputum, discharge from the nose, throat, bronchial tree, conjunctival sac, tears, and stool). Both the fecal-oral and conjunctival route remain likely.

COVID-19 is a complex disease that mainly affects the lower respiratory tract. Its main symptoms are a fever and a cough that can be both dry and wet. However, fever, the most constant feature of this disease, may not be present in the elderly and in immunocompetent individuals. Other symptoms include muscle pains and general fatigue. A runny nose, sneezing and a sore throat are not specific to this disease. However, cases with different clinical symptoms such as rash, nausea, vomiting and diarrhea have been reported. Virus incubation takes 2–14 days, and median incubation period is approximately 5 days. The median time from symptom onset to death is 18 days.

Currently, tests based on the detection of viral RNA using polymerase chain reaction (PCR) in a sample taken from the upper or lower respiratory tract or serum are used to confirm the infection. Laboratory tests show lymphopenia and elevated lactate dehydrogenase and transaminases. SARS-CoV-2 infection cannot be diagnosed on the basis of imaging studies.

Address for correspondence: Aleksandra Krasińska, Katedra i Klinika Okulistyki Uniwersytetu Medycznego im. Karola Marcinkowskiego w Poznaniu, e-mail: alex.krasinska@gmail.com

Table 1. Pre-operative TRIAGE

OPERATE	POSTPONE, IF POSSIBLE	POSTPONE
AAA: • ruptured/symptomatic AAA or TAAA • infection-related anastomotic aneurysms or vascular graft infection	**AAA and TAAA:** > 6.5 cm	**AAA:** AAA < 6.5 cm
Peripheral artery aneurysms: • symptomatic peripheral or visceral artery aneurysm • pseudoaneurysm (when treatment is not possible: thrombin injection or compression, rapidly expanding or multi-chamber aneurysms)	**Peripheral artery aneurysms:** • asymptomatic peripheral or visceral artery aneurysm	
Aortic dissecting aneurysm: • acute dissection or impaired blood supply		
Acute aortic syndromes — not reviously mentioned: • aortoduodenal fistula with septic/ /hemorrhagic shock or signs of impending rupture		
Vascular graft complications: • arterial prosthesis infection without overt sepsis, or hemorrhagic shock, or impending hemorrhage **Carotid stenosis:** • symptomatic carotid stenosis — classic endarterectomy or revascularization via carotid puncture	**Vascular graft complications:** • Repair procedures in significant/ /symptomatic restenosis	**Vascular graft complications:** • asymptomatic stenosis of the vascular graft or in-stent restenosis
Dialysis: • vascular access thrombosis or malfunction • vascular access infection and ulceration • tunneled dialysis catheters • kidney failure, requiring dialysis	**Dialysis:** • fistula revision for steal syndrome or ischemia • angiographic examination of malfunctional fistula (blood supply disorders) • creation of native fistulas or using grafts — end-stage renal disease, stage 4 or 5	**Carotid stenosis:** • asymptomatic carotid artery stenosis
Acute visceral artery occlusion	**Chronic visceral artery occlusion**	
Peripheral vascular disease • acute limb ischemia • limb ischemia — progressive ischemia, colliquative necrosis, gangrene • fasciotomy for compartment syndrome	**Peripheral vascular disease** • Chronic limb-threatening ischemia, pain at rest or ulceration	**Peripheral vascular disease:** • Angiography or endovascular procedures in intermittent claudication syndrome • Classic (open) surgery in the treatment of intermittent claudication
	Thrombolytic treatment: venous or arterial thrombosis	
	TOS: • Symptomatic thoracic outlet syndrome (TOS) with acute venous or arterial thrombosis and severe edema	**TOS:** • Thoracic outlet syndrome, neurogenic
Trauma: • Traumatic injury with hemorrhage or ischemia		

→

Table 1. Cont. Pre-operative TRIAGE

OPERATE	POSTPONE, IF POSSIBLE	POSTPONE
Venous: • acute iliofemoral deep venous thrombosis with *phlegmasia*	**Venous:** • inferior vena cava filter placement • massive iliofemoral venous thrombosis in oligosymptomatic patients • procedures in patients with leg ulcers	**Venous:** • asymptomatic May-Thurner syndrome • removal of the filter from the inferior vena cava • varicose vein surgery or saphenous vein ablation
Wounds/Gangrene/Amputations: • due to infection/necrosis (major amputations) • amputations in patients for whom revascularization is not possible	**Wounds/Gangrene/Amputations:** surgical debridement • wounds requiring skin grafting • toes amputations due to ischemia or gangrene	
Others: • surgery or embolization for uncontrolled bleeding in unstable patients	**Others**: • surgery or embolization for bleeding in stable patients • vascular ports • vascular-port-related complications	

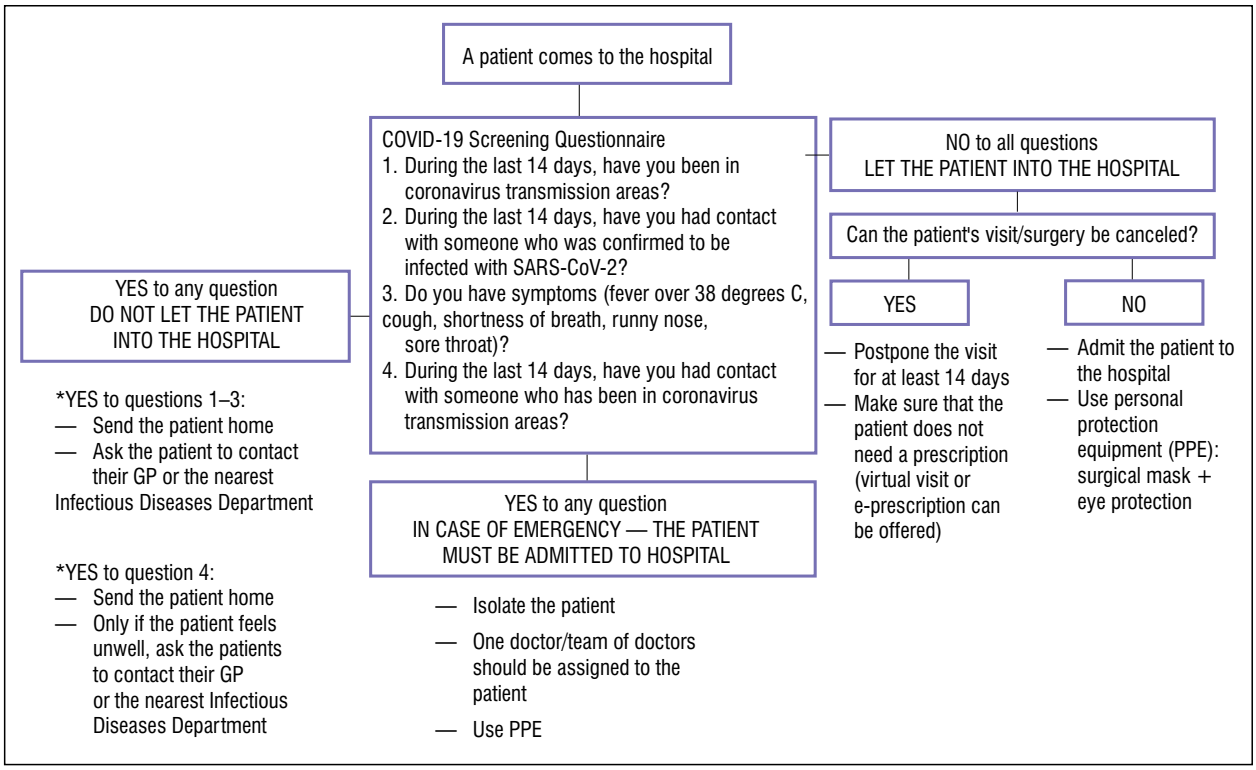

Figure 1. Pre-admission TRIAGE

There is currently no causal treatment. Conservative treatment, antipyretic drugs, fluid therapy to maintain hemodynamic balance and oxygen therapy are applied. Lung fibrosis may develop during the disease, but opinions as to the pathomechanism of these lesions are divided – it is not clear whether they result from the course of the disease or are iatrogenic, caused by high oxygen concentrations during the patient's oxygen therapy. There are studies suggesting the effectiveness of antimalarial drugs (chloroquine) in alleviating the

course of the disease. In Poland, Arechin (cholorochine) has been registered for the treatment of COVID-19. Research is also underway on the usefulness of retroviral drugs used for the treatment of HIV infection (in some countries they are already used in supportive therapy).

Due to the lack of causal treatment, we should focus primarily on prevention. Our activities in the field of cardiac and vascular surgery regarding patients with COVID-19 or suspected patients should be based on simple and clear principles.

General rules that can be implemented:

1. Consider nonsurgical treatment, if possible.
2. For a patient suspected of COVID-19, wait for the test result.
3. Aerosol-generating procedures should be performed while wearing full personal protective equipment: an N95 mask, goggles and a protective suit. The aerosol-generating procedures include: intubation, extubation, bronchoscopy, cauterization, laparoscopy, thoracoscopy, and endoscopy.
4. There are currently no conclusive data on the advantage of laparoscopy or classical open surgery in terms of the risk of coronavirus infection. However, the surgeon should make their own decision based on the safety criteria (considering both their own safety and that of the patient) and their own experience.
5. Consider creating a team to decide whether an operation is justified, based on the triage criteria. The team should consist of a surgeon, an anesthesiologist and a nurse.

The detailed recommendations we propose are based on the guidelines of the American College of Surgeons, Society for Vascular Surgery and the recommendations of the Polish Society of Ophthalmologists. In order to maximize the safety of the patient and surgeon in the era of the COVID-19 epidemic, it is recommended:

Level 1

1. Elective admissions to hospital wards and patient visits to clinics should be suspended and surgical procedures limited only to urgent/acute cases.
2. No visitors should be allowed in the hospital.
3. Telemedicine — as far as possible, services for patients can be provided using electronic devices – prescription extension/issuing exemptions.
4. Pre-admission TRIAGE — when a patient has to be hospitalized, he/she should complete an epidemiological questionnaire before entering the hospital.
5. Limit aerosol generating procedures.
6. Staff training to reduce the risk of infection.

Level 2

1. Disinfection of staff hands and equipment of patient examination rooms.
2. Medical personnel should be careful about symptoms such as fever, chills, weakness, muscle pain, sore throat, diarrhea, cough, runny nose, vomiting, and pneumonia. It is also recommended to take body temperature daily.

Level 3

1. Pre-operative TRIAGE (Table 1).
2. Masks should be worn by both medical staff and patients.
3. Separate rooms for patients suspected of or diagnosed with COVID-19, including: a separate operating room, space in ICU and other areas for infected patients.
4. COVID-19 patients should be separated from other patients.
5. Medical personnel should be assigned to only care for COVID-19 patients.

Conflict of interest

None.

References:

1. World Health Organization. WHO Director-General's opening remarks at the media briefing on COVID-19 [Internet]. 2020 Mar 11; https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200323-sitrep-63-covid-19.pdf?sfvrsn=b617302d_2
2. Polskie Towarzystwo Okulistyczne. Rekomendacje PTO dotyczące postępowania z pacjentem okulistycznym w czasie epidemii COVID-19 [Internet]. 2020 Mar 26; https://www.termedia.pl/zalecenia/Rekomendacje-PTO-dotyczace-postepowania-z-pacjentem-okulistycznym-w-czasie-epidemii-COVID-19,37317.html
3. American College of Surgeons. COVID-19: Elective Case Triage Guidelines for Surgical Care [Internet]. 2020 Mar 24. Available from: https://www.facs.org/covid-19/clinical-guidance/elective-case
4. Guan W, Ni Z, Hu Y, Liang W, Ou C, He J, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med [Internet]. 2020 Feb 28; https://doi.org/10.1056/NEJMoa2002032
5. Lai THT, Tang EWH, Chau SKY, Fung KSC, Li KKW. Stepping up infection control measures in ophthalmology during the novel coronavirus outbreak: an experience from Hong Kong. Graefe's Archive for Clinical and Experimental Ophthalmology [Internet]. 2020 Mar 3; https://doi.org/10.1007/s00417-020-04641-8
6. Society for Vascular Surgery. COVID-19 Resources for Members [Internet]. 2020 Mar 31. Available from: https://vascular.org/news-advocacy/covid-19-resources#Guidelines&Tools
7. Chan JF-W, Yuan S, Kok K-H, To KK-W, Chu H, Yang J, et al. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. The Lancet. 2020; 395(10223): 514––523.

VIA MEDICA

ORIGINAL ARTICLE

Acta Angiol
Vol. 26, No. 2, pp. 51–57
Doi: 10.5603/AA.2020.0009

ISSN 1234–950X
www.journals.viamedica.pl/acta_angiologica

The association between vascular risk factors and the occurrence of non-thrombotic iliac vein lesions in patients with chronic venous disorders

Radosław Krzyżański, Łukasz Dzieciuchowicz

Department of Vascular Surgery and Vascular Diseases, Institute of Medical Sciences, Collegium Medicum, University of Zielona Góra, Poland

Abstract

Introduction: *Recently non-thrombotic iliac vein lesions (NIVL) due to their possible role in chronic venous insufficiency on one side and to the development of endovascular venous techniques on the other side have gained much interest. The purpose of this study was to establish if vascular risk and anthropometric factors are associated with the occurrence of NIVL in patients with chronic venous disorders.*

Material and methods: *Thirty-three patients (8 men and 25 women) of the median age of 48 years with primary varicose veins that were qualified for great saphenous veins high ligation and stripping were included. The data concerning age, sex, body mass, height, body mass index, body surface area, hypertension, hypercholesterolemia, smoking and diabetes have been collected. During the varicose vein surgery, both iliac venous axis were interrogated with intravascular ultrasound. Percentage of stenosis of interrogated veins was calculated. The association between analyzed factors and morphology of iliac veins was statistically determined.*

Results: *In a univariate analysis age negatively correlated with left common iliac vein (LCIV) stenosis and male sex, greater weight and body surface area and hypertension were associated with lesser stenosis of left external iliac vein. In a multivariate analysis, only age significantly negatively correlated with LCIV stenosis ($p = 0.027$). There was a correlation of borderline statistical significance between female sex and LCIV stenosis ($p = 0.073$). No other correlations were observed.*

Conclusions: *Except for age and possibly sex, there is no association between NIVL and other anthropometric and vascular risk factors.*

Key words: intravascular ultrasound, non-thrombotic iliac vein lesions, primary varicose veins

Acta Angiol 2020; 26, 2: 51–57

Introduction

Chronic non-thrombotic iliac vein lesions (NIVL) described by May and Turner in 1957 develop as a consequence of compression of iliac vein, predominantly left common iliac vein, between artery and bones [1]. As suspected earlier by Virchov and McMurrich, they may predispose to deep venous thrombosis, but they also may contribute to a wide range of symptoms of chronic venous disorders (CVD) [2, 3]. Since nowadays these lesions can be treated by angioplasty and stenting their diagnosis may have important treatment implications. In distinction to venous reflux or obstruction in below inguinal ligament segment, NIVL are more difficult to diagnose and for that purpose usually more sophisticated and/or invasive tests such as computed tomography, magnetic resonance imaging, contrast phlebography or intravascular ultrasound is required. Taking into account the widespread prevalence of CVD, peaking to 40–50% of western populations, it is obvious and even inappropriate to perform these tests in all patients with the sign and symptoms of the disease [4–6]. Thus,

Address for correspondence: Radosław Krzyżański, Department of Vascular Surgery and Vascular Diseases, Institute of Medical Sciences, Collegium Medicum, University of Zielona Góra, Zyty 26, 65–046 Zielona Góra, Poland, e-mail: radzinek@gmail.com

the identification of clinical factors that would point to the possibility of the existence of such lesions would be helpful in the selection of CVD patients for further, more sophisticated imaging tests. Since the principal cause of this lesion is the compression of the iliac veins, most commonly left common iliac vein, between the artery and bone we hypothesized that either factor affecting a body habitus such as demographics and body size or factors affecting behaviour of the arteries such as hypertension, diabetes, hypercholesterolemia or smoking may have an influence on occurrence of NIVL.

The purpose of the study was to determine an association between clinical factors and occurrence and severity of non-thrombotic iliac vein lesions in patients with chronic venous disorders.

Material and methods

The protocol of the study was approved by the institutional bioethical committee. All of the enrolled patients gave informed consent for participation in the investigation.

The study included patients presenting with unilateral primary varicose veins (PVV) associated with great saphenous vein (GSV) incompetence, scheduled for GSV ligation and striping. Before the inclusion, a clinical examination and a duplex Doppler of the lower limb venous system was performed.

The following exclusion criteria have been adopted: history or ultrasound signs of proximal deep venous thrombosis, patients under 18 years of age, pregnancy and breastfeeding, severe chronic venous insufficiency defined as the C4b-C6 class of CEAP classification [7], chronic and acute lower limb ischemia, known thrombophilia or other coagulation disorders, lymphedema, any acute or chronic inflammatory disease, active cancer or history of chemo- or radiotheraphy, symptomatic coronary artery disease, history of major pelvic or retroperitoneal surgery or trauma, aortic or iliac aneurysms or portal hypertension, patients with cirrhosis.

Thirty-three patients, 8 men and 25 women were included. The median age of the patients was 48.2 ± 13.8 years. Before the procedure, the patients' weight and height were determined and body mass index (BMI) and body surface area (BSA) were calculated. The data concerning following vascular risk factors: hypertension, hypercholesterolemia, smoking and diabetes were collected.

During the varicose vein surgery, an intravenous ultrasound interrogation of inferior vena cava and both right and left common and external iliac veins was performed with Volcano s5 Imaging System (Volcano Corporation, Rancho Cordova, CA, USA) according to the technique described in the literature [8]. In short, through a 9Fr introducer sheath inserted under direct vision into proximal GSV at the operated side and through ultrasound-guided percutaneous puncture at the non-operated side, a Visions PV.035 catheter, with 10MHz frequency transducer, and the maximum imaging diameter of 60 mm was advanced over a guidewire, at the level of the right atrium. During the manual pull-back, the veins of interest were interrogated with IVUS and the images obtained were archived on the hard drive of the device and DVD.

The morphometric analysis was carried out on the Volcano s5 Imaging System, using the standard software installed on the device. Inferior vena cava (IVC) and both, left and right, common iliac veins (CIV) and external iliac veins (EIV) were measured. In each analyzed vein cross-sectional area (CSA) of a non-stenotic segment of the vessel and of the most stenosed segment were determined and denominated a reference cross-sectional area (ref-CSA) and a Minimal Lumen Area (MLA), respectively (Fig. 1). While determining the ref-CSA the areas of venous confluence were excluded from the measurement. Percentage of stenosis (S%) of each analyzed vessel was determined according to the following formula:

$$S\% = (\text{ref-CSA} - \text{MLA}) / \text{ref-CSA} \times 100$$

In the further analysis, the influence of the vascular risk factors, anthropometric and demographic factors on the morphological parameters of examined veins were studied.

Statistical analysis

- For quantitative variables mean, SD, median, quartiles and range were shown.
- For qualitative variables, absolute and percentage distributions were shown.
- Quantitative variables were compared between two groups by the means of t-Student (in case of normality of distribution in both groups) and Mann-Whitney test (otherwise).
- Correlations between quantitative variables were analyzed with Spearman's correlation coefficient.
- Normality was checked with the Shapiro-Wilk test.
- A linear regression model was used for a multivariate analysis.
- Significance level was set at 0,05.
- Analysis was conducted in R package, version 3.2.3.

Results

The procedure was carried out according to the protocol in all included patients. Fourteen (43%) of the thirty-three patients enrolled in the study had

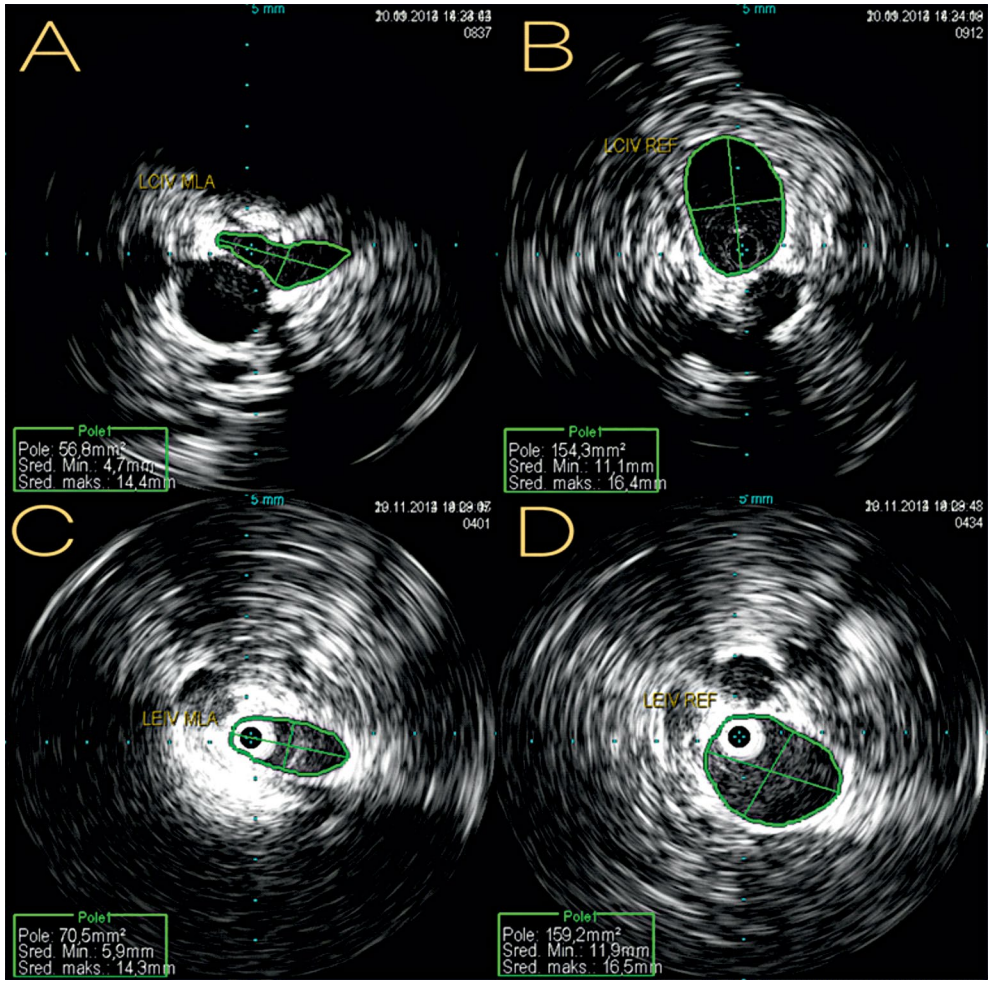

Figure 1. An intravascular ultrasound (IVUS) images of left common iliac vein (LCIV) and external iliac vein (LEIV) showing a minimal lumen area (MLA) (panels A and C) and a reference cross-sectional area (REF) (panels B and D)

varicose veins in the left lower limb. The mean height, body weight, body mass index (BMI) and body surface area (BSA) were 170 (9.2) cm, 79 (13.2) kg, 27.3(4.2) kg/m^2 and 1.9 (0.2) m^2, respectively. The prevalence of vascular risk factors is presented in Table 1. The median values of S% of the examined veins limb were 68.65 (48.43–78.99) % for LCIV, 45.47 (38.03–57.8) % for LEIV, 34.45 (24.44–48.18) % for RCIV and 45.24 (36.05–57.42) % for REIV.

In the univariate analysis with regard to common iliac veins, there was a statistically significant, moderate and negative correlation between LCIV stenosis and age of the patients (Fig. 2). None of the other analyzed anthropometrics and vascular risk factors had a statistically significant influence on the stenosis of common iliac veins. Since none of the patients had diabetes its influence could not be analyzed. The details are presented in Tables 2 and 3. With regard to external iliac veins male sex and the presence of hypertension was related to lesser LEIV stenosis and there was a statistically significant, moderate and negative correlation between LEIV stenosis and weight and BSA (Figs 3, 4). None of the other analyzed anthropometrics and vascular risk factors had a statistically significant influence on the stenosis of external iliac veins. The details are presented in Tables 3 and 4.

Table. 1. The prevalence of vascular risk factors in the examined group of patients

Clinical factor	All patients n (%)	Female group n (%)	Male group n (%)
Hypertension	6 (18.18)	3 (12)	3 (37.5)
Hypercholesterolemia	4 (12.1)	3 (12)	1 (12.5)
Smokers	10 (30.30)	8 (32)	2 (25)
Diabetes	0 (0)	0 (0)	0 (0)

The multivariate analysis confirmed a statistically significant, negative correlation between LCIV and age

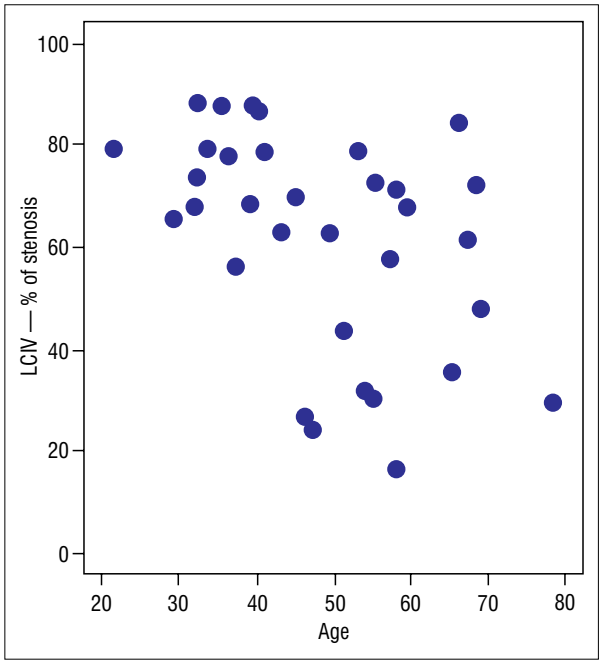

Figure 2. A scatterplot presenting a correlation between the percentage of stenosis of left common iliac vein (LCIV) and age of the patients. Spearman coefficient r = –0.47, p = 0.01

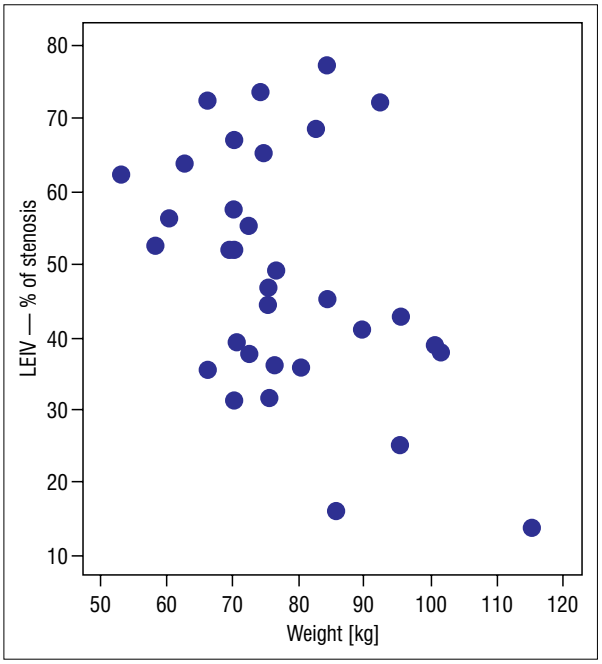

Figure 3. A scatterplot presenting a correlation between the percentage of stenosis of left external iliac vein (LEIV) and weight of the patients. Spearman coefficient r = –0.37, p = 0.04

Table 2. Stenosis of the left (LCIV) and right (RCIV) common iliac veins in relation to the presence of vascular risk factors

	LCIV – % S		RCIV – % S	
	Median (Q1-Q3)	p	Median (Q1-Q3)	p
Men	60.54 (53.49–69.08)	p = 0.254	32.84 (26.98–42.52)	p = 0.984
Women	70.16 (48.43–79.47)		34.45 (21.5–49.76)	
Hypertension	59.86 (41.69–69.09)	p = 0.398	37.17 (16.77–49.98)	p = 0.838
No hypertension	68.93 (52.55–79.12)		34.45 (24.62–46.45)	
Hypercholesterolemia	71.69 (68.08–74.67)	p = 0.477	15.61 (11.44–29.22)	p = 0.183
No hypercholesterolemia	67.11 (47.31–74.45)		31.39 (26.22–44.64)	
Smokers	65.96 (56.67–78.09)	p = 0.432	40.58 (26.69–44.71)	p = 0.967
No smokers	71.51 (61.83–79.47)		34.45 (24.79–49.76)	

Table 3. Correlation of stenosis of left common iliac vein (LCIV), left external iliac vein (LEIV), right common iliac vein (RCIV) and right external iliac vein (REIV) with anthropometrics

Correation with	LCIV – % S		LEIV – % S		RCIV – % S		REIV – % S	
	Coefficient	p	Coefficient	p	Coefficient	p	Coefficient	p
Age	–0.466	0.006	–0.258	0.147	–0.08	0.656	–0.048	0.79
height	0.16	0.374	–0.228	0.202	–0.019	0.917	0.283	0.111
weight	0.109	0.545	–0.365	0.036	0.03	0.869	0.046	0.801
BMI	–0.028	0.875	–0.234	0.189	–0.102	0.572	0.01	0.956
BSA	0.133	0.459	–0.377	0.031	0.036	0.842	0.097	0.592

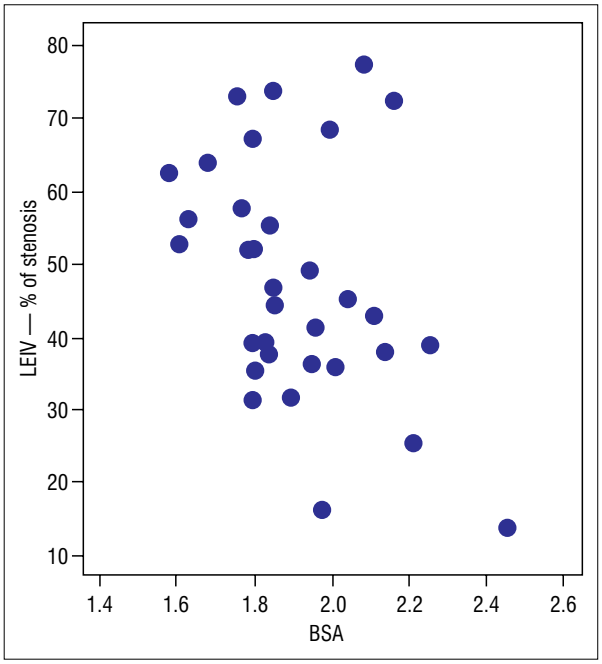

Figure 4. A scatterplot presenting a correlation between the percentage of stenosis of left external iliac vein (LEIV) and body surface area (BSA) of the patients. Spearman coefficient r = –0.38, p = 0.03

(p = 0.029). There was also a borderline statistical significance (p = 0.073) trend towards greater LCIV stenosis in women. No other statistically significant correlations were observed. The details are presented in Table 5.

Discussion

To the best of our knowledge, this is the first published study that analyzed the association between anthropometrics and vascular risk factors and the occurrence of non-thrombotic iliac vein stenosis. To determine the presence and severity of iliac vein stenoses an intravascular ultrasound was used that is considered the most sensitive modality to diagnose these lesions [9–12]. The main findings of this study are that except for age and possibly gender there are not relations between non-thrombotic iliac veins stenosis and vascular risk and anthropometric factors. The multivariate analysis confirmed a negative correlation between LCIV and age There was also a borderline statistical significance trend towards greater LCIV stenosis in women. With regard to LEIV though the univariate analysis has shown correlations between male sex, hypertension, greater

Table 4. Stenosis of left (LEIV) and right (REIV) external iliac veins in relation to the presence of vascular risk factors

	LEIV – % S		REIV – % S	
	Median (Q1-Q3)	p	Median (Q1-Q3)	p
Men	37.23 (33.64–40.86)	p = 0.036	51.73 (42.9–56.54)	p = 0.445
Women	52.23 (39.56–62.68)		44.1 (33.01–59.06)	
Hypertension	37.23 (21.55–38.28)	p = 0.027	45.39 (38.66–51.67)	p = 0.633
No hypertension	49.31 (39.54–63.45)		45.24 (35.72–58.98)	
Hypercholesterolemia	37.48 (27.9–50.64)	p = 0.477	46.8 (36.75–58)	p = 0.794
No hypercholesterolemia	46.2 (37.88–58.12)		41.5 (32.88–58.94)	
Smokers	46.93 (38.36–53.13)	p = 1	54.46 (38.33–56.98)	p=0.483
No smokers	45.47 (36.28–62.68)		42.53 (36.05–58.9)	

Table 5. Linear regression model of the influence of vascular risk factors and anthropometrics on the stenosis (S%) of LCIV and LEIV in the analyzed group of patients

	LCIV – % S				LEIV– % S			
	Coefficient	SE	t	p	Coefficient	SE	t	p
Female sex (Males as reference)	20.854	11.192	1.863	p = 0.073	5.921	8.955	0.661	p = 0.514
Age [years]	–0.725	0.315	–2.299	p = 0.029	–0.18	0.252	–0.713	p = 0.482
Weight [kg]	–1.178	1.299	–0.907	p = 0.372	–0.609	1.039	–0.586	p = 0.563
BSA	121.685	96.656	1.259	p = 0.219	19.772	77.334	0.256	p = 0.8
Hypertension	11.793	11.479	1.027	p = 0.313	–7.874	9.184	–0.857	p = 0.399

weight and greater BSA and lesser LEIV stenosis, these correlations were not confirmed in the multivariate analysis which means that none of these factors was an independent predictor of LEIV stenosis. Since women weigh less, are shorter and are less frequently hypertensive then men it might have pointed to a tendency towards greater LEIV stenosis in them. However further studies are required to confirm this speculation.

The negative correlation between age and left iliac vein stenosis hasbeen previously observed. In a study of 50 consecutive abdominal computed tomography scans performed for abdominal pain a moderate negative correlation between left iliac vein compression and age, the patients were found [13]. The question arises how this negative correlation between LCIV stenosis and age that at first glance seems counterintuitive can be explained. One would think that with age the arteries become wider, stiffer and more calcified and the vertebral column more deformed that would increase the compression between these structures. However, this not the case. The diameter of iliac artery increases with age, but it does not increase the compression of LCIV [13]. And as it has been shown in the present study the atherosclerotic risk factors such as hypertension, hypercholesterolemia and smoking are not associated with iliac vein compression. Interesting data comes from the study that compared iliac vein compression between 100 patients with abdominal aortic aneurysm with 100 patients without an abdominal aneurysm. The iliac vein compression was significantly decreased in patients with abdominal aortic aneurysm [14]. The authors of that study contributed to this finding to increased tortuosity of the iliac arteries. But the fact is that the patients without abdominal aortic aneurysm were significantly younger than those with aneurysm what could be associated with greater compression of the iliac vein.

The most probable explanation of decreasing of iliac vein compression with age is a change in the geometry of the spine. It has been demonstrated that together with age there is a loss of lumbar lordosis [15, 16]. And this phenomenon may increase the distance between vertebral column and iliac artery thus decreasing the compression of iliac vein.

The greater LCIV compression in women was also documented in the aforementioned study of 50 consecutive abdominal computed tomography scans [13]. Women also prevail in the groups of patients undergoing stenting of the iliac vein [17]. It was also observed that lordosis is greater in women what may explain the observed trend towards greater LCIV compression [18, 19].

In conclusion, the younger age remains the only proved clinical factor associated with non-thrombotic iliac vein compression. Further studies are required to determine the mechanism of this association and the influence of gender.

Conflict of interest

None.

References:

1. May R, Thurner J. The Cause of the predominantly sinistral occurrence of thrombosis of the pelvic veins. Angiology. 2016; 8(5): 419–427, doi: 10.1177/000331975700800505.
2. Virchow R. Uber die Erweiterung kleiner Gefasse. Arch Path Anat. 1851; 3: 427.
3. MCMURRICH J. The occurrence of congenital adhesions in the common iliac veins and their relation to the thrombosis of the femoral and iliac veins. Am J Med Sci. 1908; 135(3): 342–345, doi: 10.1097/00000441-190803000-00004.
4. Carpentier PH, Maricq HR, Biro C, et al. Prevalence, risk factors, and clinical patterns of chronic venous disorders of lower limbs: a population-based study in France. J Vasc Surg. 2004; 40(4): 650–659, doi: 10.1016/j.jvs.2004.07.025, indexed in Pubmed: 15472591.
5. Sisto T, Reunanen A, Laurikka J, et al. Prevalence and risk factors of varicose veins in lower extremities: mini-Finland health survey. Eur J Surg. 1995; 161(6): 405–414, indexed in Pubmed: 7548376.
6. Lee AJ, Robertson LA, Boghossian SM, et al. Prevalence of venous reflux in the general population on duplex scanning: the Edinburgh vein study. J Vasc Surg. 1998; 28(5): 767–776, doi: 10.1016/s0741-5214(98)70051-5, indexed in Pubmed: 9808843.
7. Eklöf Bo, Rutherford R, Bergan J, et al. Revision of the CEAP classification for chronic venous disorders: Consensus statement. Journal of Vascular Surgery. 2004; 40(6): 1248–1252, doi: 10.1016/j.jvs.2004.09.027.
8. Dzieciuchowicz Ł, Krzyżański R, Kruszyna Ł, et al. Prevalence of non-thrombotic iliac vein lesions in patients with unilateral primary varicose veins. Eur J Vasc Endovasc Surg. 2016; 51(3): 429–433, doi: 10.1016/j.ejvs.2015.11.012, indexed in Pubmed: 26739803.
9. Hingorani A, Alhabouni S, Ascher E, et al. Role of IVUS versus venograms in assessment of iliac-femoral vein stenosis. Journal of Vascular Surgery. 2010; 52(3): 804, doi: 10.1016/j.jvs.2010.06.029.
10. Neglén P, Raju S. Intravascular ultrasound scan evaluation of the obstructed vein. J Vasc Surg. 2002; 35(4): 694–700, doi: 10.1067/mva.2002.121127, indexed in Pubmed: 11932665.
11. Montminy M, Thomasson J, Tanaka G, et al. A comparison between intravascular ultrasound and venography in identifying key parameters essential for iliac vein stenting. Journal of Vascular Surgery: Venous and Lymphatic Disorders. 2019; 7(6): 801–807, doi: 10.1016/j.jvsv.2019.03.015.
12. Gagne PJ, Tahara RW, Fastabend CP, et al. Venography versus intravascular ultrasound for diagnosing and treating iliofemoral vein obstruction. J Vasc Surg Venous Lymphat Disord. 2017; 5(5): 678–687, doi: 10.1016/j.jvsv.2017.04.007, indexed in Pubmed: 28818221.

13. Kibbe MR, Ujiki M, Goodwin AL, et al. Iliac vein compression in an asymptomatic patient population. J Vasc Surg. 2004; 39(5): 937–943.
14. Moreland NC, Ujiki M, Matsumura JS, et al. Decreased incidence of left common iliac vein compression in patients with abdominal aortic aneurysms. J Vasc Surg. 2006; 44(3): 595–600, doi: 10.1016/j.jvs.2006.05.046, indexed in Pubmed: 16950440.
15. Dreischarf M, Albiol L, Rohlmann A, et al. Age-related loss of lumbar spinal lordosis and mobility--a study of 323 asymptomatic volunteers. PLoS One. 2014; 9(12): e116186, doi: 10.1371/journal.pone.0116186, indexed in Pubmed: 25549085.
16. Pries E, Dreischarf M, Bashkuev M, et al. The effects of age and gender on the lumbopelvic rhythm in the sagittal plane in 309 subjects. J Biomech. 2015; 48(12): 3080–3087, doi: 10.1016/j.jbiomech.2015.07.030, indexed in Pubmed: 26294355.
17. Raju S, Neglen P. High prevalence of nonthrombotic iliac vein lesions in chronic venous disease: a permissive role in pathogenicity. J Vasc Surg. 2006; 44(1): 136–43; discussion 144, doi: 10.1016/j.jvs.2006.02.065, indexed in Pubmed: 16828437.
18. Arshad R, Pan F, Reitmaier S, et al. Effect of age and sex on lumbar lordosis and the range of motion. A systematic review and meta-analysis. J Biomech. 2019; 82: 1–19, doi: 10.1016/j.jbiomech.2018.11.022, indexed in Pubmed: 30503255.
19. Leven D, Merrill R, Kim J, et al. Fundamental differences and changes in pelvic parameters depending on age, gender and race. The Spine Journal. 2016; 16(10): S277, doi: 10.1016/j.spinee.2016.07.386.

VIA MEDICA

ORIGINAL ARTICLE

Acta Angiol
Vol. 26, No. 2, pp. 58–64
Doi: 10.5603/AA.2020.0010

ISSN 1234–950X
www.journals.viamedica.pl/acta_angiologica

Prognostic significance of serum potassium level for major adverse cardiac events and death in patients with coronary atherosclerotic disease

Afrasyab Altaf[1], Aftab Alam[1], Momin Salahuddin[2], Momin Khan[1], Mazhar Mahmood[1], Hammad Shah[3], Karamat Ali Shah[2]

[1]Assistant Professor, Cardiology Department, Rehman Medical Institute, Peshawar, Pakistan
[2]Professor, Cardiology Department, Rehman Medical Institute, Peshawar, Pakistan
[3]Fellow in Training, Cardiology Department, Rehman Medical Institute, Peshawar, Pakistan

Abstract

Introduction: *Serum potassium levels have been shown in some animal studies to be associated with the process of atherosclerosis. We decided to assess the correlation of serum potassium level in ischemic heart disease patients with disease severity and its relationship with prognosis in terms of major acute cardiac events (MACE).*

Material and methods: *This was a cross-sectional cohort study carried out at cardiology department of Rehman Medical Institute, from July 2016 to 31st Aug. 2018 a period of 26 months. 622 patients were included in the study. Clinical and angiographic characteristics were assessed based on the serum potassium level. Correlation of serum potassium level with Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery (SYNTAX) and Gensini scores was also evaluated. Follow up for MACE was carried out after one year.*

Results: *Mean serum potassium level was 3.93 ± 0.95 (mEq/l) in coronary artery disease patients. Serum potassium level showed negative correlation with SYNTAX score ($r = –0.60$, $p < 0.05$) and Gensini score ($r = –0.64$, $p < 0.05$). There was also a significant difference between low and high potassium level in relation to the multi-vessel disease on coronary angiography ($p < 0.05$). Low potassium level was a good predictor of adverse outcomes as shown by Kaplan-Meier analysis. Multivariate Cox regression analysis showed that serum potassium level and diabetes were independent predictors of MACE ($p < 0.05$).*

Conclusion: *Low serum potassium level is correlated with more severe coronary atherosclerosis. Low potassium levels are associated with significantly poor outcomes.*

Key words: coronary artery disease, coronary angiography, prognosis, potassium

Acta Angiol 2020; 26, 2: 58–64

Introduction

Cardiovascular disease is the leading cause of morbidity and mortality globally [1]. A lot of research is underway to better understand the causes of cardiovascular disease as well as the means to reduce such an alarming incidence. One such modifiable factor which has come under light recently is serum potassium level.

Hypokalemia has multiple effects on the myocardium and predisposes to arrhythmias while on the other hand hyperkalemia slows down conduction [2].

Studies have shown that elevated potassium levels induce arterial smooth muscle relaxation and cause vasodilatation due to involvement of K+ channels and Na+/K+-ATPase [3–6]. Elevated serum potassium levels also play a role in the inhibition of platelet ag-

Address for correspondence: Afrasyab Altaf, Cardiology Department, Rehman Medical Institute, 5/B-2, Hayatabad, Peshawar, Pakistan, e-mail: afrasyabaltaf@gmail.com

gregation and arterial thrombus formation, and hence coronary atherosclerosis [7–10].

However, a few recent studies [11, 12] have demonstrated the correlation between elevated serum potassium levels and increased atherosclerosis as well as the severity of coronary artery disease, which would contradict the above-given explanations. So, keeping in mind the results of such studies, we hypothesized that lower serum potassium may be associated with an increased risk of cardiovascular events and mortality.

Material and methods

This was a cross-sectional (for correlation) and cohort (for MACE) study carried out at cardiology department of Rehman Medical Institute, Peshawar, which is one of the biggest tertiary care hospitals in KPK, Pakistan providing 24/7 cath. lab facility, from July 2016 to August 2018, a period of 26 months. A total of 622 patients were included in the study population using universal sampling technique. All those patients were included who gave consent for inclusion and were admitted or discharged with the diagnosis of ischemic heart disease fulfilling the criteria of either stable angina, unstable angina or myocardial infarction [13]. Patients who were admitted due to non-cardiac causes like severe pneumonia, ARDS, and renal failure were excluded from the study population. All baseline demographic characteristics including age, gender, diabetes, hypertension, body mass index (BMI), smoking, alcohol consumption, and medication use were noted for each patient from history and hospital records. For measured variables, blood samples were taken at admission and sent for analysis of serum potassium, hemoglobin level, troponin level, CRP level, creatinine, and urea, total cholesterol (TC), low-density lipoprotein cholesterol (LDL), triglyceride (TG), high-density lipoprotein cholesterol (HDL) levels (Cobas B221 and 6000, Roche-Switzerland). All cases were divided into two groups (Low and High potassium groups) based on median serum potassium levels.

Definition of risk factors and clinical syndromes

Hypercholesterolemia was diagnosed in patients who had been given lipid-lowering medication or had a history of total cholesterol levels > 200 mg/dl [14]. Patients were diagnosed as hypertensive if they were documented to have a systolic blood pressure 140 mm Hg or a diastolic blood pressure 90 mm Hg on more than two occasions (but not during the angiogram procedure) or were already on antihypertensive therapy [15]. Patients were diagnosed with diabetes mellitus if they had a documented fasting glucose value > 126 mg/dl or HbA1C of >7 on one or more occasion or were taking insulin or oral hypoglycemic medications for diabetes mellitus. Myocardial infarction (MI) on presentation was diagnosed by a history of chest pain, electrocardiogram showing new ST-segment/T wave changes or new pathological Q waves or new left bundle branch block (LBBB), echocardiographic evidence of new regional wall motion abnormality and two recordings of hs-troponin levels showing rise and/or fall in values with at least one value above 99th percentile upper reference limit (URL). Body mass index was calculated by dividing the weight of the patient in kilograms by the square of height in meters. Active Smokers were defined as someone who smoked > 100 cigarettes, cigars, or pipes in their lifetime and still smoked in the last 28 days. Smokers were classified as former only if they had smoked > 100 cigarettes, cigars, or pipes in their lifetime and has not smoked in the last 28 days preceding the date of angiography [16].

Angiographic evaluation

Coronary angiography was performed with Seldinger technique in all the patients [17]. All angiographic assessments were done by two independent cardiologists. In case of difference in opinion, a third cardiologist was consulted. Patients were then divided into a control group (normal coronary vessels) and cases group (coronary arteries with the disease). Control group included 100 subjects and 622 cases with coronary artery stenosis ≥ 50% of the vessel diameter were included in the CAD group (622 cases: 371 men and 251 women). SYNTAX and Gensini scoring systems were used to assess the severity of coronary stenosis in all cases. In SYNTAX score calculation each coronary lesion producing ≥ 50% diameter stenosis in vessels ≥ 1.5 mm was scored separately using the SYNTAX score algorithm available on the Internet from the and added to obtain the overall SYNTAX score. Gensini score is based on the severity of lesion narrowing, number of lesions, lesion location, and influence of collaterals [18, 19].

Major adverse cardiac events (MACE) for the purposes of follow-up were as follows: (1) acute myocardial infarction; (2) decompensated heart failure; (3) target vessel revascularization and (4) mortality due to cardiac disease [20].

This study was evaluated and approved by the Research evaluation and Ethics Committee of Rehman Medical Institute. The study abided by the principles of the Declaration of Helsinki. Written and informed consent was obtained from each patient included in the study.

Statistical analysis

Data were analyzed for normality using the Kolmogorov-Smirnov (KS) test. Continuous data are presented

Table 1. Baseline characteristics and angiographic features of study groups based on serum potassium levels

Variable	Serum potassium (< 4 mEq/l)	Serum potassium (4 mEq/l or above)
Number of patients	349	273
Age (years)	63.72 ± 4.35	62.54 ± 10.23
Gender (m/f)	210/139 (60/40%)	161/112 (59/41%)
Ejection fraction (%)	49.98 ± 10.55	49.87 ± 10.35
Blood sugar	147.31 ± 96.06	146.40 ± 80.14
Serum creatinine	1.01 ± 0.23	1.01 ± 0.22
Hemoglobin (g/dl)	14.2 ± 1.71	14.39 ± 1.72
BNP (pg/ml)	395.12 ± 629.35	487.12 ± 800.72
Hs-Troponin	3443 ± 4414	4584 ± 5796
CRP	8.00 ± 11.19	7.91 ± 10.59
Diabetes	122 (35%)	85 (31%)
Hypertension	192 (55%)	158 (58%)
Smoking	105 (30%)	90 (33%)
Hyperlipedemia	98 (28%)	68 (25%)
Anti-Platelet drugs	345 (99%)	273 (100%)
Beta blocker	311 (89%)	235 (86%)
RAAS inhibitors	195 (56%)	145 (53%)
Nitrates	188 (54%)	156 (57%)
Digoxin	70 (20%)	49 (18%)
Diuretics	70 (20%)	46 (17%)
Lipid lowering agents	209 (60%)	169 (62%)
SYNTAX score	37.48 ± 7.28	26.76 ± 6.34*
Gensini score	77.56 ± 13.05	56.46 ± 12.24*
Multi-vessel disease	174/(50%)	96/(35%)*
LAD	220/(63%)	150/(55%)
LCX	157/(45%)	109/(40%)
RCA	132/(38%)	93/(34%)

*P ≤ 0.05; CRP: C-reactive protein; RAA: renin angiotensin aldosterone system inhibitors; LAD: left anterior descending artery; LCX: left circumflex artery; RCA: right coronary artery

as means ± SD Between-group comparisons were performed using t-test. Categorical data were presented as percentages and analyzed using χ^2 test. The correlation between serum potassium level, Syntax and Gensini scores were examined by Pearson correlation analysis. and Kaplan Meyer analysis was used for survival analysis. Differences with p values < 0.05 were considered statistically significant. Multivariate Cox regression analysis was done to examine the independent predictors of MACE

Results

General clinical data comparison

Mean serum potassium level was 3.93 ± 0.95 (mEq/l) in coronary artery disease patients. Patients were divided based median serum potassium level (4 mEq/l) and comparison was made of baseline characteristics. There were no significant differences in clinical characteristics at baseline between the two groups with high and low potassium levels (p > 0.05) (Table 1). All patients received similar medication such as anti-platelets, beta-blockers, Renin Angiotensin Aldosterone system (RAAS) inhibitors, statins, nitrates and diuretics. Patients' characteristics with and without MACE were also compared which showed a significant difference in serum potassium level, BMI, ejection fraction, SYNTAX score, Gensini Score and multi-vessel disease (p ≤ 0.05) (Table 2).

Angiographic assessment and correlation

Angiographic analysis based on serum potassium level demonstrated that there was a significant difference

Table 2. Patient characteristics and angiographic features of study groups according to MACE

Variable	Patients without MACE	Patients with MACE
Number of patients	601	21
Age (years)	61.35 ± 5.62	63.32 ± 8.46
Gender (m/f)	330/271 (55/45%)	12/9 (60/41%)
Serum potassium (< 4 mEq/l)	3.38 ± 0.44	4.62 ± 0.56*
BMI	22.43 ± 1.12	25.11 ± 1.15*
Ejection fraction (%)	54.51 ± 8.14	42.35 ± 7.29*
Blood sugar	140.31 ± 87.27	148.40 ± 72.44
Serum creatinine	1.11 ± 0.35	1.23 ± 0.28
Hemoglobin (g/dl)	13.4 ± 1.53	14.38 ± 1.67
BNP (pg/ml)	346.19 ± 601.45	501.17 ± 780.58
Hs-troponin	3566 ± 3942	4731 ± 5385
CRP	6.00 ± 9.12	8.34 ± 11.89
Diabetes	222 (37%)	13 (62%)*
Hypertension	301 (50%)	12 (57%)
Smoking	186 (31%)	7 (35%)
Hyperlipedemia	144 (24%)	6 (29%)
Anti-platelet drugs	601 (100%)	20 (95%)
Beta blocker	541(90%)	18 (86%)
RAAS inhibitors	330 (55%)	11 (54%)
Nitrates	330 (55%)	12 (57%)
Digoxin	108 (18%)	4 (20%)
Diuretics	150 (25%)	6 (30%)
Lipid lowering agents	360 (60%)	13 (62%)
SYNTAX score	25.48 ± 6.24	39.76 ± 7.37*
Gensini score	57.56 ± 12.16	79.46 ± 10.43*
Multi-vessel disease	204/(34%)	12/(57%)*
LAD	348/(58%)	13/(62%)
LCX	288/(42%)	9/(43%)
RCA	198/(33%)	8/(38%)

*P ≤ 0.05; CRP: C-reactive protein; RAA: renin angiotensin aldosterone system inhibitors; LAD: left anterior descending artery; LCX: left circumflex artery; RCA: right coronary artery

between low and high potassium level groups in terms of multi-vessel disease, SYNTAX score and Gensini score ($p < 0.05$). The involvement of the type of vessel was similar in both groups ($p > 0.05$) (Table 1).

The mean SYNTAX score all patients was 32.78 ± 8.70 while the Gensini score was 68.30 ± 16.46. The results of Pearson's correlation indicate that there was a significant negative correlation between the concentration of potassium and SYNTAX score ($r = –0.60$, $p < 0.05$). and Gensini score ($r = –0.64$, $p < 0.05$) (Fig. 1).

Survival and multivariate analysis for MACE

For analysis, we assessed Kaplan-Meier curves according to median value of serum Potassium level (median = 4 mEq/l) (Fig. 2). The Kaplan-Meier curves revealed a significantly worse cumulative outcome in patients with serum Potassium level below 4 mEq/l.

Cumulative MACE for this study was 3.4% (21 patients). The 180 days mortality was 1.28% (8 patient), myocardial infarction 1.76% (11 patients), target vessel revascularization was 1.1% (7 patients) and cardiac failure was 1.1% (7 patients) (Tables 3, 4).

Discussion

Data from the Systolic Hypertension in the Elderly Program (SHEP) [21] trial has shown that normal potassium level has significantly reduced hazard ration

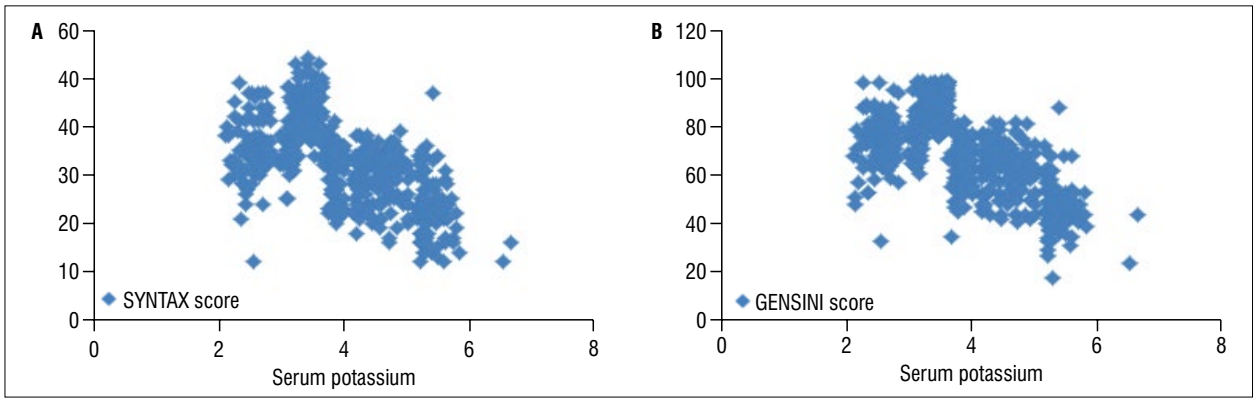

Figure 1. Correlation of serum potassium level with (a) SYNTAX score and (b) Gensini score. Pearson's correlation analysis show negative correlation for both [SYNTAX score (r = –0.06) and Gensini score (r = – 0.64)]

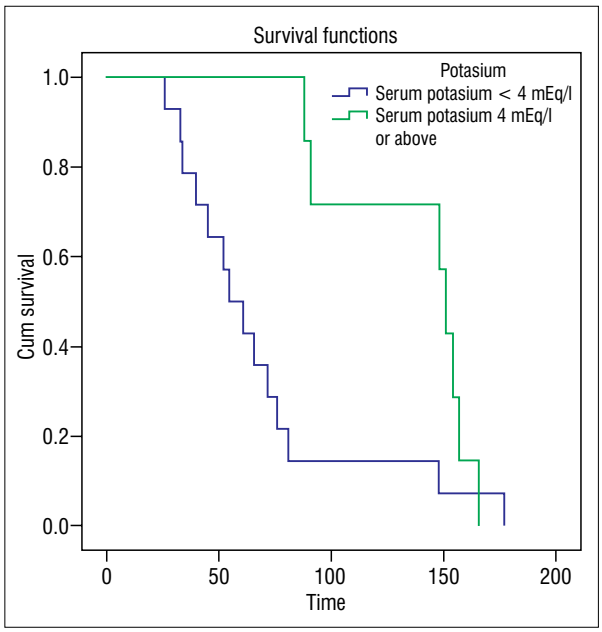

Figure 2. Kaplan Meier analysis based on median serum potassium level. A significant difference between low and high potassium for adverse outcomes (p < 0.05). Time in number of days

Table 3. Univariate analysis for MACE

	Univariate analysis	
	HR (95%CI)	p value
Gender (M vs. F)	1.131 (0.151–3.167)	0.31
Age (≥ 60 vs. < 60)	0.519 (0.212–1.926)	0.32
Serum potassium (≥ 4 mEq/l vs. < 4mEq/l)	1.426 (1.077–1.413)	0.02
Ejection fraction (≥ 50% vs. < 50%)	1.242 (0.551–1.236)	0.05
Hypertension (present vs. absent)	1.986 (0.191–47.626)	0.45
Diabetes (present vs. absent)	1.378 (1.107–1.412)	0.03
BMI (≥ 25 vs. < 25)	0.658 (0.421–1.229)	0.19
Smoking (yes vs. no)	1.716 (0.635–66.137)	0.67
Total cholesterol (≥ 200 mg/dl vs. < 200 mg/dl)	1.109 (0.229–6.443)	0.75
BNP (≥ 100 pg/ml vs. < 100 pg/ml)	0.582 (0.316–1.572)	0.37
Troponin (≥ 14 mg/l vs. < 14 ng/l)	0.088 (0.087–1.983)	0.31
Creatinine (≥ 1.2 mg/dl vs < 1.2 mg/dl)	0.865 (0.794–1.181)	0.28
Family history of CAD[c] (present vs. absent)	1.927 (0.251–59.172)	0.43
Multi-vessel disease (present vs. absent)	0.229 (0.026–67.472)	0.14

BMI: body mass index; BNP: basic natriuretic peptide; CAD: coronary artery disease

for cardiovascular events including stroke and coronary vessels related events. Moreover, animal studies have shown that high potassium diets normalize blood pressure and provide protection against atherosclerosis in arteries [22].

Increased potassium content in diets plays a role reduction of vascular lesions owing to decreased endothelial injuries and less adherence and infiltration of macrophages into the vascular wall [11].

Other mechanisms explaining the role of increased potassium levels in the maintenance of normal blood pressure as well as prevention of coronary atherosclerosis are as follows; a) inhibition of platelet aggregation and arterial thrombosis; b) reduction in renal vascular resistance and increase in glomerular filtration rate;

Table 4. Multivariate regression analysis for MACE

	Multivariate analysis	
	HR (95%CI)	p value
BMI (≥ 100 pg/ml vs. < 100 pg/ml)	0.481 (0.613–2.754)	0.54
Serum potassium (≥ 4 mEq/l vs. < 4 mEq/l)	1.278(1.073–1.662)	0.03
Ejection fraction (≥ 50% vs. < 50%)	1.481 (0.737–1.551)	0.32
Diabetes (present vs. absent)	1.331 (1.109–1.517)	0.04
Multi-vessel disease (present vs. absent)	0.316 (0.030–71.482)	0.68

c) inhibition of free radical formation from vascular endothelial cells and macrophages; d) inhibition of vascular smooth muscle cell proliferation; and e) suppression of reactive oxygen species overproduction [23].

Such established findings are in contradiction to two previous studies [11, 12] which have reported that hyperkalemia is associated with increased atherosclerosis. Multiple factors can affect serum potassium levels including renal function, dietary intake, hormonal status, renin-angiotensin–aldosterone system, heart failure, myocardial infarction and drugs. The major limitation in the study conducted by Cavusoglu et al. [11] was that they only included subjects of the male gender. Diane et al. [24] previously reported that male sex was associated with higher potassium levels as compared to females. This could have clearly affected the results obtained by Cavusoglu and his research team.

In the second study conducted by Guang et al. [12] the study group has no patients with myocardial infarction. Although studies have shown that in acute stress such as myocardial infarction, the potassium level is higher due to various mechanisms involving necrosis induced activation of aldosterone system and sympathetic-adrenal induced involvement of sodium-potassium pumps [25–27]. But by the exclusion of such group from the study also means that patients with more severe could not be assessed for the observed results.

We, in our study, not only included subjects of both genders but also myocardial infarction patients along with patients of chronic and stable coronary artery disease. We believe such a study group would a better understanding of patients in real-life situation. Moreover, we in our study not only assessed severity of coronary atherosclerosis not only by Gensini score which assesses the severity of coronary vasculature on the anatomical basis and has been described elsewhere [19], but also SYNTAX score which is well-established system for quantification of coronary lesions as well as for prediction of major adverse cardiac events (MACE) in patients undergoing percutaneous coronary intervention (PCI) [18, 28–30]. Such measures were taken in order to ensure more reliable and comprehensive results.

Limitations

It is a single centered study and was not designed to interpret results based on ethnicity and dietary habits. Selecting a large population with multi-centered study would address such concerns.

Conclusion

Serum potassium level is lower in coronary artery disease and is correlated with severity of atherosclerosis on coronary angiography. Serum potassium is an independent predictor of adverse outcomes in coronary artery disease patients.

Acknowledgement of grant support

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of interest:

None.

References:

1. American Heart Association. Heart disease and stroke statistics: 2005 Update. Dallas, Tex: American Heart Association. 2004.
2. Sica DA, Struthers AD, Cushman WC, et al. Importance of potassium in cardiovascular disease. J Clin Hypertens (Greenwich). 2002; 4(3): 198–206, doi: 10.1111/j.1524-6175.2002.01728.x, indexed in Pubmed: 12045369.
3. Smith PD, Brett SE, Luykenaar KD, et al. KIR channels function as electrical amplifiers in rat vascular smooth muscle. J Physiol. 2008; 586(4): 1147–1160, doi: 10.1113/jphysiol.2007.145474, indexed in Pubmed: 18063660.
4. Jin CZi, Kim HS, Seo EY, et al. Exercise training increases inwardly rectifying K(+) current and augments K(+)-mediated vasodilatation in deep femoral artery of rats. Cardiovasc Res. 2011; 91(1): 142–150, doi: 10.1093/cvr/cvr050, indexed in Pubmed: 21349874.
5. Haddy FJ, Vanhoutte PM, Feletou M. Role of potassium in regulating blood flow and blood pressure. Am J Physiol Regul Integr Comp Physiol. 2006; 290(3): R546–R552, doi: 10.1152/ajpregu.00491.2005, indexed in Pubmed: 16467502.
6. Seo EY, Kim HJ, Zhao ZH, et al. Low K. current in arterial myocytes with impaired K-vasodilation and its recovery by exercise in hypertensive rats. Pflugers Arch. 2014; 466(11): 2101–2111, doi: 10.1007/s00424-014-1473-7, indexed in Pubmed: 24557713.
7. Young DB, Lin H, McCabe RD. Potassium's cardiovascular protective mechanisms. Am J Physiol. 1995; 268(4 Pt 2): R825–

R837, doi: 10.1152/ajpregu.1995.268.4.R825, indexed in Pubmed: 7733391.
8. Ando K, Matsui H, Fujita M, et al. Protective effect of dietary potassium against cardiovascular damage in salt-sensitive hypertension: possible role of its antioxidant action. Curr Vasc Pharmacol. 2010; 8(1): 59–63, doi: 10.2174/157016110790226561, indexed in Pubmed: 19485915.
9. Tobian L, Jahner TM, Johnson MA. High K diets markedly reduce atherosclerotic cholesterol ester deposition in aortas of rats with hypercholesterolemia and hypertension. Am J Hypertens. 1990; 3(2): 133–135, doi: 10.1093/ajh/3.2.133, indexed in Pubmed: 2306340.
10. Zhang Y, Zhu CG, Guo YL, et al. Higher fibrinogen level is independently linked with the presence and severity of new-onset coronary atherosclerosis among Han Chinese population. PLoS One. 2014; 9(11): e113460, doi: 10.1371/journal.pone.0113460, indexed in Pubmed: 25426943.
11. Cavusoglu E, Chopra V, Gupta A. Relation of baseline serum potassium levels to angiographic findings in patients with known or suspected coronary artery disease. Am J Hypertens. 2009; 22: 754–762.
12. Guang Xian Zhao, Xiang Lan Jin, Ji Long Kang, Chun Zi Jin. Serum potassium levels are associated with coronary artery lesion severity in coronary artery disease. Int J Clin Exp Med. 2016; 9(2): 3705–3710.
13. Thygesen K, Alpert JS, Jaffe AS, et al. Joint ESC/ACCF/AHA/WHF Task Force for the Universal Definition of Myocardial Infarction. Third universal definition of myocardial infarction. Circulation. 2012; 126(16): 2020–2035, doi: 10.1161/CIR.0b013e31826e1058, indexed in Pubmed: 22923432.
14. Catapano AL, Graham I, De Backer G, et al. ESC Scientific Document Group. 2016 ESC/EAS Guidelines for the Management of Dyslipidaemias. Eur Heart J. 2016; 37(39): 2999–3058, doi: 10.1093/eurheartj/ehw272, indexed in Pubmed: 27567407.
15. Williams B, Mancia G, Spiering W, et al. Authors/Task Force Members:, ESC Scientific Document Group . 2018 ESC/ESH Guidelines for the management of arterial hypertension. Eur Heart J. 2018; 39(33): 3021–3104, doi: 10.1093/eurheartj/ehy339, indexed in Pubmed: 30165516.
16. https://www.health.govt.nz/our-work/preventative health wellness/tobacco control/tobacco-control information-practitioners/definitions smoking-status.
17. https://www.medscape.com/answers/80279-119321/what is the seldinger technique for femoral central venous access and how is it performed.
18. Palmerini T, Genereux P, Caixeta A, et al. Prognostic value of the SYNTAX score in patients with acute coronary syndromes undergoing percutaneous coronary intervention: analysis from the ACUITY (Acute Catheterization and Urgent Intervention Triage StrategY) trial. J Am Coll Cardiol. 2011; 57(24): 2389–2397, doi: 10.1016/j.jacc.2011.02.032, indexed in Pubmed: 21658558.
19. Gensini GG. A more meaningful scoring system for determining the severity of coronary heart disease. Am J Cardiol. 1983; 51(3): 606, doi: 10.1016/s0002-9149(83)80105-2, indexed in Pubmed: 6823874.
20. Ahn MJ, Kim MC, Ahn Y, et al. Impact of Complete Revascularization on Six-Year Clinical Outcomes and Incidence of Acute Decompensated Heart Failure in Patients With ST-Segment Elevation Myocardial Infarction and Multivessel Coronary Artery Disease. Am J Cardiol. 2018; 121(5): 544–551, doi: 10.1016/j.amjcard.2017.11.025, indexed in Pubmed: 29325904.
21. Franse LV, Pahor M, Di Bari M, et al. Hypokalemia associated with diuretic use and cardiovascular events in the Systolic Hypertension in the Elderly Program. Hypertension. 2000; 35(5): 1025–1030, doi: 10.1161/01.hyp.35.5.1025, indexed in Pubmed: 10818057.
22. Tobian L. Protecting arteries against hypertensive injury. Clin Exp Hypertens A. 1992; 14(1-2): 35–43, doi: 10.3109/10641969209036169, indexed in Pubmed: 1541045.
23. Li X, Li Y, Jin J, et al. Increased serum cathepsin K in patients with coronary artery disease. Yonsei Med J. 2014; 55(4): 912––919, doi: 10.3349/ymj.2014.55.4.912, indexed in Pubmed: 24954318.
24. Wysowski DK, Kornegay C, Nourjah P, et al. Sex and age differences in serum potassium in the United States. Clin Chem. 2003; 49(1): 190–192, doi: 10.1373/49.1.190, indexed in Pubmed: 12507983.
25. Goyal A, Spertus JA, Gosch K, et al. Serum potassium levels and mortality in acute myocardial infarction. JAMA. 2012; 307(2): 157–164, doi: 10.1001/jama.2011.1967, indexed in Pubmed: 22235086.
26. Sekiyama H, Nagoshi T, Komukai K. et.al. Transient decrease in serum potassium level during ischemic attack of acute coronary syndrome: paradoxical contribution of plasma glucose level and glycohemo¬globin. Cardiovasc Diabetol. 2013; 12: 4.
27. Zhang H, Zhou CY. and Fu HY. The level of potassium in early patients with acute myocardial infarction and the analysis of its relevant factors. Chinese Journal of Prevention and Control of Chronic Diseases. 2011; 3: 026.
28. Sianos G, Morel MA, Kappetein AP, et al. The SYNTAX Score: an angiographic tool grading the complexity of coronary artery disease. EuroIntervention. 2005; 1(2): 219–227, indexed in Pubmed: 19758907.
29. Serruys PW, Onuma Y, Garg S, et al. Assessment of the SYNTAX score in the Syntax study. EuroIntervention. 2009; 5(1): 50–56, doi: 10.4244/eijv5i1a9, indexed in Pubmed: 19577983.
30. Kato S, Saito N, Kirigaya H, et al. Incremental prognostic value of the SYNTAX score to late gadolinium-enhanced magnetic resonance images for patients with stable coronary artery disease. Heart Vessels. 2016; 31(6): 871–880, doi: 10.1007/s00380-015-0685-x, indexed in Pubmed: 25904244.

VIA MEDICA

REVIEWS

Acta Angiol
Vol. 26, No. 2, pp. 65–71
Doi: 10.5603/AA.2020.0011

ISSN 1234–950X
www.journals.viamedica.pl/acta_angiologica

Management of isolated distal deep vein thrombosis. A persistent conundrum?

Nalaka Gunawansa, Thilina Gunawardena

National Institute of Nephrology and Transplantation, Colombo, Sri Lanka

Abstract

Isolated distal deep vein thrombosis (IDDVT) accounts for approximately 50% of all patients diagnosed with DVT. While the definitive management of patients with proximal deep vein thrombosis is fairly well defined, IDDVT remains shrouded uncertainty. The great majority of patients with IDDVT may remain with little or no symptoms and have spontaneous resolution of the thrombi. However, a small but significant fraction may show proximal thrombus extension and may proceed to cause pulmonary embolism or late deep venous reflux. Identification of this subgroup of patients with IDDVT who have a greater propensity for thrombus extension or further sequelae remains the cornerstone of individualized management for optimal results.

Key words: deep vein thrombosis, pulmonary embolism, calf vein thrombus, venous thromboembolism

Acta Angiol 2020; 26, 2: 65–71

Introduction

Systemic anticoagulation remains the standard of care in managing proximal deep vein thrombosis (PDVT). However, the optimal management of isolated distal deep vein thrombosis (IDDVT) remains heavily debated and controversial. IDDVT refers to the deep venous thrombi occurring in the veins distal to and not involving the popliteal vein. These include the tibial and peroneal veins as well as the intramuscular venous plexus of soleus and gastrocnemius muscles. At present, there is no clear consensus among clinicians regarding the clinical significance nor the optimal management of IDDVT. While some argue the probability of proximal propagation, risk of pulmonary embolism (PE) and late post-thrombotic syndrome (PTS) in untreated IDDVT, others argue that it is primarily a self-limiting benign disease and routine treatment is 'overkill'. Hence, an informed precise decision needs to be made regarding the management of IDDVT on an individual basis. This requires balancing the benefits of avoiding short and long-term sequelae by anti-coagulation against potential adverse effects of the treatment and economic burden of such treatment. This update will attempt to revisit the said areas of controversy with a look at the available evidence regarding the optimal management of IDDVT.

Epidemiology

The estimated annual incidence of deep vein thrombosis (DVT), both PDVT and IDDVT, is approximately 1 in 1000 adults[1]and recurs frequently. VTE is a complex (multifactorial. Among the diagnosed patients with DVT and PE, the mean prevalence of IDDVT is estimated to be around 50% (20–70%) [1]and recurs frequently. VTE is a complex (multifactorial. However, this could be a gross underestimate as the majority of patients with IDDVT remain asymptomatic and may not present to hospital, contributing to under-reporting. The wide variability in IDDVT prevalence across the literature is attributed to the lack of consensus on reporting the patient cohort (symptomatic vs asymptomatic and in-patient vs out-patient). There is further discordance in the modality of diagnostic imaging (duplex ultra-sound — DUS vs venography) used in the diagnosis of IDDVT.

Address for correspondence: Nalaka Gunawansa, National Institute of Nephrology and Transplantation, Jayantha Weerasekera Mw, 00700 Colombo, Sri Lanka, e-mail: vascular@drnalakagunawansa.com

The immediate danger of DVT is the risk of propagation and PE. Therefore, the primary debate regarding management of IDDVT revolves around the possibility and prevention of PE and associated other complications. According to the Center for Disease Control (CDC) data in the United States, reviewed in 2020, the annual estimated deaths due to PE range between 60,000 to 100,000 [2]. Accordingly, PE is seen as a bigger contributor to annual mortality than motor accidents, breast carcinoma and HIV combined. Wei et al. [3] studied the prevalence of IDDVT among hospitalized patients with diagnosed DVT and PE (collectively referred to as venous thromboembolism; VTE). They reported an IDDVT prevalence of 25% among all patients with diagnosed PE. In an earlier publication, Mattos et al. [4], reported an IDDVT prevalence of 45% among outpatients and 27% among in-patients with confirmed VTE. According to a comprehensive study on DUS based DVT diagnoses, Sapp et al. [5] reported that simultaneous calf vein DVT is found in over 98% of patients diagnosed with PDVT. The incidence of true IDDVT was 54%, indicating that unless targeted imaging of the calf veins is performed, over half the patients with DVT would be missed and a false negative report would ensue.

Diagnosis

Given the high prevalence of IDDVT among patients who require hospitalization for VTE, it is imperative that the diagnostic modality used in VTE can detect IDDVT in the absence of PDVT. However, diagnosis of IDDVT itself poses numerous issues. While the vast majority of patients may remain asymptomatic till proximal thrombus extension, even those who do develop symptoms may have negative test results due to the reduced sensitivity of available diagnostic tools. The Wells prediction rule is globally accepted as a pre-test prediction tool in the diagnosis of both DVT and PE [6]. However, the accuracy of the Wells score in predicting the stand-alone IDDVT sub-population is questionable and is considered more predictive only in the presence of proximal DVT [7]. Sartori et al. [8] found that in IDDVT, the sensitivity of Wells predictive rule was only 47% with a specificity of only 74%. The corresponding negative and positive predictive values for IDDVT were 91% and 20% respectively. Serum D-dimer testing is well established as an excellent predictive tool in the diagnosis of VTE, with a reported sensitivity > 92% although with a poor specificity of 45% [9]. However, here again, the usefulness of D-dimer in the diagnosis of IDDVT is limited with a reported sensitivity of only 84% [8].

DUS is the commonest imaging modality used in the confirmation of DVT. The reported sensitivity of DUS in the diagnosis of IDDVT is significantly lower than that of PDVT. According to a meta-analysis by Goodacre et al. [10], the sensitivities of DUS in diagnosing PDVT and IDDVT were 96% and 71% respectively. Another recent meta-analysis by Zhang et al. [11] actually found the sensitivity of DUS in diagnosing IDDVT to be as low as 43%. This stark contrast in diagnostic sensitivities of available predictive and diagnostic tools for PDVT and IDDVT, underlines the issues inherent to the accurate diagnosis of IDDVT.

When using DUS, two common imaging protocols have been described for the diagnosis of DVT. The first is to perform a limited scan of the proximal veins, targeting the popliteal vein and above, where the diagnostic sensitivity is very high. However, this targeted proximal scan will miss those with IDDVT, that amounts to 20–70% of all patients with DVT [12]. While those who become positive on the proximal scan are treated as for DVT, the 'high-risk' patients with a negative scan get a repeat scan of the proximal veins after one week. This repeat scan is performed with the intention of picking any IDDVT which may have propagated to the popliteal vein after one week. The rationale behind this protocol of imaging is that the PDVT are picked up in the first scan and any clinically significant IDDVTs that show proximal extension are picked up on the second scan. Any such proximal extension of IDDVT is known to occur within 5–7 days while the others are known to resolve spontaneously, thereby being considered clinically insignificant. The second imaging strategy is to perform a whole lower limb scan (inguinal ligament to ankle) as a single test in an effort to diagnose all DVT including IDDVT. While this second strategy allows for more IDDVTs to be picked up early, doubts exist regarding its relevance in the absence of proximal extension. Furthermore, due to the inherent low sensitivity of DUS in detecting IDDVT, a fair number of such patients are likely to be missed on the whole limb scan. The lack of a clear protocol on DUS for DVT diagnosis has led to misinterpretation and variability in reporting among individual radiologists, literature and institutions [7].

In 2018, A multi-disciplinary consensus meeting was held that included the Society of Radiologists, Society for Vascular Ultrasound and American College of Radiologists, to formulate guidelines on DUS for diagnosis of DVT [13]. Accordingly, a consensus guideline was issued that recommends complete leg scanning from inguinal ligament to ankle including tibial and calf veins with compression at 2 cm intervals. A consensus was also reached regarding the need and place for follow up DUS after an initial positive or negative scan (Table 1).

Natural history and complications

The study by Sapp et al. [5] mentioned above also contributed to the growing opinion that all DVT originates in

Table 1. Duplex Ultra Sound scan protocol in the presence of suspected IDDVT. Adapted from Needleman et al. [13]

A. Initial positive whole leg DUS	
Clinical condition	**Recommendation**
IDDVT — untreated	Repeat DUS in 1 week (or earlier if symptoms progress) Start treatment if propagated to the popliteal vein If no propagation at 1 week, repeat scan at 2 weeks If still no propagation at 2 weeks, no further scan warranted
IDDVT — treated	Repeat scan not indicated
B. Initial negative whole leg DUS	
Clinical condition	**Recommendation**
Persistent/worsening symptoms	Repeat DUS in 5–7 days
'High risk' for DVT (hospitalized, active cancer, post-operative etc.)	Consider repeat scan unless another viable aetiology for symptoms has been established
Incomplete study/technical failure	Repeat scan in 5–7 days
Suspected ileo-caval DVT	Specialized imaging (CT/MR venography)

CT: computed tomography; MR: magnetic resonance

the calf veins. However, it is also postulated that although it originates in the calf veins, the majority do not present or experience symptoms until the thrombus has already propagated to the popliteal vein or proximally [14] and most probably resolve spontaneously. Thrombi that remain confined to the calf rarely cause leg symptoms or symptomatic pulmonary embolism (PE). This results in a gross underestimate on the prevalence of IDDVT as well as the limitation in the number of studies available that deals with IDDVT alone in terms of its sequelae. Conversely, there is a different school of thought that considers IDDVT as a separate entity and compares it with isolated proximal PDVT.

Two major epidemiological studies have been published that compared the individual risk factors for PDVT and IDDVT; the OPTIMEV study and RIETE registry [15, 16] clinical presentation and estimated 3-month survival for each form of VTE were evaluated. Results: Of 5889 patients, 426 had PE. Both studies described IDDVT associated more with transient risk factors such as recent surgical procedure, immobilization, hospitalization, long-distance travel etc. On the contrary, PDVT was associated more with chronic risk factors such as thrombophilia, malignancy and congestive cardiac failure (Table 2).

The vast majority of IDDVT is thought to resolve spontaneously without ever causing significant symptoms. Although PE with IDDVT in the absence of proximal propagation has been observed, the risk of PE is dramatically increased only after proximal propagation [17]. This emphasizes the importance of understanding the natural history of IDDVT with possible early recognition in an effort to minimize proximal extension. Although the associated risk is significantly lower than with PDVT, the possibility of PE and long-term PTS should always be borne in mind during the assessment of IDDVT.

Table 2. Risk factors for proximal extension of calf vein thrombus

Isolated distal deep vein thrombosis. Risk factors for proximal extension
1. Positive D-dimer result
2. Extensive thrombus (> 5 cm in length)
3. Involvement of multiple veins
4. Thrombus diameter > 7 mm
5. Close proximity to the proximal (popliteal) vein
6. Unprovoked DVT
7. Active malignancy
8. Prior history of VTE
9. In-patient status (hospitalized)

Proximal extension

While the vast majority of IDDVT will resolve spontaneously without propagation, proximal extension into the popliteal veins remains the commonest complication. The reported rates of the proximal extension are highly variable due to the heterogeneous nature of study populations, diagnostic methods and treatment plans among study groups. A systematic review by Garry et al. [18] studied over 12 papers that discussed the rate

of proximal extension of IDDVT to be between 0–35% (mean 8.9%). Other studies have previously stated higher rates of proximal extension around 25%, within 1–2 weeks of presentation [14]and most probably resolve spontaneously. Thrombi that remain confined to the calf rarely cause leg symptoms or symptomatic PE. Hence, the overall rate of proximal extension is likely to be between 10–20% of all IDDVT. Furthermore, such proximal extension, if it occurs, is likely to occur within the first 1–2 weeks from onset, giving rise to the current practice of DUS surveillance for 2 weeks in those patients who do not undergo anti-coagulation. Identification of the 'high-risk' sub-group (Table 2) who are likely to have proximal extension allows selective ant-coagulation in such patients [19].

Pulmonary embolism

The afore-mentioned review by Garry et al. looked at over 8 studies that described the risk of PE from IDDVT. The reported rates of PE varied between 0–5.8% with a mean of 1.4% and is significantly lower compared to PDVT [18]. There were no reported PE-related deaths in any of the studies. This becomes an important determining factor in the decision regarding treatment of IDDVT, as the sole basis for treating such patients actively as opposed to DUS surveillance is based on the immediate risk of PE. Nevertheless, the fact that a small fraction of these patients can actually have PE without proximal thrombus extension needs to be considered in the final decision regarding treatment.

Recurrent thromboembolism

Another controversial aspect of the management of IDDVT is the risk of recurrent VTE compared to patients with PDVT. Galanaud et al. [20] compared the risk of recurrent VTE in those with PDVT versus IDDVT, 3 years after discontinuation of anticoagulation. The risk of recurrent DVT was significantly lower in the IDDVT group (5.2% vs. 2.7%), while the corresponding risk of PE was similar in both groups (1% vs. 0.9%). A subgroup analysis found that among those with IDDVT, age > 50 years, unprovoked IDDVT and involvement of > 1 calf vein were associated with a higher risk of recurrence. In a separate study, Sartori et al. [21] described that male gender and the presence of coexisting active malignancy were associated with a higher risk of recurrence after IDDVT. Another single-center study that enrolled over 800 patients with a first episode of DVT with a mean follow up of 7.6 years found that IDDVT carried a significantly lower risk of recurrent VTE and death compared to IPDVT [22]. Table 3 summarizes the risk factors for recurrence after IDDVT.

Table 3. Risk factors for VTE recurrence after IDDVT

Isolated distal deep vein thrombosis. Risk factors for VTE recurrence
1. Age > 50 yrs
2. Unprovoked IDDVT
3. Involvement of 2 or more calf veins
4. Male gender
5. Active malignancy

Post-thrombotic syndrome (PTS)

The risk of PTS after PDVT is estimated to be around 40% according to the Villata scale [23]. The definitive incidence of PTS after IDDVT is not clearly defined. Available data suggest that patients with IDDVT experience far fewer symptoms of PTS compared to those with PDVT [24, 25]. Meissner et al. [24] reported that at 1-year post-diagnosis, 23% of patients with IDDVT still had symptoms of pain and swelling in the affected leg. This contrasts with PDVT, where up to 54% are found to be having residual symptoms at 1 year follow up.

McLafferty et al. [26] studied the long term haemodynamic effects following IDDVT and described the persistence of deep vein reflux in approximately 1/3 of patients after 3.4 years of follow-up. Interestingly, these changes were seen predominantly in proximal venous segments that did not appear to have thrombi in the initial DUS. Hence, they postulated the resulting reflux was caused by previously unseen occult thrombi co-existent with the IDDVT. The CACTUS-PTS study (2020) studied the long-term effects, after 6 years since the first episode of IDDVT. The results showed an overall PTS incidence of 30%, still considerably less than the reported values for patients after PDVT [27].

Management

Do all patients with IDDVT require treatment?

While the majority of IDDVT may be self-limiting, the preceding discussion shows that a fair proportion of patients go on to develop significant complications including proximal extension, PE, recurrent VTE and late PTS. The said adverse sequelae are commoner in a subset of patients who carry 'high risk 'characteristics and are left untreated. Hence, a clear distinction needs to be made with regards to the identification of the said 'high-risk' subgroup and initiation of definitive treatment over serial DUS surveillance. While there is no uncertainty with regards to the treatment of PDVT, the decision is often debated in IDDVT due to the potential to do more harm by systemic anti-coagulation.

The American College of Chest Physicians (ACCP) Consensus Conference in 2008 on the management of DVT failed to distinguish between IDDVT and PDVT, recommending anti-coagulation for a minimum of 3 months for all patients with DVT [28]. The latest ACCP consensus (2016) was more descriptive in its plan for PDVT and IDDVT separately [19]. Accordingly, it recommends identifying the subgroup of patients with IDDVT having 'high-risk' of thrombus extension (Table 2). These patients, as well as, those having severe symptoms are recommended therapeutic anti-coagulation over serial DUS monitoring. Conversely, those patients who do not have high-risk factors for thrombus extension or and are not severely symptomatic can be managed with weekly DUS surveillance. However, both these recommendations were classified grade-2C based on a weak evidence base. Hence, the exact therapeutic approach in a given situation with IDDVT remains heavily debated and leaves room for tremendous individual variations in practice.

Anti-coagulation

Once a decision was made to start anti-coagulation, the recommended duration of therapy was a minimum of 3 months, the same as for PDVT [19]. In the subgroup of patients where therapeutic anti-coagulation is not commenced and are monitored by serial DUS, initiation of treatment is recommended only if there is a proximal extension on repeat imaging. The choice of anti-coagulation agent can be based on individual preference and feasibility ranging from low molecular weight heparin (LMWH), vitamin-K antagonists (warfarin) or one of the novel oral anti-coagulants such as rivaroxaban or apixaban. The use of compression stockings was not routinely recommended in the absence of clear benefit in reducing the incidence of PTS. However, it was stated that stockings may be used on an individual basis for symptom relief [29]singlecentre studies without placebo control. We aimed to assess the efficacy of ECS, compared with placebo stockings, for the prevention of PTS. Methods We did a multicentre randomised placebo-controlled trial of active versus placebo ECS used for 2 years to prevent PTS after a first proximal DVT in centres in Canada and the USA. Patients were randomly assigned to study groups with a web-based randomisation system. Patients presenting with a first symptomatic, proximal DVT were potentially eligible to participate. They were excluded if the use of compression stockings was contraindicated, they had an expected lifespan of less than 6 months, geographical inaccessibility precluded return for follow-up visits, they were unable to apply stockings, or they received thrombolytic therapy for the initial treatment of acute DVT. The primary outcome was PTS diagnosed at 6 months or later using Ginsbergs criteria (leg pain and swelling of ≥ 1 month duration.

What is the optimal duration of anti-coagulation?

Due to the relatively poor evidence base behind the above ACCP recommendations, individual practices in IDDVT management still vary with no clear consensus. In his publication, Palareti argues that it is impossible to classify patients as asymptomatic IDDVT, as when a patient is either referred to or presents to hospital for DUS to exclude DVT, he/she is invariably symptomatic [30]. He goes on to point out that once IDDVT is diagnosed and the diagnosis is informed to the patient, they are likely to request some form of treatment, at least for symptomatic relief. Hence, in his perspective, he recommends treatment for all patients diagnosed with IDDVT, with possibly a shorter duration (4–6 weeks) for those deemed 'low-risk'. He defines this 'low-risk' subgroup as those having the first episode of DVT, provoked by a reversible risk factor and are not hospitalized or immobilized. This abbreviated 6-week regime has also been recommended by other studies who found it as effective as the standard duration of 12 weeks. Pinede et al. (DOVTAK tria-2001) [31] reported no advantage of a 12-week treatment schedule over the abbreviated 6-week course. Conversely, Ferrara et al. [32] reported a significantly higher rate of proximal thrombus extension with 6 weeks treatment as opposed to 12 weeks, especially among those with 2 or more calf veins involved. A meta-analysis by Franco et al. [33] also found a significantly lower rate of VTE recurrence among those who were treated for 12 weeks as opposed to 6 weeks.

The ongoing debate

The question of whether all patients diagnosed with IDDVT require anti-coagulant therapy remains one of the biggest conundrums in clinical practice. To date, there appears to be no final solution with conflicting reports from available studies, especially in the 'low-risk' patient with the first episode of IDDVT. Few prospective randomized studies have assessed the efficacy of anti-coagulation versus serial DUS and selective treatment in IDDVT.

Schwarz et al. [34] compared 10 days of LMWH with 3 months of compression therapy versus compression therapy alone. The study failed to show any superiority of this short duration LMWH therapy in reducing proximal extension or PE among the 'low-risk' patients with IDDVT. The CACTUS study was a randomized double-blind placebo-controlled study looking at standard anticoagulation for the same 'low-risk' patient population [35]. The study had to be prematurely ter-

minated due to expiry of the study drug before reaching the desired level of recruitment and hence carries low predictive value. However, from the intention to treat analysis, LMWH (nadroparin) for 6 weeks was found to be not superior to placebo in preventing proximal clot extension or reducing the incidence of PE. The treatment arm was actually found to have significantly higher rates of major as well as non-major bleeding events; risk difference 4.1% (95% CI 0.4 to 9.2; p = 0.0255). In a comprehensive meta-analysis by Franco et al. [33], the authors reported a significantly lower risk of VTE recurrence as well as PE in those who were treated with LMWH or oral anti-coagulants compared to no treatment with serial DUS only. They also reported no significant increase in major bleeding episodes among those who underwent anti-coagulation.

The most recent Cochrane review (2020) by Kirkilesis et al. [36] looked at the evidence for anti-coagulation against no-treatment or placebo in IDDVT. It concluded that the overall rate of VTE and DVT recurrence was reduced in those who underwent anti-coagulation compared to those in the placebo group or no-treatment group. However, there was no clear advantage of anti-coagulation in terms of prevention of PE. As for the duration of anti-coagulation, there was no difference between groups treated for 6 weeks as opposed to 12 weeks. Similar to the analysis by Franco and colleagues, this also found no significant difference in major bleeding episodes with the anti-coagulation. However, there was an increased incidence of clinically relevant, non-major bleeding.

Conclusions

While therapeutic anti-coagulation remains the benchmark in management of PDVT, the place and need for anti-coagulation in IDDVT remain a clinical conundrum. IDDVT remains an extremely common clinical condition accounting to approximately 50% of all diagnosed patients with DVT. Nevertheless, the number of good quality prospective randomized trials studying the place of routine anti-coagulation in IDDVT are few. Furthermore, as shown above, findings from these available studies are conflicting and do not offer clear guidance in formulating a management protocol.

While some studies show a benefit in anti-coagulation for all patients detected with IDDVT, other studies concluded that such treatment did not show any conclusive benefit over no intervention and possibly carries a higher risk of clinically significant bleeding episodes. Given the uncertainty and the lack of quality data to offer conclusive evidence, the final decision lies with the treating clinician to decide on an individualized plan of management. Those with severe symptoms, recurrent DVT or considered 'high-risk' for thrombus extension would benefit by therapeutic anti-coagulation over serial DUS monitoring. On the contrary, a careful assessment of risk-benefit balance is required in the low-risk patient with minimal symptoms where the probable benefit of anti-coagulation has to be balanced against potential adverse effects such as clinically significant bleeding. Such low-risk patients with IDDVT are possibly best managed by serial DUS screening if the logistics for such screening and follow up are feasible. Possible treatment of such patients with prophylactic dose anti-coagulation rather than therapeutic doses is a possible trade-off between minimising the bleeding risk and achieving the desired anti-coagulant effect. However, such interventions have not yet been tested in large scale studies at present time.

Conflict of interest

None.

References:

1. Heit JA, Spencer FA, White RH. The epidemiology of venous thromboembolism. J Thromb Thrombolysis. 2016; 41(1): 3–14, doi: 10.1007/s11239-015-1311-6, indexed in Pubmed: 26780736.
2. https://www cdc gov/ncbddd/dvt/data. Data and Statistics on Venous Thromboembolism | CDC.
3. Wei M, Zhu J, Yi X, et al. The prevalence of isolated calf deep vein thrombosis in patients with pulmonary embolism. Int Angiol. 2013; 32(5): 465–470, indexed in Pubmed: 23903304.
4. Mattos MA, Melendres G, Sumner DS, et al. Prevalence and distribution of calf vein thrombosis in patients with symptomatic deep venous thrombosis: a color-flow duplex study. J Vasc Surg. 1996; 24(5): 738–744, doi: 10.1016/s0741-5214(96)70006-x, indexed in Pubmed: 8918317.
5. Sapp B, Craddock G, Sapp J. Patterns and Distribution of Deep Vein Thrombus in the Lower Extremity. Journal for Vascular Ultrasound. 2018; 39(2): 71–77, doi: 10.1177/1544316715039002O1.
6. Wells PS, Ginsberg JS, Anderson DR, et al. Use of a clinical model for safe management of patients with suspected pulmonary embolism. Ann Intern Med. 1998; 129(12): 997–1005, doi: 10.7326/0003-4819-129-12-199812150-00002, indexed in Pubmed: 9867786.
7. Goodacre S, Sutton AJ, Sampson FC. Meta-analysis: The value of clinical assessment in the diagnosis of deep venous thrombosis. Ann Intern Med. 2005; 143(2): 129–139, doi: 10.7326/0003-4819-143-2-200507190-00012, indexed in Pubmed: 16027455.
8. Sartori M, Cosmi B, Legnani C, et al. The Wells rule and D-dimer for the diagnosis of isolated distal deep vein thrombosis. J Thromb Haemost. 2012; 10(11): 2264–2269, doi: 10.1111/j.1538-7836.2012.04895.x, indexed in Pubmed: 22906051.
9. Di Nisio M, Squizzato A, Rutjes AWS, et al. Diagnostic accuracy of D-dimer test for exclusion of venous thromboembolism: a systematic review. J Thromb Haemost. 2007; 5(2): 296–304, doi: 10.1111/j.1538-7836.2007.02328.x, indexed in Pubmed: 17155963.

10. Goodacre S, Sampson F, Thomas S, et al. Systematic review and meta-analysis of the diagnostic accuracy of ultrasonography for deep vein thrombosis. BMC Med Imaging. 2005; 5: 6, doi: 10.1186/1471-2342-5-6, indexed in Pubmed: 16202135.
11. Zhang Y, Xia H, Wang Y, et al. The rate of missed diagnosis of lower-limb DVT by ultrasound amounts to 50% or so in patients without symptoms of DVT: A meta-analysis. Medicine (Baltimore). 2019; 98(37): e17103, doi: 10.1097/MD.0000000000017103, indexed in Pubmed: 31517841.
12. Heit J, Petterson T, Farmer S, et al. Trends in the incidence of deep vein thrombosis and pulmonary embolism: a 35-year population-based study. Blood. 2006; 108(11): 1488–1488, doi: 10.1182/blood.v108.11.1488.1488.
13. Needleman L, Cronan J, Lilly M, et al. Ultrasound for lower extremity deep venous thrombosis. Circulation. 2018; 137(14): 1505–1515, doi: 10.1161/circulationaha.117.030687.
14. Kearon C, Kearon C. Natural history of venous thromboembolism. Circulation. 2003; 107(23 Suppl 1): I22–I30, doi: 10.1161/01.CIR.0000078464.82671.78, indexed in Pubmed: 12814982.
15. Sevestre MA, Quashié C, Genty C, et al. Clinical presentation and mortality in pulmonary embolism: The Optimev study. Journal des Maladies Vasculaires. 2010; 35(4): 242–249, doi: 10.1016/j.jmv.2010.05.004.
16. Galanaud JP, Quenet S, Rivron-Guillot K, et al. RIETE INVESTIGATORS. Comparison of the clinical history of symptomatic isolated distal deep-vein thrombosis vs. proximal deep vein thrombosis in 11 086 patients. J Thromb Haemost. 2009; 7(12): 2028–2034, doi: 10.1111/j.1538-7836.2009.03629.x, indexed in Pubmed: 19793188.
17. Fleck D, Albadawi H, Wallace A, et al. Below-knee deep vein thrombosis (DVT): diagnostic and treatment patterns. Cardiovasc Diagn Ther. 2017; 7(Suppl 3): S134–S139, doi: 10.21037/cdt.2017.11.03, indexed in Pubmed: 29399516.
18. Garry J, Duke A, Labropoulos N. Systematic review of the complications following isolated calf deep vein thrombosis. Br J Surg. 2016; 103(7): 789–796, doi: 10.1002/bjs.10152, indexed in Pubmed: 27060255.
19. Kearon C, Akl EA, Ornelas J, et al. Antithrombotic therapy for VTE disease: CHEST guideline and expert panel report. Chest. 2016; 149(2): 315–352, doi: 10.1016/j.chest.2015.11.026, indexed in Pubmed: 26867832.
20. Galanaud JP, Sevestre MA, Genty C, et al. OPTIMEV-SFMV investigators. Incidence and predictors of venous thromboembolism recurrence after a first isolated distal deep vein thrombosis. J Thromb Haemost. 2014; 12(4): 436–443, doi: 10.1111/jth.12512, indexed in Pubmed: 24450376.
21. Sartori M, Migliaccio L, Favaretto E, et al. Two years outcome of isolated distal deep vein thrombosis. Thromb Res. 2014; 134(1): 36–40, doi: 10.1016/j.thromres.2014.03.033, indexed in Pubmed: 24713107.
22. Barco S, Corti M, Trinchero A, et al. Survival and recurrent venous thromboembolism in patients with first proximal or isolated distal deep vein thrombosis and no pulmonary embolism. J Thromb Haemost. 2017; 15(7): 1436–1442, doi: 10.1111/jth.13713, indexed in Pubmed: 28439954.
23. Galanaud JP, Monreal M, Kahn SR, et al. Epidemiology of the post-thrombotic syndrome. Thromb Res. 2018(164): 100–109.
24. Meissner MH, Caps MT, Bergelin RO, et al. Early outcome after isolated calf vein thrombosis. J Vasc Surg. 1997; 26(5): 749–756, doi: 10.1016/s0741-5214(97)70086-7, indexed in Pubmed: 9372811.
25. Saarinen JP, Domonyi K, Zeitlin R, et al. Postthrombotic syndrome after isolated calf deep venous thrombosis: the role of popliteal reflux. J Vasc Surg. 2002; 36(5): 959–964, doi: 10.1067/mva.2002.127523, indexed in Pubmed: 12422091.
26. McLafferty RB, Moneta GL, Passman MA, et al. Late clinical and hemodynamic sequelae of isolated calf vein thrombosis. J Vasc Surg. 1998; 27(1): 50–56; discussion 56, doi: 10.1016/s0741-5214(98)70291-5, indexed in Pubmed: 9474082.
27. Galanaud JP, Righini M, Le Collen L, et al. Long-term risk of postthrombotic syndrome after symptomatic distal deep vein thrombosis: The CACTUS-PTS study. J Thromb Haemost. 2020; 18(4): 857–864, doi: 10.1111/jth.14728, indexed in Pubmed: 31899848.
28. Kearon C, Kahn SR, Agnelli G, et al. Antithrombotic therapy for venous thromboembolic disease: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest. 2008; 133(6 Suppl): 454S–545S, doi: 10.1378/chest.08-0658, indexed in Pubmed: 18574272.
29. Kahn SR, Shapiro S, Wells PS, et al. SOX trial investigators. Compression stockings to prevent post-thrombotic syndrome: a randomised placebo-controlled trial. Lancet. 2014; 383(9920): 880–888, doi: 10.1016/S0140-6736(13)61902-9, indexed in Pubmed: 24315521.
30. Palareti G. How I Treat isolated distal DVT. Blood. 2015; 123: 1802–1810.
31. Pinede L, Ninet J, Duhaut P, et al. Investigators of the "Durée Optimale du Traitement AntiVitamines K" (DOTAVK) Study. Comparison of 3 and 6 months of oral anticoagulant therapy after a first episode of proximal deep vein thrombosis or pulmonary embolism and comparison of 6 and 12 weeks of therapy after isolated calf deep vein thrombosis. Circulation. 2001; 103(20): 2453–2460, doi: 10.1161/01.cir.103.20.2453, indexed in Pubmed: 11369685.
32. Ferrara F, Meli F, Amato C, et al. Optimal duration of treatment in surgical patients with calf venous thrombosis involving one or more veins. Angiology. 2006; 57(4): 418–423, doi: 10.1177/0003319706290745, indexed in Pubmed: 17022376.
33. Franco L, Giustozzi M, Agnelli G, et al. Anticoagulation in patients with isolated distal deep vein thrombosis: a meta-analysis. J Thromb Haemost. 2017; 15(6): 1142–1154, doi: 10.1111/jth.13677, indexed in Pubmed: 28316124.
34. Schwarz T, Buschmann L, Beyer J, et al. Therapy of isolated calf muscle vein thrombosis: a randomized, controlled study. J Vasc Surg. 2010; 52(5): 1246–1250, doi: 10.1016/j.jvs.2010.05.094, indexed in Pubmed: 20630682.
35. Righini M, Galanaud JP, Guenneguez H, et al. Anticoagulant therapy for symptomatic calf deep vein thrombosis (CACTUS): a randomised, double-blind, placebo-controlled trial. Lancet Haematol. 2016; 3(12): e556–e562, doi: 10.1016/S2352-3026(16)30131-4, indexed in Pubmed: 27836513.
36. Kirkilesis G, Kakkos SK, Bicknell C, et al. Treatment of distal deep vein thrombosis. Cochrane Database Syst Rev. 2020; 4: CD013422, doi: 10.1002/14651858.CD013422.pub2, indexed in Pubmed: 32271939.

VIA MEDICA

CASE REPORTS

Acta Angiol
Vol. 26, No. 2, pp. 72–75
Doi: 10.5603/AA.2020.0014

ISSN 1234–950X
www.journals.viamedica.pl/acta_angiologica

Retained neuroprotection filter after stenting of the internal carotid artery

Piotr Myrcha[1, 2], Dawid Siemieniuk[2], Mariusz Kozak[2], Dorota Różański[3], Tomasz Miłek[1], Witold Woźniak[1, 2], Piotr Ciostek[1]

[1]First Chair and Department of General and Vascular Surgery, The Faculty of Medicine, Medical University of Warsaw, Poland
[2]Department of General, Vascular and Oncological Surgery, Masovian Brodnowski Hospital, Warsaw, Poland
[3]Department of Neurology, Faculty of Health Science, Medical University of Warsaw, Poland

Abstract

Retained neuroprotection filter after carotid stenting (CAS) is an extremely rare complication. We report the case of a 61-year old patient with an accidentally retained neuroprotection filter after urgent CAS. The patient did not consent to open surgical removal of the retained basket. We did not observe any flow disturbances in the filter and the patient remains asymptomatic in ten years follow-up. In some cases, the neuroprotection filter left in the internal carotid artery may not cause cerebral flow disturbances or occlusion of the stent. In case of the poor neurological or general condition of the patient, we can wait for its improvement or stenting.

Key words: carotid stenting, embolic protection filter, retained neuroprotection, acute stroke, thrombolysis

Acta Angiol 2020; 26, 2: 72–75

Introduction

The use of cerebral protection device (CPD) during CAS is a standard procedure [1, 2]. However, using distal CPD may be associated with complications [3–5]. Some meta-analysis found no evidence that CPD usage was associated with reduced perioperative stroke rates [6]. Retained neuroprotection filter after stenting of the internal carotid artery is an extremely rare complication but requires reintervention. Instruction for use does not include leaving the filter after the procedure in the artery.

This article was conducted according to the recommendations of the CARE — case report guidelines.

Case report

We report herein the case of a patient with a history of ischemic stroke, intravenous thrombolysis and stenting of the right ICA stenosis complicated by accidentally retained neuroprotection filter above the stent. Informed consent has been obtained from the patient for publication of the case report and accompanying images.

In October 2008, a 61-year-old man suffered a right hemispheric stroke (Table 1). Intracranial bleeding was excluded on computed tomography (CT). An ischemic stroke was confirmed by magnetic resonance imaging (MR-DWI). Occlusion of the right ICA was found in duplex ultrasound (DUS).

The patient underwent intravenous thrombolysis. Alteplase (Actilyse-Boehringer-Ingelheim) — a dose of 0.9 mg/kg/h, following a 10 mg intravenous bolus injection for one hour. A significant reduction of the left hemiparesis was observed. 90% stenosis of the right ICA was found in DUS. In the following hours the symptoms, however, intensified. Arteriography showed occlusion of this artery. Alteplase was therefore administered via a vascular sheet positioned in the right common carotid artery, in two boluses of 5mg each, with an interval of 2 minutes. Repeat arteriogram con-

Address for correspondence: Piotr Myrcha, Department of General and Vascular Surgery, Brodnowski Hospital 03–242 Warsaw, Kondratowicza 8, Poland, Phone: +48 22 326 56 35, Mobile phone: +48 607 366 683, e-mail: piotrmyr@poczta.fm, piotr.myrcha@wum.edu.pl

Table 1. Patient characteristic data

Sex		Male
Age		61
Weight		95 kg
Height		185 cm
BMI		27.8
ABI		1.1
Hba1c		< 6.5%
Neurological symptoms		TIA — weeks before CAS RICA Stroke — immediately before CAS RICA
Commorbidities Nicotinism		Hypertension, Diabetes — insulin dependent No
Neurological status		
	NIHSS Scale	Modified Rankin Scale
Before trombolysis	11	5
After CAS RICA	5	3
Current status (02.12.2020)	2	1

BMI: body mass index; ABI: ankle brachial index; Hba: glycosylated haemoglobin; TIA: transient ischemic attack; CAS: carotid artery stenting; RICA: right internal carotid artery; NIHSS: The National Institutes of Health Stroke Scale

firmed patency of the right ICA with 90% stenosis. An Accunet (Abbott Vascular) CPD was deployed, followed by implantation of an Acculink (Abbott Vascular) 6–8/ /30 mm stent. Then we used a recovery catheter and we removed it from the carotid artery after (as we thought) folding the basket. The patient did not cooperate during the procedure and we had no chance to angiographically control all this process. During CPD removal, the filter and guidewire were disconnected. Filter has stayed in artery. Control angiography showed a well-positioned, patent stent and excellent cerebral flow. Arteriogram also confirmed a retained neuroprotection filter above the stent. Due to the poor general and neurological condition of the patient no open surgical removal of the filter was attempted at this time.

The patient recovered without important complications. Clopidogrel (1 × 75 mg), ASA (1 × 75 mg) and Enoxaparine (1 × 40 mg) were administered postoperatively and he was discharged five days after CAS. The patient did not consent to elective filter removal.

DUS performed at 3-month intervals showed a patent stent without any relevant stenosis. Control CTA was performed in 2013 and 2018 (Fig. 1A). In October of 2016, he underwent CAS due to a 75% asymptomatic left ICA stenosis, without any complications. A right ICA angiography showed no evidence of stenosis nor migration of the filter (Fig. 1B). Eleven years after CAS and retained filter the patient remained asymptomatic with patent RICA (Figs 2A, B).

Discussion

Using a distal CPD during CAS may be challenging due to the ICA anatomy, the type of filter and the technical skill required of interventionists [7, 8]. The most common causes of difficult retrieval of CPD are strongly calcified plaques, residual in-stent stenosis, carotid tortuosity and re-CAS due to stent fracture [9–12]. Neurological complications may occur due to vasospasm, filter thrombosis, cerebral embolism or carotid artery dissection [13, 14]

The first choice in the retrieval of entangled CPD is endovascular technique, effective in most cases [15, 16]. In case of failure, conversion to open surgery is necessary [17–19]. In the available literature, both techniques are burdened with a small percentage of serious complications.

Our complication is very rare, but the risk of device entrapment should be considered during stenting procedures. We found a similar case described in the ARCHeR3 study [20]. The interventionist implanted stent pressing the basket to the artery wall. There was no description as to whether IFU was followed at the time of surgery. In our case, the neuroprotection basket was on the upper edge of the stent. It was against the IFU. On the other hand, the patient was not cooperated during the procedure, the effect of which basket became entangled with the deployed stent and detached from the guide wire during the retrieval attempt.

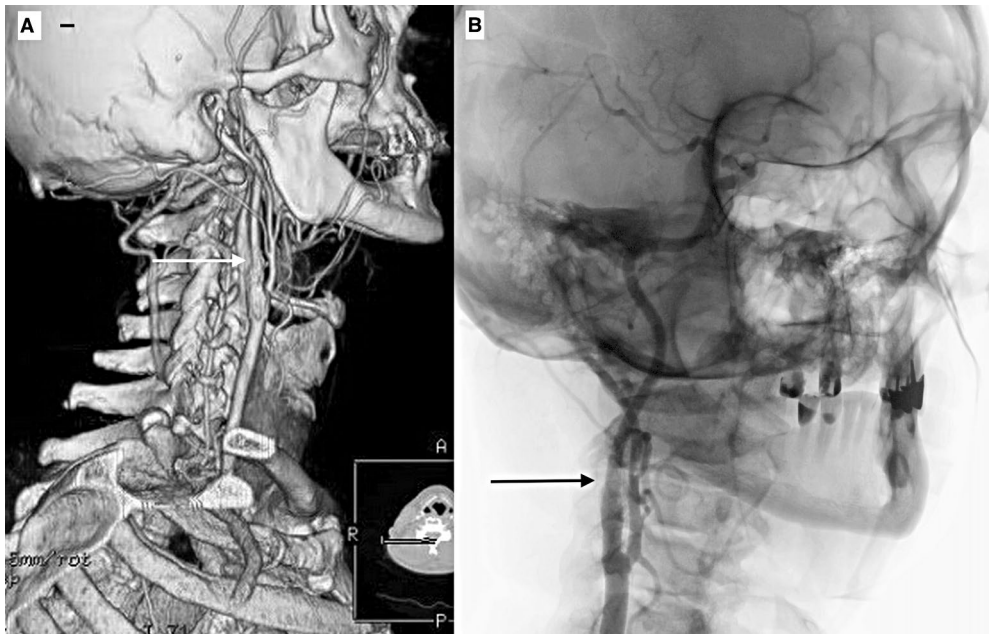

Figure 1. A — computed tomography angiography of the right carotid arteries — 10 years after RICA stenting. White arrow — a place of the retained filter; **B** — angiography of the right carotid arteries — 8 years after RICA stenting. Black arrow — a place of the retained filter

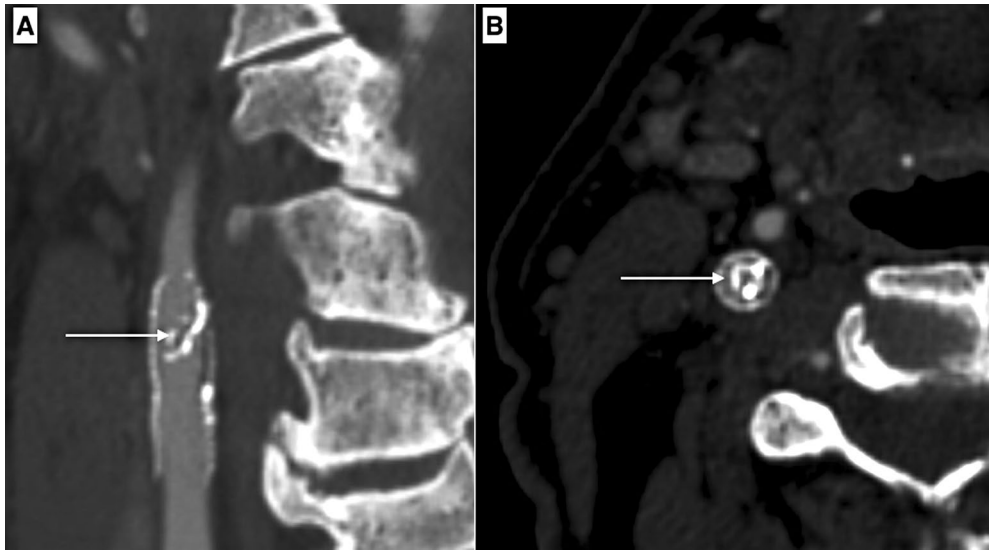

Figure 2. A — retained neuroprotection filter (arrow); **B** — retained neuroprotection filter (arrow)

A guidewire connected to the basket would give a chance for endovascular removal of the device.

Filter of the distal CPD is not suitable to leave it in situ like, such for example, vena cava filters. According to many authors, there is a huge risk of occlusion of the filter caused by thrombosis and occlusion of filter pores by embolization and hyperplasia. However, these observations concern acute, intraoperative occlusion [5, 16]. We did not find results regarding late carotid filter patency in the literature.

Application of the conversion to the open surgery or filter stenting should depend on the condition of the patient. Lack of patient cooperation was the main factor causing insufficient control in subsequent stages of the procedure. In the case of significant flow restriction by neuroprotection or the appearance of

neurological symptoms, we will propose the patient surgical treatment.

Conclusion

The removal of neuroprotection filter left in carotid artery does not have to be done at all costs- in some cases it is more reasonable to adopt a strategy „watch and wait".

Conflicts of interest

None.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

References:

1. Zahn R, Ischinger T, Mark B, et al. Arbeitsgemeinschaft Leitende Kardiologische Krankenhausärzte (ALKK). Embolic protection devices for carotid artery stenting: is there a difference between filter and distal occlusive devices? J Am Coll Cardiol. 2005; 45(11): 1769–1774, doi: 10.1016/j.jacc.2005.02.067, indexed in Pubmed: 15936604.
2. Touzé E, Trinquart L, Felgueiras R, et al. Carotid Stenting Trialists' Collaboration. Systematic review of the perioperative risks of stroke or death after carotid angioplasty and stenting. Stroke. 2009; 40(12): e683–e693, doi: 10.1161/STROKEAHA.109.562041, indexed in Pubmed: 19892997.
3. Cremonesi A, Castriota F, Secco GG, et al. Carotid artery stenting: an update. Eur Heart J. 2015; 36(1): 13–21, doi: 10.1093/eurheartj/ehu446, indexed in Pubmed: 25535085.
4. Kwon BJu, Han MH, Kang HS, et al. Protection filter-related events in extracranial carotid artery stenting: a single-center experience. J Endovasc Ther. 2006; 13(6): 711–722, doi: 10.1583/06-1900.1, indexed in Pubmed: 17154708.
5. Sorimachi T, Nishino K, Morita K, et al. Obstruction of pores in distal protection filters and angiographically-documented flow impairment during carotid artery stenting. J Endovasc Ther. 2010; 17(5): 661–670, doi: 10.1583/10-3142MR.1, indexed in Pubmed: 20939728.
6. Bonati LH, Dobson J, Featherstone RL, et al. International Carotid Stenting Study investigators. Long-term outcomes after stenting versus endarterectomy for treatment of symptomatic carotid stenosis: the International Carotid Stenting Study (ICSS) randomised trial. Lancet. 2015; 385(9967): 529–538, doi: 10.1016/S0140-6736(14)61184-3, indexed in Pubmed: 25453443.
7. Featherstone RL, Dobson J, Ederle J, et al. Carotid artery stenting compared with endarterectomy in patients with symptomatic carotid stenosis (International Carotid Stenting Study): a randomised controlled trial with cost-effectiveness analysis. Health Technol Assess. 2016; 20(20): 1–94, doi: 10.3310/hta20200, indexed in Pubmed: 26979174.
8. Bonati LH, Fraedrich G. Carotid Stenting Trialists' Collaboration. Age modifies the relative risk of stenting versus endarterectomy for symptomatic carotid stenosis--a pooled analysis of EVA-3S, SPACE and ICSS. Eur J Vasc Endovasc Surg. 2011; 41(2): 153–158, doi: 10.1016/j.ejvs.2011.01.001, indexed in Pubmed: 21269847.
9. Lian X, Liu W, Li M, et al. Risk factors and complications associated with difficult retrieval of embolic protection devices in carotid artery stenting. Cardiovasc Intervent Radiol. 2012; 35(1): 43–48, doi: 10.1007/s00270-011-0117-y, indexed in Pubmed: 21387123.
10. Arai S, Ikeda H, Kawamo M, et al. Surgical Rescue Retrieval of a Filter Protection Device in Carotid Artery Stenting with Stent Deformation: Case Report and Literature Review. World Neurosurg. 2019; 122: 215–219, doi: 10.1016/j.wneu.2018.10.214, indexed in Pubmed: 30415040.
11. Coppi G, Moratto R, Veronesi J, et al. Carotid artery stent fracture identification and clinical relevance. J Vasc Surg. 2010; 51(6): 1397–1405, doi: 10.1016/j.jvs.2010.02.009, indexed in Pubmed: 20488322.
12. Chang CK, Huded CP, Nolan BW, et al. Prevalence and clinical significance of stent fracture and deformation following carotid artery stenting. J Vasc Surg. 2011; 54(3): 685–690, doi: 10.1016/j.jvs.2011.03.257, indexed in Pubmed: 21889703.
13. Texakalidis P, Letsos A, Kokkinidis DG, et al. Proximal embolic protection versus distal filter protection versus combined protection in carotid artery stenting: A systematic review and meta-analysis. Cardiovasc Revasc Med. 2018; 19(5 Pt A): 545–552, doi: 10.1016/j.carrev.2017.12.010, indexed in Pubmed: 29502959.
14. Cremonesi A, Manetti R, Setacci F, et al. Protected carotid stenting: clinical advantages and complications of embolic protection devices in 442 consecutive patients. Stroke. 2003; 34(8): 1936–1941, doi: 10.1161/01.STR.0000081000.23561.61, indexed in Pubmed: 12843347.
15. Daugherty WP, White JB, Cloft HJ, et al. Rescue retrieval of AngioGuard embolic capture system after failure of capture sheath retrieval in carotid angioplasty and stenting. AJNR Am J Neuroradiol. 2008; 29(8): 1594–1595, doi: 10.3174/ajnr.A1118, indexed in Pubmed: 18499793.
16. Lee JH, Youn SW, Kim HoK. Locking between a cerebral protection device and a stent-delivering catheter during carotid artery stenting. Interv Neuroradiol. 2014; 20(1): 100–105, doi: 10.15274/INR-2014-10015, indexed in Pubmed: 24556307.
17. Shilling K, Uretsky BF, Hunter GC. Entrapment of a cerebral embolic protection device--a case report. Vasc Endovascular Surg. 2006; 40(3): 229–233, doi: 10.1177/153857440604000308, indexed in Pubmed: 16703211.
18. Page P, Niemann D, Son C, et al. Retained distal protection device during carotid artery stenting necessitating carotid endarterectomy: A complication and management considerations. Surg Neurol Int. 2018; 9: 123, doi: 10.4103/sni.sni_32_18, indexed in Pubmed: 30009087.
19. Li T, Zha Y, Bo L, et al. Surgical management for retained distal embolic protection device and fractured guidewire after carotid artery stenting. J Surg Case Rep. 2016; 2016(6), doi: 10.1093/jscr/rjw105, indexed in Pubmed: 27316621.
20. Gray WA, Hopkins LN, Yadav S, et al. ARCHeR Trial Collaborators. Protected carotid stenting in high-surgical-risk patients: the ARCHeR results. J Vasc Surg. 2006; 44(2): 258–268, doi: 10.1016/j.jvs.2006.03.044, indexed in Pubmed: 16890850.

VIA MEDICA

CASE REPORTS

Acta Angiol
Vol. 26, No. 2, pp. 76–80
Doi: 10.5603/AA.2020.0012

ISSN 1234–950X
www.journals.viamedica.pl/acta_angiologica

Aortoesophageal fistula as a complication of thoracic aorta stent graft implantation: two cases and literature review

Olga Basiak[1], Laretta Grabowska-Derlatka[2], Tomasz Jakimowicz[3], Olgierd Rowiński[2]

[1]Students Scientific Association at the 2nd Department of Clinical Radiology Medical University of Warsaw, Poland
[2]2nd Department of Clinical Radiology, Medical University of Warsaw, Warsaw, Poland
[3]Department of General, Vascular and Transplant Surgery, Medical University of Warsaw, Poland

Abstract

Thoracic endovascular aortic repair (TEVAR) is a method of choice in the treatment of thoracic aorta aneurysms and dissections. In case of a thoracoabdominal aneurysm, endovascular treatment is also being chosen more often, especially in patients with multimorbidity. Despite better results and less invasiveness in comparison to classic open surgery, endovascular treatment is also associated with complications. One of the rarer and usually fatal complications are aortoesophageal fistula (AEF). We present two cases, in which TEVAR complication was AEF. Case 1 was an 87-year-old woman with a history of TEVAR 5 years earlier, who presented increased inflammation parameters, massive gastrointestinal bleeding, and progressive anemia. Case 2 was a 66-year-old woman with a history of TEVAR 6 months earlier, who on admission presented medium increased inflammatory markers and anemia. None of the patients was qualified for surgical treatment. Both patient 1 and patient 2 died during hospitalization. Diagnostic imaging plays a key role in the diagnosis of AEF. CT angiography performed in patients with AEF can show the presence of gas in the sac of aneurysm as a result of infection, a defect in the aortic wall, or thickened esophagus with fluid level. CT angiography of the aorta combined with esophagogastroduodenoscopy (EGD) and contrast-enhanced X-ray examination of the gastrointestinal tract, enables to confirm or exclude the diagnosis of AEF. Atypical clinical feature and increased parameters of inflammation in patients with the history of TEVAR should always suggest the presence of AEF.

Key words: computer tomography, aortoesophageal fistula, aortobronchial fistula esophagogastroduodenoscopy, thoracic endovascular aortic repair

Acta Angiol 2020; 26, 2: 76–80

Introduction

Thoracic endovascular aortic repair (TEVAR) is a method of choice in the treatment of thoracic aorta aneurysms and dissections. In case of thoracoabdominal aneurysm, endovascular treatment is also being chosen more often, especially in patients with multimorbidity. Despite better results and less invasiveness in comparison to classical open surgery, endovascular treatment is also associated with complications. The most common complications are endoleaks to the aneurysmal sac. Rare complications include migration of stent graft, spinal cord ischemia and aortoesophageal fistula (AEF) [1]. We present two cases after thoracic stent graft implantation. We also review the literature.

Case report 1

87-year-old woman, who had undergone stent graft implantation due to thoracic aortic aneurysm, was admitted to the hospital with weakness and dehydration. On admission the patient was in medium condition, and hemodynamically stable. Laboratory test results

Address for correspondence: Olga Basiak, Students Scientific Association at the 2nd Department of Clinical Radiology Medical University of Warsaw, Banacha 1a, 02–097 Warsaw, Poland, e-mail: basiakolga3@gmail.com

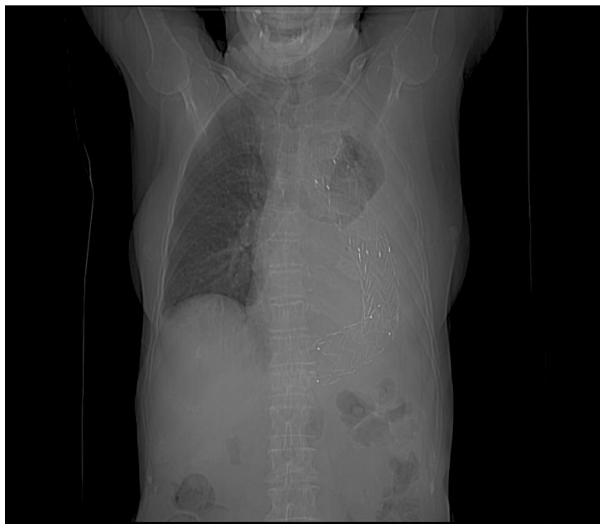

Figure 1. Case report 1. Chest radiograph showing pleural effusion and atelectasis of left lung

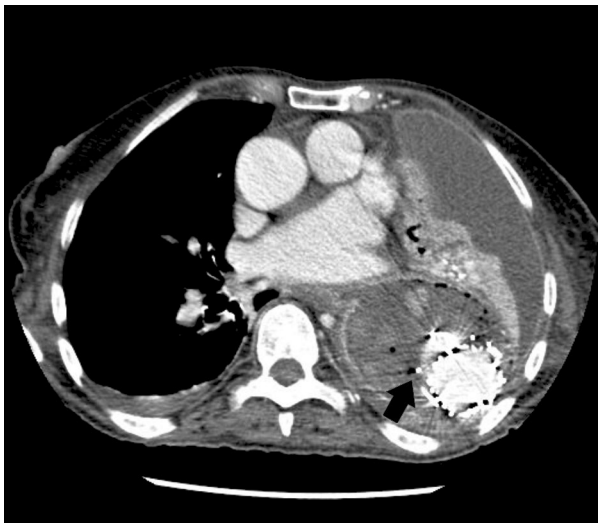

Figure 2. Case report 1. Computer tomography showing the presence of gas in the aneurysmal sac (black arrow)

showed anemia (Hb 9,4 g/dl, RBC 3,27 × $10^6\mu$l), increased inflammatory markers (WBC 17,05 × $10^6\mu$l, CRP 143,8 mg/dl) and extremely elevated D-dimer (5477 ng/dl). Chest radiography showed pleural effusion and atelectasis of the left lung as a result of compression by the fluid and aortic aneurysm (Fig. 1). Antibiotics were implemented due to clinical, laboratory and auscultatory symptoms of pneumonia. During hospitalization, melaena and progressive anemia have been occurred (with the marginal level of Hb 6 g/dl). Due to the patient's clinical status, the blood products were transfused. CT angiography of aorta showed the presence of gas in aneurysm sac, defect in the aortic wall and thickened esophagus with the level of fluid (Figs 2–4). The whole radiological feature had shown the presence of AEF. Oral water contrast-enhanced X-ray of the esophagus revealed extraesophageal leakage of contrast, most likely into the aneurysmal sac (Fig. 5). EGD under general anesthesia was performed and demonstrated the presence of a wide fistula between aneurysmal sac and the mid-thoracic esophagus. The SEMS prosthesis was implanted under endoscopy control. In addition, control esophagus x-ray examination revealed the tightness of the prosthesis (Fig. 6). Open surgical repair of the aneurysm after the patient's general condition improvement was planned. Despite the temporary clinical stabilization and no significant improvement, the patient died 13 days after admission to the hospital.

Case report 2

66-year-old woman, who had undergone endovascular treatment of the thoracoabdominal aneurysm using stent graft with branches to the visceral arteries

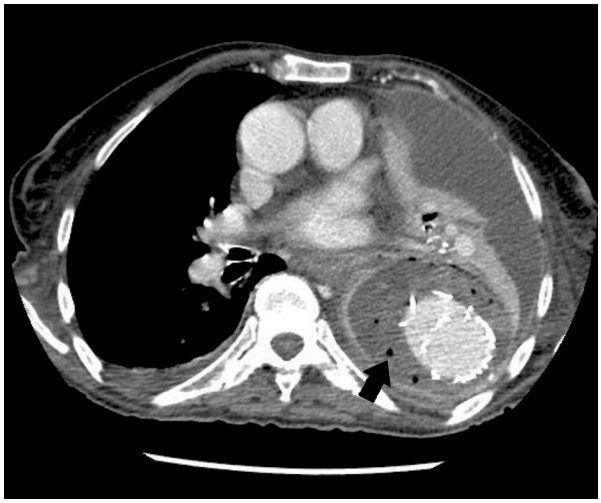

Figure 3. Case report 1. Computer tomography showing the presence of gas in the aneurysmal sac (black arrow)

6 months ago, was admitted to the hospital in bad general condition. Based on the angio-CT examination, AEF (defect in the aortic wall and aneurysmal sac), mediastinitis and infection of the aneurysm sac were suspected (Figs 7, 8). The patient had symptoms of dyspnoea, chest pain and fever. On admission, blood tests and blood culture had been taken. Blood biomarkers of bacterial infection were increased (procalcitonin 96 ng/ml, CRP 328 mg/dl, WBC 12,4 × $10^6\mu$l) and blood culture was positive for Enterococcus species. Antibiotherapy and oxygen therapy had been introduced. Anemia was found with no decline dynamics, which would suggest active bleeding. Taking into considera-

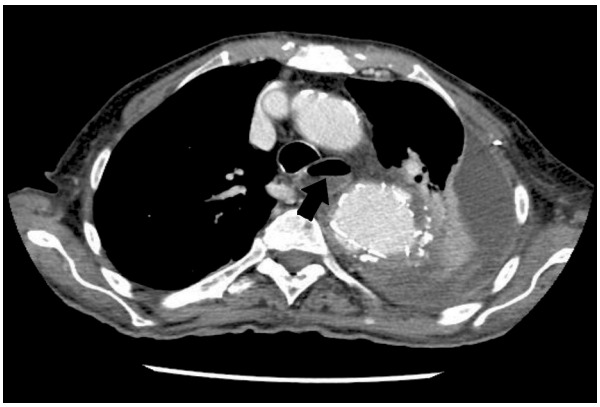

Figure 4. Case report 1. Computer tomography showing thickened esophagus with the level of fluid (black arrow)

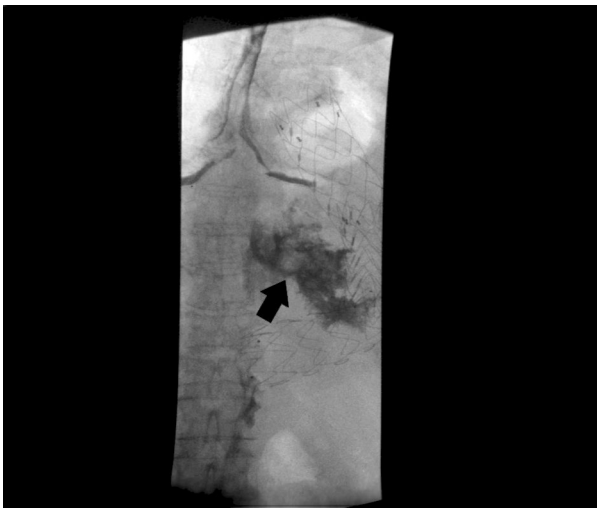

Figure 5. Case report 1. Oral water contrast-enhanced X-ray examination of the esophagus showing extraesophageal leakage of contrast (black arrow)

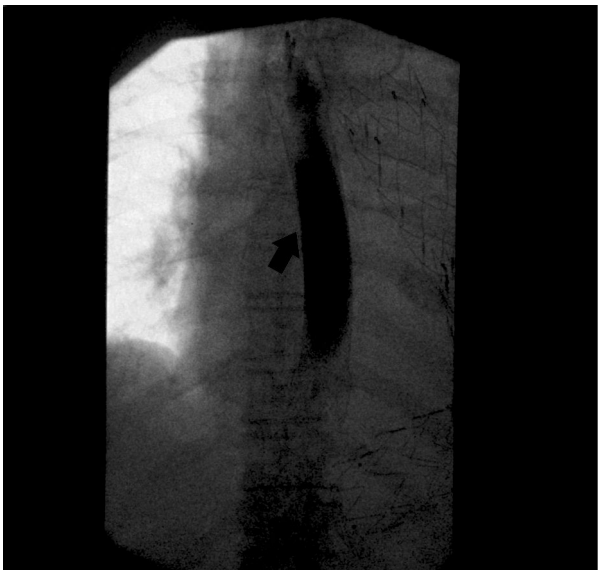

Figure 6. Case report 1. Esophagus x-ray examination showing the tightness of the SEMS prosthesis (black arrow)

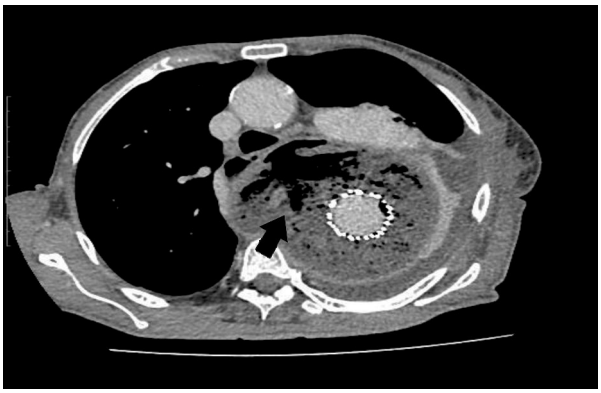

Figure 7. Case report 2. Computer tomography showing the presence of gas in the aneurysmal sac (black arrow)

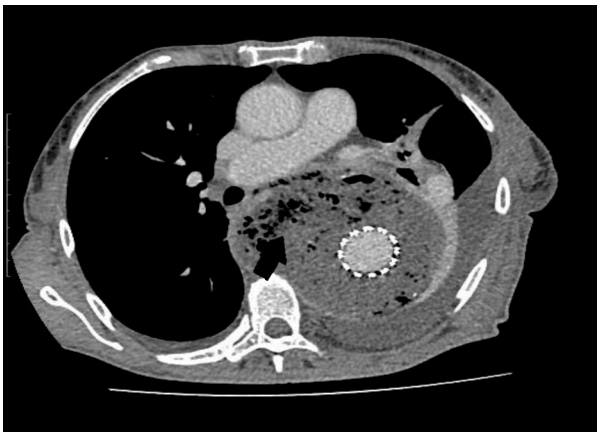

Figure 8. Case report 2. Computer tomography showing the presence of gas in the aneurysmal sac (black arrow)

tion bad general condition and no chance of survival, the patient was disqualified from open surgical repair of the thoracoabdominal aneurysm. The patient died 4 days after admission.

Discussion

Aortoesophageal fistula (AEF) is a rare complication after TEVAR [1, 2]. In the literature, authors underline the great role of quick diagnostics due to difficult to control anemia [2, 3]. Computer tomography is an examination of choice in patients who had undergone TEVAR in case of suspected complications. In patients with AEF, CT angiogram shows the presence of gas in aneurysm sac [2, 4, 5], thickening of esophagus [6], and new nonhomogenous masses between aorta and

esophagus [2, 7]. In our cases, the presence of gas in aneurysm sac (Patient 1 and 2), as well as thickened esophagus and defect in the aortic wall (Patient 1) were detected. Esophagus x-ray examination with contrast can confirm or exclude the presence of AEF (as per case 1 which confirmed preliminary diagnosis based on CT). EGD not always identifies the place and cause of bleeding [5, 6]. However, in combination with CT scans, it significantly increases the probability of confirmation or exclusion of AEF [2–8]. Therefore, it seems that EGD should be the examination of choice when AEF is suspected, despite the risk of additional transmission of bacteria from the esophagus to the aneurysmal sac.

The time to develop AEF after TEVAR varies. Analyzing literature, we can conclude that AEF develops within 1 to 16 months after the endovascular procedure [2–8]. Nevertheless, patient 1 developed AEF much later — 5 years after TEVAR.

There are many hypotheses regarding the cause of AEF. Mechanisms of AEF development after TEVAR include: 1) pressure necrosis of the esophageal wall due to the ongoing forces of the self-expanding stent-graft, 2) direct erosion of the rigid stent-graft through the aorta into the esophagus, 3) ischemic esophageal necrosis due to stent-graft occlusion of aortic side branches that directly feed the esophagus, 4) infection of stent-graft prosthesis and aneurysmal sac that eventually extends to the esophagus eroding its wall [7, 9]. Due to uncertain pathophysiologic mechanisms, we cannot isolate patients at high-risk, neither the time at which complications may occur.

Patients with AEF after TEVAR usually die before the beginning of treatment due to the presence of bleeding and general bad condition [3, 6, 8]. In these cases, the only option is open surgery with removal of the stent graft and replacement of the aorta with a vascular prosthesis. The majority of patients, such as those described in our article, do not qualify for open surgery [2, 5, 5]. Then, therapeutic opportunities are limited. Therefore, esophageal stent implantation may be palliative procedure [2, 5, 7]. However, this method doesn't provide long-term effectiveness. There was the only one case of a patient with AEF free of the gastrointestinal bleeding reported [7].

Eggebrecht et al. described 6 patients who developed AEF after TEVAR. 4 of 6 patients were admitted to the hospital due to vomiting blood, and 2 other due to elevated markers of inflammation (such as patient 1 and 2). Surgical repair was performed in only 1 patient and declined in the remaining because of comorbidities and multiorgan failure. In 2 remaining patients who had undergone EGD for massive hematemesis self-expanding esophageal stents were implanted in order to control bleeding. Although conservative treatment was applied (percutaneous endoscopy-guided gastrostomy PEG, broad-spectrum antibiotics and proton pump inhibitor), all patients died due to massive bleeding and mediastinitis within 20-221 days after admission to the hospital [2].

Leung reported a 74-year-old patient with a history of TEVAR, who was admitted to the hospital due to recurrent hemoptysis. On admission, the patient wasn't presenting any abnormalities in physical examination, nor in laboratory tests. EGD, bronchoscopy and CT angiography were performed. EGD detected no active bleeding, while bronchoscopy indicated external compression of the distal trachea. CT angiogram revealed the presence of pseudoaneurysm of the thoracic aorta distal to the take-off of the subclavian artery, suggesting vasculitis of the thoracic aorta. Endobronchial ultrasound showed aortic diverticulum in the place of tracheal compression. The whole radiological findings confirmed the presence of aortobronchial fistula (ABF). Therefore, it seems that the presence of the pseudoaneurysm, as well as compression of the airways in patients after TEVAR, may also suggest ABF [10].

During 1998–2013, Mosquera et al. [11] reviewed 26 patients with thoracic aorta fistulas (18 with aortobronchial, 7 with aortoesophageal, and 1 with co-existing aortic fistulas to the esophagus and bronchial tree). Authors were analyzing CT findings performed in all patients. The most common CT scan findings (in descending order of frequency) were: an intramural hematoma, an aortic pseudoaneurysm bulge, and bronchial compression. Interestingly, none of the patients with ABF presented periaortic gas. Both active contrast extravasation and the ectopic gas occurred exclusively in those with AEF and were associated with a worse prognosis. Intramural hematoma, an aortic pseudoaneurysm bulge and bronchial compression were common for those with AEF and ABF. All the authors underline the key role that CT plays in diagnosing patients with AEF and ABF.

Conclusions

Gastrointestinal bleeding, as well as elevated inflammatory markers and atypical clinical feature after TEVAR may suggest the presence of AEF. CT imaging combined with EGD and gastrointestinal X-ray examination may confirm or exclude AEF. Nevertheless, the ineffectiveness of treatment indicates that AEF remains a challenge for the medical team.

Conflict of interest

None.

References:

1. Kulesza J. Evaluation of effectiveness and safety of endovascular treatment of patients with thoracic aorta disease by means of a stent-graft. 2017; WBC Poznań.
2. Eggebrecht H, Mehta R, Dechene A, et al. Aortoesophageal fistula after thoracic aortic stent-graft placement. JACC: Cardiovascular Interventions. 2009; 2(6): 570–576, doi: 10.1016/j.jcin.2009.03.010.
3. Nazarewicz GV, Jain R. Upper gastrointestinal bleeding caused by aortoesophageal fistula. Clin Gastroenterol Hepatol. 2016; 14(12): A22, doi: 10.1016/j.cgh.2016.08.013, indexed in Pubmed: 27546580.
4. Karb DB, Mansoor E, Sullivan J, et al. Atypical presentation of aortoesophageal fistula without hemorrhage. ACG Case Rep J. 2019; 6(2): e00004, doi: 10.14309/crj.0000000000000004, indexed in Pubmed: 31616713.
5. Rawala MS, Badami V, Rizvi SB, et al. Aortoesophageal fistula: a fatal complication of thoracic endovascular aortic stent-graft placement. Am J Case Rep. 2018; 19: 1258–1261, doi: 10.12659/AJCR.911441, indexed in Pubmed: 30348937.
6. Akin M, Yalcinkaya T, Alkan E, et al. A cause of mortal massive upper gastrointestinal bleeding: aortoesophageal fistula. Med Arch. 2016; 70(1): 79–81, doi: 10.5455/medarh.2016.70.79-81, indexed in Pubmed: 26980940.
7. Tao M, Shlomovitz E, Darling G, et al. Secondary aorto-esophageal fistula after thoracic aortic aneurysm endovascular repair treated by covered esophageal stenting. World J Clin Cases. 2016; 4(8): 233–237, doi: 10.12998/wjcc.v4.i8.233, indexed in Pubmed: 27574612.
8. Akaraviputh T, Sriprayoon T, Prachayakul V, et al. Endoscopic diagnosis of secondary aortoesophageal fistula. Endoscopy. 2008; 40 Suppl 2: E90, doi: 10.1055/s-2007-995549, indexed in Pubmed: 18633903.
9. Hance KA, Hsu J, Eskew T, et al. Secondary aortoesophageal fistula after endoluminal exclusion because of thoracic aortic transection. J Vasc Surg. 2003; 37(4): 886–888, doi: 10.1067/mva.2003.159, indexed in Pubmed: 12663993.
10. Leung AD, Yamanouchi D. Case report of retrograde in situ fenestration of the thoracic stent graft with reentry device in a patient with aortobronchial fistula. Medicine (Baltimore). 2018; 97(24): e11050, doi: 10.1097/MD.0000000000011050, indexed in Pubmed: 29901605.
11. Mosquera VX, Marini M, Pombo-Felipe F, et al. Predictors of outcome and different management of aortobronchial and aortoesophageal fistulas. J Thorac Cardiovasc Surg. 2014; 148(6): 3020–6.e1, doi: 10.1016/j.jtcvs.2014.05.038, indexed in Pubmed: 24974780.

VIA MEDICA

CASE REPORTS

Acta Angiol
Vol. 26, No. 2, pp. 81–84
Doi: 10.5603/AA.2020.0013

ISSN 1234–950X
www.journals.viamedica.pl/acta_angiologica

Type I cryoglobulinemia related to Sjögren's syndrome and MGUS: a case report

Kamil Klimas, Rafał Małecki

Department of Angiology, Systemic Hypertension and Diabetology, Wrocław Medical University, Poland

Abstract

Cryoglobulinemia is a rare disease caused by the specific antibodies which precipitate at low temperatures being present within the blood serum. It is observed in the course of disorders such as autoimmune diseases, lymphoproliferative neoplasms, and infectious diseases — mainly HCV infections. Three types of cryoglobulinemia have been identified, differing in the type of immunoglobulins involved and symptoms being manifested. We are presenting a case of a 61-year-old female patient with type I cryoglobulinemia related to Sjögren's syndrome and complicated by monoclonal gammopathy of undetermined significance.

Key words: cryoglobulinemia, monoclonal gammopathy of uncertain significance (MGUS), Sjögren's syndrome (SS)

Acta Angiol 2020; 26, 2: 81–84

Introduction

Cryoglobulinemia is a rare disease (1 case per 100,000 individuals) [1], consisting of antibodies which precipitate at low temperatures (i.e. temperatures of below 37°C) being present within the blood serum [2]. It is observed in the course of various disorders such as lymphoproliferative neoplasms, autoimmune diseases, and viral infections, with HCV being the main agent responsible for the latter [2]. Three types of cryoglobulinemia have been identified, differing in the type of immunoglobulins involved, the most common being referred to as type II. We are presenting a case of a 61-year-old female patient with monoclonal cryoglobulinemia (of type I) related to Sjögren's syndrome and complicated by monoclonal gammopathy of undetermined significance (MGUS).

Case report

A 61-year-old female patient with a 4-year history of Sjögren's syndrome was admitted to the Department of Angiology, Systemic Hypertension, and Diabetology with calf ulcers which had appeared several years before presentation. Upon admission, the patient was in severe overall condition with the disease affecting both calves and involving extensive and strongly adherent necrotic lesions reaching down to the fascial and muscular levels and requiring administration of high-dose opioid analgesics (Figs 1, 2). Laboratory investigations revealed features of activated inflammatory response (CRP 43 mg/l [reference range 0–5 mg/l], leukocytosis12.14 G/l, normocytic anemia) and reduced levels of complement C4 [< 0.08 g/l, reference range 0.1–0.4 g/l] with unremarkable levels of complement C3 [1.46 g/l, reference level 0.9–1.8 g/l]. High levels of rheumatoid factor [323 IU/ml] and presence of anti-Ro (SS-A) and anti-La (SS-B) antibodies at the titer of 1:3200 were also demonstrated. No deviations from reference ranges were identified in urinalysis results. HBV and HCV screening tests were negative.

The scope of diagnostic laboratory investigations was broadened due to the unclear origin of severe necrotic lesions. Refrigeration test revealed the presence of cryoglobulins, later to be confirmed in serum immunofixation assays (monoclonal IgM kappa immu-

Address for correspondence: Kamil Klimas, Department of Angiology, Systemic Hypertension and Diabetology. Wrocław Medical University, Borowska 213, 50–556 Wroclaw, Poland, e-mail: kamkli17@gmail.com

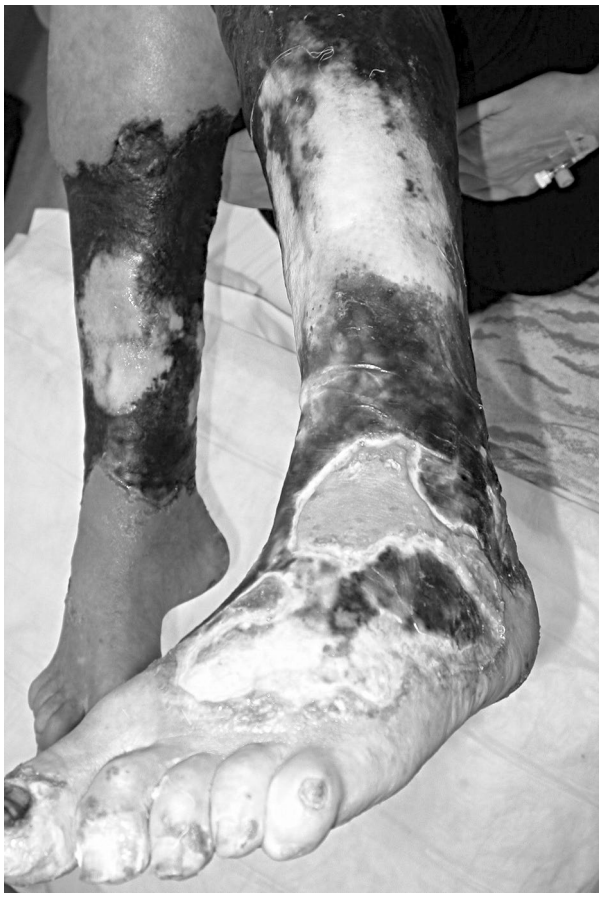

Figure 1. Lesions before admission to the hospital

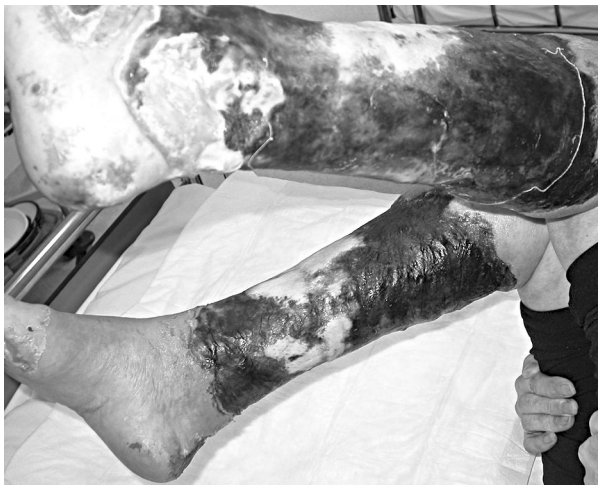

Figure 2. Lesions before admission to the hospital

noglobulin). Despite numerous additional assays (such as pANCA, cANCA, anti-dsDNA titers, HCV and HBV screening assays) symptoms of vasculitis related to other system dysfunctions were excluded. The patient had been subjected to hematological consultation which revealed monoclonal gammopathy of undetermined significance (MGUS). On the basis of clinical presentation and the results of laboratory investigations, the patient was diagnosed with vasculitis in the course of type I cryoglobulinemia secondary to MGUS which had developed as a complication of previously diagnosed Sjögren's syndrome.

Due to the aggressive course of the disease and the risk of resulting limb loss, a decision to initiate immunosuppressive therapy was made following hematological consultation. Between May 2014 and October 2016, a total of 7.6 g of cyclophosphamide was administered in pulses as an addition to local management (including mechanical debridement of ulcers under general anesthesia) to achieve partial healing of lesions. In October 2014, the patient was diagnosed with asymptomatic proximal deep vein thrombosis and vertebral fractures at levels L2 and L4 (treated by vertebroplasty at the Department of Neurosurgery); after several days, another two fractures at Th12 and L1 were detected (and also subjected to surgical treatment). During subsequent hospitalizations, several episodes of airway infections were observed as was pulmonary and tricuspid regurgitation and dilatation of the aortic bulb.

Establishment of an efficient maintenance immunosuppression regimen was a significant problem. As the attempts to introduce methotrexate and azathioprine had failed (several airway infections), cyclosporine was identified as the best-tolerated drug. Currently, the ulcers are nearly completely healed (Figs 3, 4), and the patient is capable of ambulating using a Zimmer frame. Laboratory investigations continue to show elevated CRP levels (12 mg/l), microcytic anemia, and reduced GFR (78 ml/min/1.73 m^2). Cyclosporine is found to be present at optimum (therapeutic) levels.

Discussion

Sjögren's syndrome is a connective tissue disorder characterized by particularly profound and dangerous immunological disorders. Observations include increased proliferation of B cells, and, as a consequence, production of numerous autoantibodies (anti-Ro/SSA, anti-La/SSB, AMA, anti-centromere antibodies) and rheumatoid factor as well as increased expression of pro-inflammatory cytokines, i.e. IL-1β, IL-6, IL-17, TNF-α, interferon γ [3]. As a result of numerous immunological mechanisms, the risk of non-Hodgkin lymphoma (NHL) is 4 to 44 times higher in patients with Sjögren's syndrome as compared to the overall population [4]. Monoclonal antibodies were detected in 7–22% of patients [5, 6]; in some cases, the synthesized gamma-globulins presented with cryoglobulin features.

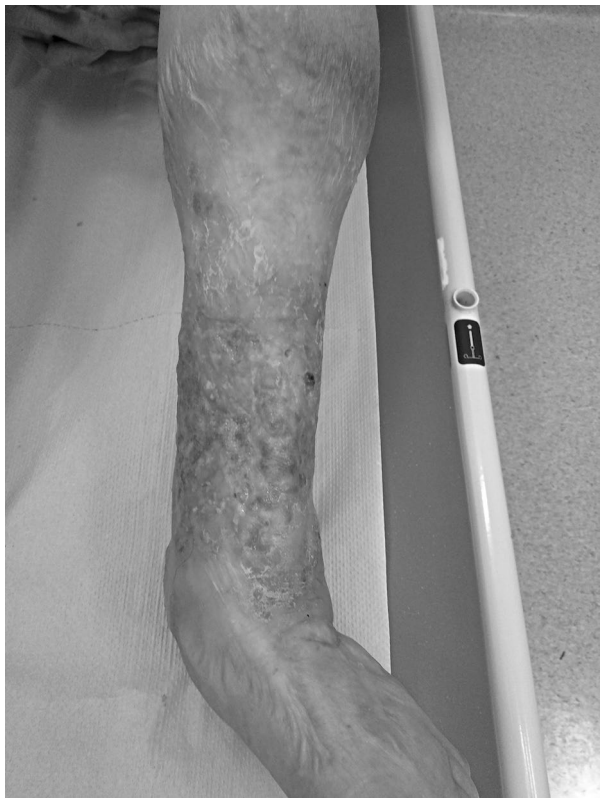

Figure 3. The left calf after treatment

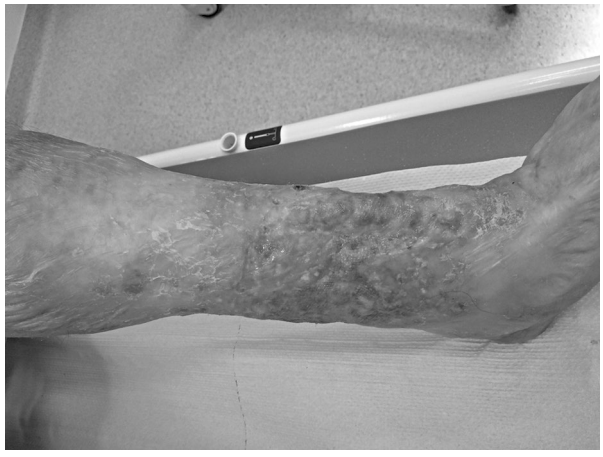

Figure 4. The left calf after treatment

Three types of cryoglobulinemia are identified on the basis of laboratory investigations: monoclonal (type I) cryoglobulinemia, mixed monoclonal/polyclonal (type II) cryoglobulinemia and polyclonal (type III) cryoglobulinemia. Each type may be manifested by a different set of symptoms. Type I cryoglobulinemia is characterized mainly by the presence of skin lesions such as purple-colored papulae on lower limbs, livedo reticularis, and Raynaud's phenomenon as well as the most serious lesions including ulcers and tissue necrosis which were predominant in the clinical presentation of the reported patient. Types II and III more frequently present with symptoms within other systems, with strong muscle and joint pains becoming more intensive at lower temperatures, peripheral polyneuropathy, hepatic dysfunction, respiratory symptoms (cough, dyspnea, pleuritis) or membranoproliferative glomerulitis. These symptoms are associated with cryoglobulins being deposited within small vessels (mainly capillaries, venules, or arterioles) and present in the blood.

Symptoms observed in the reported case, i.e. skin lesions including calf ulcers and soft tissue necrosis correspond to type I cryoglobulinemia. Other disorders taken into consideration in differential diagnosis included i.a. Schnitzler syndrome (absence of typical urticaria, recurrent fever, lymphadenopathy, or joint pains), secondary vasculitis related to Sjögren's syndrome and Waldenström macroglobulinemia (absence of recurrent epistaxis).

No standard of treatment has been established to date for cryoglobulinemia. The treatment must target the diseases involved in the development of the disorder. Cryoglobulinemia-causing neoplasms (chronic lymphocytic leukemia, Waldenström macroglobulinemia, and other types of lymphoma) are treated with chemotherapy, sometimes with adjuvant radiotherapy. Cryoglobulinemia in the course of HCV or HBV infection (mixed type II or type III cryoglobulinemia) is treated with antiviral regimens (the authors' experience suggests that eradication of the hepatitis C virus leads to symptom resolution). Patients with symptomatic cryoglobulinemia and vasculitis syndromes, as in the presented case, are treated with immunosuppressants.

Cyclophosphamide (an alkylating agent) was shown to efficiently induce remission in the presented case; however, the choice of remission maintenance treatment proved to be problematic. Glucocorticosteroids cause resolution of symptoms while simultaneously reducing cryocrit values. Cytotoxic drugs such as azathioprine (a purine antimetabolite) and methotrexate (a folic acid antagonist)) facilitate inhibition of immunoglobulin production by B cells. In the reported patient, however, this treatment proved ineffective due to disease complications. Cyclosporine was identified as the most effective and well-tolerated treatment. Cyclosporine belongs to the group of calcineurin inhibitors and inhibits humoral and cellular immune responses modifies chronic inflammatory processes, reduces the production and secretion of lymphokines (such as IL-2) and T-cell growth factor (TCGF) as well as affects the activity of T helper cells. In addition, cyclosporine inhibits the induction phase of the lymphatic cell proliferation process.

We are presenting this case due to the extraordinary intensity of necrotic lesions resulting from the presence of monoclonal proteins with cryoglobulin properties rather than from secondary vasculitis. It appears that every case of unexplained skin lesions or necrotic lesions in patients suffering from Sjögren's syndrome or, in a broader sense, an autoimmune disease, requires that this disease entity is taken into consideration in differential diagnostics.

Conflict of interest

None.

References:

1. Takada S, Shimizu T, Hadano Y, et al. Cryoglobulinemia (review). Mol Med Rep. 2012; 6(1): 3–8, doi: 10.3892/mmr.2012.861, indexed in Pubmed: 22484457.
2. Muchtar E, Magen H, Gertz MA. How I treat cryoglobulinemia. Blood. 2017; 129(3): 289–298, doi: 10.1182/blood-2016-09-719773, indexed in Pubmed: 27799164.
3. Huang Yf, Cheng Q, Jiang Cm, et al. The immune factors involved in the pathogenesis, diagnosis, and treatment of Sjogren's syndrome. Clin Dev Immunol. 2013; 2013: 160491, doi: 10.1155/2013/160491, indexed in Pubmed: 23935646.
4. Pillemer SR. Lymphoma and other malignancies in primary Sjögren's syndrome. Ann Rheum Dis. 2006; 65(6): 704–706, doi: 10.1136/ard.2005.044362, indexed in Pubmed: 16699050.
5. Tomi AL, Belkhir R, Nocturne G, et al. Brief report: monoclonal gammopathy and risk of lymphoma and multiple myeloma in patients with primary Sjögren's syndrome. Arthritis Rheumatol. 2016; 68(5): 1245–1250, doi: 10.1002/art.39534, indexed in Pubmed: 26636425.
6. Brito-Zerón P, Retamozo S, Gandía M, et al. Monoclonal gammopathy related to Sjögren syndrome: a key marker of disease prognosis and outcomes. J Autoimmun. 2012; 39(1-2): 43–48, doi: 10.1016/j.jaut.2012.01.010, indexed in Pubmed: 22297146.

PATRONAT MEDIALNY

ACTA ANGIOLOGICA

tvmed

ORGANIZATOR

VIA MEDICA

IX Konferencja Postępy Terapii Przeciwkrzepliwej i Przeciwpłytkowej

VIRTUAL MEETING

20–21 listopada 2020 roku

Bezpłatne uczestnictwo *online*

Kontakt:
VM Media sp. z o.o. VM Group sp.k.
ul. Świętokrzyska 73
80–180 Gdańsk
tel.: 58 320 94 94
faks: 58 320 94 60

www.ptpip.viamedica.pl

19-0254.001.011

Virtual Meeting jest skierowany 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.).

XII Konferencja *online*

Choroby Serca i Naczyń

3–5 grudnia 2020 roku

VIRTUAL MEETING

Przewodniczący Komitetu Naukowego:
prof. dr hab. n. med. Krzysztof Narkiewicz

XI Zimowe Spotkanie Sekcji Farmakoterapii Sercowo-Naczyniowej Polskiego Towarzystwa Kardiologicznego

ORGANIZATOR
VIA MEDICA

PATRONAT MEDIALNY
tvmed

Szczegółowe informacje i rejestracja na stronie internetowej:
www.chorobyserca.viamedica.pl

19-0367.001.011

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.)