ISSN 1234–950X
e-ISSN: 1644–3276

ACTA ANGIOLOGICA

2020, Vol. 26, No. 4

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

VI Konferencja *online* czasopisma

FOLIA CARDIOLOGICA

9 kwietnia 2021 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

21-0021.001.002

Virtual Meeting jest skierowany tylko do osób uprawnionych do wystawiania recept lub osób prowadzących obrót produktami leczniczymi — podstawa prawna: Ustawa z dnia 6 września 2001r. Prawo farmaceutyczne (t.j. Dz.U. z 2019 r. poz. 499).

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

19-0178.004.001

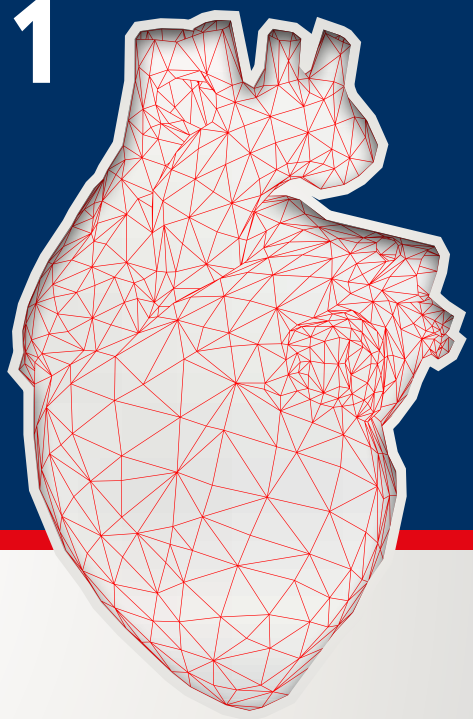
Acta Angiologica is indexed at: Thomson Reuters (Emerging Sources Citation Index), Index Copernicus (113,15), Scopus, EMBASE, EBSCO, Google Scholar, CrossRef, Ulrich's Periodicals Directory, Ministry of Education (20) and Polish Medical Bibliography (GBL). Website www.journals.viamedica.pl/acta_angiologica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

BEZPŁATNE UCZESTNICTWO

PATRONAT

Sekcja Farmakoterapii Sercowo-Naczyniowej • PTK •

IX Forum Chorób Sercowo-Naczyniowych z Lipidologią 2021



PRZEWODNICZĄCY KOMITETU NAUKOWEGO:

prof. dr hab. n. med. Beata Wożakowska-Kapłon

prof. dr hab. n. med. Krzysztof J. Filipiak, FESC

VIRTUAL MEETING

Terminy spotkań:

- GDAŃSK 25.03.2021
- KATOWICE 26.03.2021
- KRAKÓW 23.04.2021
- BYDGOSZCZ 24.04.2021
- POZNAŃ 7.05.2021
- OLSZTYN 8.05.2021
- KIELCE 21.05.2021
- LUBLIN 22.05.2021
- WARSZAWA 29.10.2021
- BIAŁYSTOK 30.10.2021
- WROCŁAW 26.11.2021
- ŁÓDŹ 27.11.2021

www.forum.viamedica.pl

ORGANIZATOR VIA MEDICA

PARTNER ikamed.pl internetowa księgarnia medyczna

PATRONAT MEDIALNY tvmed

20-6093.001.002

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

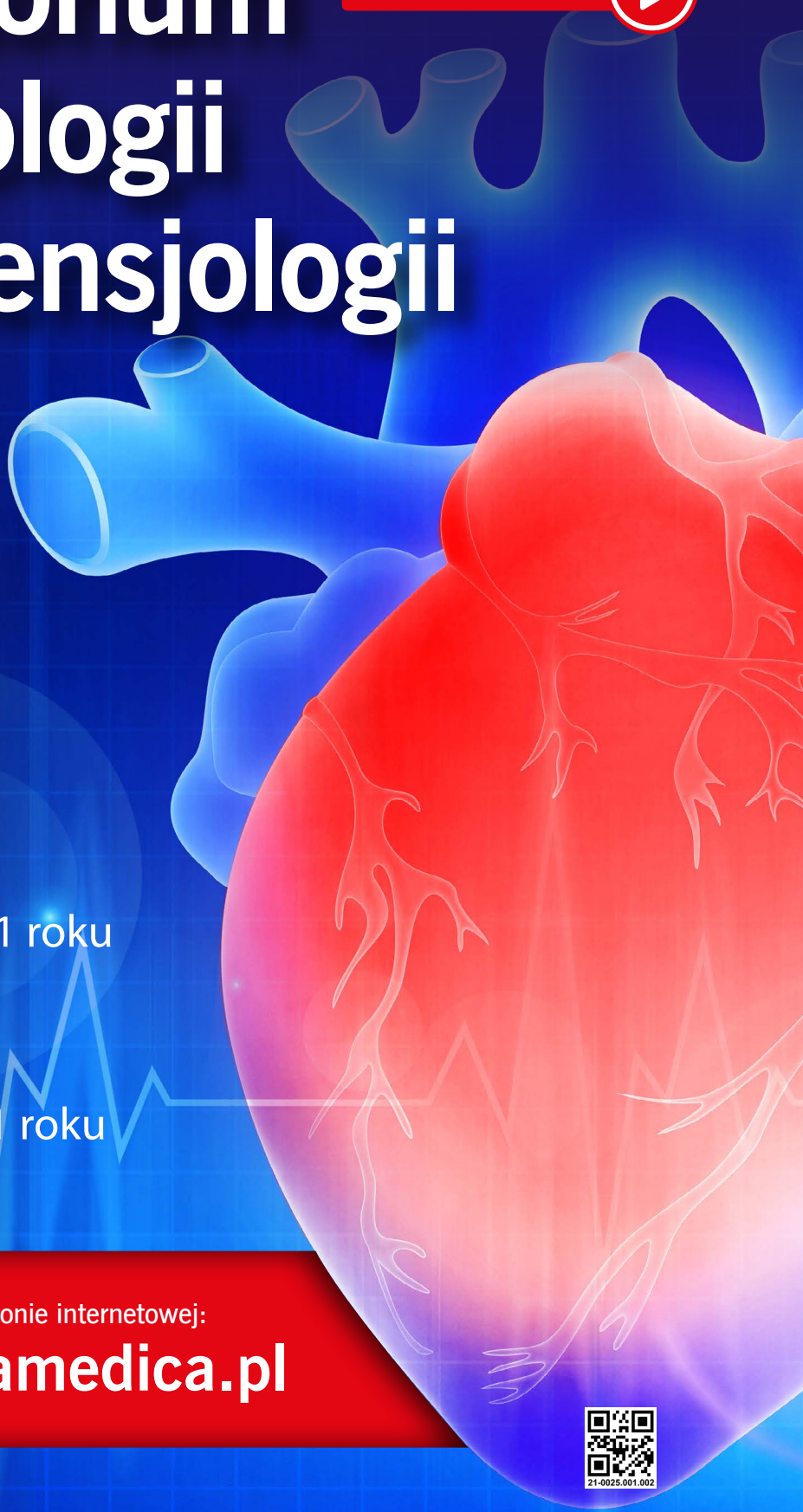
2020, Vol. 26, No. 4

www.journals.viamedica.pl/acta_angiologica

Contents

Repetytorium z Kardiologii i Hipertensjologii 2021

VIRTUAL MEETING



- **WIOSENNE**
  Online,
  7 marca 2021 roku
- **LETNIE**
  Gdynia,
  12–13 czerwca 2021 roku
- **JESIENNE**
  Warszawa,
  2 października 2021 roku

Więcej informacji i rejestracja na stronie internetowej:

www.kardio.viamedica.pl

21-0025.001.002

Virtual Meeting jest skierowany tylko do osób uprawnionych do wystawiania recept lub osób prowadzących obrót produktami leczniczymi — podstawa prawna: Ustawa z dnia 6 września 2001 r. Prawo farmaceutyczne (t. j. Dz.U. z 2019 r. poz. 499).

ORGANIZATOR

VIA MEDICA

VIA MEDICA

ORIGINAL PAPER

Acta Angiol
Vol. 26, No. 4, pp. 119–128
Doi: 10.5603/AA.2020.0024

ISSN 1234–950X
e-ISSN: 1644–3276

Assessment of platelet function and resistance to aspirin and clopidogrel in patients with peripheral arterial disease undergoing percutaneous transluminal angioplasty

Grzegorz Borowski[1], Aleksandra Nowaczyńska[2]

[1]Department of Vascular Surgery and Angiology, Medical University of Lublin, Lublin, Poland
[2]Department of Hematooncology and Bone Marrow Transplantation, Medical University of Lublin, Lublin, Poland

ABSTRACT

Introduction: *Analysis of platelet function, acetylsalicylic acid (ASA) and clopidogrel resistance in patients with peripheral arterial disease (PAD) undergoing percutaneous transluminal angioplasty (PTA), the impact of procedure on this phenomenon, connection with diabetes, hypertension, smoking.*

Material and methods: *The study included 72 patients, with a group of patients taking ASA on a permanent basis and a group of patients in whom treatment was implemented after the procedure. Patients were also divided according to the antiplatelet therapy applied, either double-therapy, or ASA monotherapy. Daily doses were 75 mg. Three methods were used for the evaluation of the platelet function: IVY bleeding time, cytometric evaluation of platelet surface antigen (CD62p and CD63) expression and hemostasis measurement by PFA-200®.*

Results: *In the PFA-200 analysis, ASA resistance was found in 37.8% (64.7% were tobacco smokers) before surgery. Patients not taking ASA before, after PTA and first dose of ASA presented resistance in 63%. The first dose of clopidogrel after surgery was associated with resistance in 73.7%. Significant differences in the expression of CD62p and CD63 markers before and after PTA were observed. According to IVY method, aspirin resistance was found in 40% of patients permanently receiving ASA.*

Conclusions: *Patients with PAD who undergo PTA are resistant to ASA in 40%, smoking is associated with this phenomenon. PTA increases the expression of CD62P and CD63, and thus the platelet activation, which is not adequately prevented by antiplatelet drugs at a dose of 75 mg. Dual antiplatelet therapy reduces the activation of thrombocytes more than the monotherapy of ASA.*

Key words: platelet function, aspirin resistance, clopidogrel resistance, peripheral artery disease, percutaneous transluminal angioplasty

Acta Angiol 2020; 26, 4: 119–128

Introduction

Endovascular treatment, due to its low invasiveness and good results, is commonly used in the treatment of patients with peripheral arterial disease (PAD), allowing to shorten hospitalization and recovery time. Percutaneous transluminal angioplasty (PTA), apart from the fact that it is associated with an increase in the activity of platelets, carries the risk of complications, including thrombosis. The prophylaxis of these complications currently includes antiplatelet drugs most often acetylsalicylic acid (ASA) and clopidogrel. ASA is the secondary prophylaxis after PTA and the primary antithrombotic prevention in patients diagnosed with

Address for correspondence: Grzegorz Borowski, Department of Vascular Surgery and Angiology, Medical University of Lublin, Lublin, Poland, e-mail: gwborowski@gmail.com

symptomatic atherosclerosis of the lower extremities. Its use at a dose of 75–150 mg/day in patients with intermittent claudication significantly reduces the rates of strokes, myocardial infarctions and deaths caused by cardiovascular diseases. This dose of ASA was found to be as effective as higher daily doses [1]. In randomized trials [2, 3], there was also no correlation between the amount of ASA used and the achievement of antiplatelet effect. The use of high doses appears to be unjustified and is related with a higher risk of gastrointestinal bleeding [4–6]. ASA also improves vessel patency after revascularization [7]. Dual antiplatelet therapy (ASA and clopidogrel) is implemented i.a. in patients who underwent stent implantation into peripheral arteries [7, 8]. Despite the use of such therapy, adverse events, including stent thrombosis, are still observed [2, 7, 9, 10]. In patients with PAD, there is a tendency to increased platelet activity, which may be resistant to the antiplatelet effect of ASA [11, 12]. The term *aspirin resistance* was first used in the early 1990s [13]. Aspirin resistance is defined either in terms of clinical symptoms (a thromboembolic event during drug use) or on the basis of laboratory tests determining the aggregating effect of platelets [14]. According to Patrono [15], the term aspirin resistance can be applied to clinical conditions or laboratory measurements, e.g. the inability of aspirin to: protect the patient from thromboembolic complications, prolong bleeding time, block thromboxane synthesis, or produce an antiplatelet effect found in one or more *in vitro* tests. Aspirin resistance is also defined by the term high on-treatment platelet reactivity (HTPR) [16] or high residual platelet reactivity (HRPR) during aspirin treatment [17]. In current reports, HRPR is recognized in 27.7% of respondents [17]. The concept of aspirin poor responsiveness (APR) is also used [18]. As for the laboratory determination of resistance, it is possible to assess the aggregation response of thrombocytes to arachidinate, adrenaline or collagen [14, 19, 20]. Another issue in antiplatelet therapy is resistance to clopidogrel, an antagonist of the P2Y12 receptor. According to studies [21], resistance to clopidogrel at a loading dose of 600 mg was found in 1 in 5 patients. However, in the reports from 2016 [22, 23] in the Chinese population of patients after ischemic stroke, taking clopidogrel at a dose of 75 mg/day, using the aggregometry method, drug resistance was found respectively in 38.88% and 36% of them (light transmission aggregometry — LTA). According to Spiliopoulos et al., the prevalence of resistance to aspirin and clopidogrel in patients undergoing endovascular interventions due to symptomatic PAD is approximately 50% [16]. The aim of this study was to assess the occurrence of resistance to antiplatelet drugs (acetylsalicylic acid and clopidogrel) in patients undergoing angioplasty, to determine the impact of the procedure on the development of aspirin resistance, to determine whether there is a relationship between the occurrence of drug resistance and diabetes, hypertension or smoking and the assessment of platelet activity based on the expression of platelet surface glycoproteins on the day after the procedure depending on the antiplatelet therapy used (monotherapy with ASA or ASA in combination with clopidogrel).

Material and methods

The study was conducted in the Department of Vascular Surgery and Angiology of the Medical University of Lublin from December 2011 to December 2015. Cytometric tests and analysis of thrombocyte function using the INNOVANCE PFA-200® analyzer were performed in the Laboratory of Flow Cytometry and Hemostasis at the Department of Hematooncology and Bone Marrow Transplantation at the Medical University of Lublin. The study included a total of 72 patients (Table 1) with PAD, aged 44 to 89, including 20 women and 52 men. Each patient underwent PTA. The patients were qualified for angiography and endovascular treatment based on the clinical condition assessed on the basis of the Fontaine scale — grades IIB, III, IV.

After initial angiography, balloon angioplasty was performed in 34 (47.2%) patients. One or more stents were implanted in 38 (52.8%) patients. The endovascular procedure was performed on iliac arteries in 26 patients, in 46 patients on femoral, popliteal or tibio-fibular arteries (Table 2). During each procedure a bolus of unfractionated heparin *i.v.* (2500–5000 IU) was injected.

A group of 45 patients who were taking ASA at a dose of 75 mg daily for at least 2 weeks before the planned surgery was selected. The remaining 27 patients had not received any antiplatelet medication for at least 7 days prior to PTA. After returning from the operating room, patients who underwent balloon angioplasty (n = 34) received 75 mg of ASA, while those after stent implantation (n = 38) received 75 mg of ASA and 75 mg of clopidogrel (Table 3).

In studied patients, on the day of the procedure before its performance and on the first day after the procedure, the following additional tests were performed to assess platelet function: measurement of the occlusion time using the PFA-200 analyzer, cytometric analysis, bleeding time (BT) measured according to the Ivy method. The material for laboratory tests was fasting whole blood collected from the cephalic vein using a 20Gx Needle (Sarstedt S-Monovette Nümbrecht, Germany). Blood was collected in 3 polystyrene tubes (Sarstedt S-Monovette) containing 3.2% sodium

Table 1. Clinical characteristics of the study population (n = 72)

The assessed parameter	Number of patients in the entire study group	Percentage of patients in the entire study group
Gender		
Male	52	72.2%
Female	20	27.8%
Diabetes		
Yes	23	39.1%
No	49	68.1%
Arterial hypertension		
Yes	38	52.8%
No	34	47.2%
Nicotinism		
Yes	30	41.7%
No	42	58.3%

Table 2. Characteristics of the performed endovascular procedures

Number of patients who underwent balloon angioplasty	34 (47.2%)
Number of patients with stent implantation	38 (52.8%)
Number of procedures performed within iliac arteries	26 (36.1%)
Number of procedures performed within femoral, popliteal arteries and tibial-peroneal trunk	46 (63.9%)

Table 3. Pharmacological treatment in the perioperative period

Antiplatelet drugs administered permanently before the procedure	Number of patients	Antiplatelet drugs administrated at the day of the procedure, after its performance	Number of patients
ASA	45	ASA	34
Clopidogrel	0	ASA + clopidogrel	38
Without antiplatelet drug	27	Without antiplatelet drug	0

citrate in the proportion 1:9. Then, within 2 hours of collection, the occlusion time was analyzed using the PFA-200 and the expression of platelet glycoproteins with the use of a cytometric analyzer.

Description of the methods of assessing platelet function used in the study

The PFA-200® system is used to measure the primary hemostasis process. It allows for a quick assessment of platelet function based on the analysis of non-clotted whole blood collected in citrate. With its use, it is possible to diagnose congenital and acquired platelet defects, as well as to evaluate drug-induced dysfunctions. Using the flow cytometry method, the activation of platelets and their function can be tested. For this purpose, monoclonal antibodies that are directed against platelet surface antigens are used. Specific phenotypic changes in platelet glycoproteins can be determined by the use of fluorescent-labeled antibodies. Changes in the expression of CD62p (P-selectin) and CD63 (GP53 glycoprotein) surface proteins were found in numerous studies. These two molecules are the most expressive markers of platelet activation [24, 25]. In our study, the measurement of bleeding time (BT) using the Ivy method was also used. It is the only way to assess hemostasis in vivo. The bleeding time is the time between the incision is made and bleeding stops [26]. It proves the ability of platelets to form a blood clot at the site of skin damage. Standardized Surgicutt® Adult skin incision lancet were used to measure bleeding time. The correct bleeding time for the Ivy method was assumed to be 6 minutes [26–29]. The group of patients with bleeding time up to 360 seconds was defined as resistant to the antiplatelet effect of used drugs.

Statistical methods

Statistical analyzes were performed using the Statistica 9. The following methods were used: descriptive statistics (mean, median, minimum, maximum, standard deviation, standard error of the mean); percentage analysis; tests of significance of differences — Mann-Whitney U test, sign test for dependent groups, Kruskal-Wallis test, Chi^2 test; correlation analysis using the r-Pearson coefficient. The critical level of statistical significance was $p < 0.05$.

Results

Resistance to the antiplatelet effect of aspirin measured with PFA-200

The mean closure time (CT) measured with the Col/ /EPI test cartridges in the group of 45 patients receiving ASA on a permanent basis before surgery was 185.6 seconds. After the procedure, the CT was shortened to an average of 170.5 s. This means that PTA, despite the daily use of ASA, is associated with a decreased response to the antiplatelet effect of the drug. In the group of 45 patients taking ASA, drug resistance was found in 37.8% of patients using the PFA-200 device (n = 17). In the same group of patients, after PTA, a reduced response to the effects of ASA was observed in a greater number of patients 46.7% (n = 21). In the studied group of ASA-resistant patients (n = 17), a high percentage of smokers (64.7%) and a low percentage of diabetics (35.3%) were found. The coexistence of arterial hypertension is not associated with the aspirin resistance (53% in the study group are diagnosed with this disease). In the group of 27 patients not taking the drug before the procedure, CT was measured on the first day of the procedure and aspirin resistance was found in 63% of them (n = 17). ASA at a dose of 75 mg administrated only after PTA is associated with a very high percentage of resistance. In the entire group of 72 patients participating in the study, a reduced response to the effects of ASA, measured with the PFA-200, was found in 38 patients (52.8%). Therefore, regardless of whether the patients were taking ASA in the period before the procedure or they received the drug only after the procedure, an increase in resistance caused by PTA was found. When analyzing the whole study population, a low percentage of diabetic patients was found in the drug-resistant group (n = 38). However, the coexistence of arterial hypertension and smoking was not related with the occurrence of this phenomenon.

Resistance to the antiplatelet effect of clopidogrel measured with PFA-200

In a group of 38 patients in whom at least one stent was implanted, after administration of a dose of 75 mg clopidogrel immediately after surgery, a study was performed with P2Y test cartridges. The patients had not taken the drug before. The drug resistance was found in 28 subjects (73.7%). This means that clopidogrel is less effective at this dose on the first day of its use. In the group of patients resistant to the first dose of 75 mg clopidogrel after stenting (n = 28), a higher percentage of smokers (60.7%) compared to non-smokers was observed. Patients with diabetes accounted for only 28.6% of the group. The number of patients with hypertension was the same as the number without. In the group of patients responding to clopidogrel (n = 10), a very low percentage of patients with diabetes (20%) was found.

Expression of P-selectin

In the group of patient taking ASA (n = 45) before PTA, the mean percentage of platelet activation measured with CD61/CD62P was 0.36, after the procedure, it was increased to 0.51. In the group of patients who did not take the drug before PTA (n = 27), the mean percent activation for CD61/CD62P cells was 0.25 and after surgery it increased to 0.74. The mean percentage of CD61/CD62P cell activation in patients after surgery (PTA with stent implantation) and dual antiplatelet therapy (n = 38) was 0.79. Before the procedure, this value was lower, averaging 0.33. Similarly, in patients after PTA without stent implantation and using a single antiplatelet therapy with ASA (n = 34) before procedure, the value was lower than after (0.5) and was 0.37. In the entire group of patients with PAD (n = 72), the mean value of the parameter before the procedure was 0.32. The surgery, despite the used antiplatelet therapy, increased the activation of platelets to the mean value of 0.60.

Expression of CD63

Both in treated with ASA (n = 45) and ASA-free group (n = 27), the mean percentage of postoperative CD61/ /CD63 cell activity was higher than before (2.0 and 1.17 and 1.39 and 1.15). This means an increase in the expression of the platelet activation marker (CD63) as a result of the PTA, despite the use of antiplatelet therapy after the procedure (in this case, regardless of whether the patients received ASA or ASA and clopidogrel). Mean percentage of CD61/CD63 cell activity in postoperative period (PTA with stent implantation) and dual antiplatelet therapy (n = 38), as in patients (with PTA without stent implantation) and with ASA monotherapy (n = 34) as in the entire group of 72 patients before the procedure was lower (1.57; 1.76; 1.50, respectively) compared to post-procedural testing (2.05; 1.95; 1.80, respectively). The surgery, despite the antiplatelet therapy used, increases the activation

of platelets, measured with the use of CD61/CD63 antibodies.

Results of tests with assessment of bleeding time using the Ivy method

The mean bleeding time (BT) measured using the Ivy method for the group permanently receiving ASA before surgery (n = 45) was 444 seconds. In the group of patients taking ASA at a dose of 75 mg a day (n = = 45), the bleeding time was normal in 18 patients, so in 40% of patients, the drug did not prolong bleeding time, and thus this group can be considered as with low sensitivity to the antiplatelet effect of ASA. In the group of patients who underwent stenting and receiving dual antiplatelet therapy (n = 38), on the first day of PTA, the bleeding time was normal in 13 patients (34.2%). In the group of patients who were treated with ASA 75 mg monotherapy (n = 34), the correct bleeding time was detected in 14 patients, which means 41.2% of drug resistance. The mean bleeding time was 408 seconds, which was shorter than in the dual antiplatelet therapy group (477.2 seconds). The use of dual antiplatelet therapy results in a better antiplatelet effect as it increases bleeding time. In the group of ASA-resistant patients tested before the PTA procedure (n = 17), the correct bleeding time was also found before the procedure in 5 of them, which is 29.4%. In the assessment before the angioplasty procedure, in the group of 45 patients receiving ASA permanently, there were 5 patients resistant to the drug effect according to the two methods used in the study, which constitutes 11.1%.

Discussion

Numerous studies report that the resistance to the antiplatelet effect of acetylsalicylic acid may affect from 5 to 60% of patients, this discrepancy depending on the studied population and methods used to evaluate it. According to some researchers, this percentage is even as high as 83% [1, 30–34]. One of the first published reports on ASA resistance concerned its use in secondary prevention in patients with stroke — the above problem was found (using PFA-100) in 30–40% of patients [35]. In our study, with the use of the PFA-200 device, in a group of patients with PAD who took ASA on a permanent basis, drug resistance was found in a very similar percentage of patients — 37.8%. In the study of Linneman et al. [36], the change in response to the effect of ASA was tested over time in patients with PAD, using e.g. PFA analyzer. It has been found that in a significant number of patients, resistance to aspirin changes over time during treatment. It may be related to inconsistency in the methodology, incompatibility in the applied therapy, insufficient response to the selected dose of the drug or interactions with other drugs. In addition, platelet activity may change as the disease progresses. In this study, resistance to aspirin and platelet function were assessed only before the PTA procedure and in the first 24 hours after. This resulted from the planned evaluation of the drug resistance in the periprocedural period, the aim of which was to determine the impact of the procedure itself on the resistance and to assess the effectiveness of the doses of drugs used at that time. For this reason, the possible long-term dynamics of the response to antiplatelet drugs was not assessed. There were also observations that resistance to ASA progressed over time, regardless of the dose taken [37, 38]. In a study [39] where platelet function was measured several times over 12 months of ASA use, response to the drug did not matter in determining long-term outcomes. In a meta-analysis assessing the effect of aspirin in prevention of thromboembolic complications, it was found that most of the studies performed used different methods of testing the laboratory activity of thrombocytes. Furthermore, despite the same methods, different cut-off points were used. It has been found that patients presenting aspirin resistance in biochemical tests also tend to be "clinically resistant" with a significantly higher risk of cardiovascular complications. People with a significant activation of platelets, despite the use of aspirin, show an almost four times higher total risk of a cardiovascular event [40].

In our research, it was observed that in the group of patients identified as aspirin-resistant before PTA (n = 17), 64% were tobacco smokers. However, in the group of aspirin-resistant patients (n = 38) selected from the entire study population (n = 72), nicotinism coexisted in 55% of them. This confirms previous researches that smoking tobacco can cause drug resistance. It can be concluded that the increased pro-aggregation activity of thrombocytes in smokers, as in other studies [41, 42], is the main factor determining the higher incidence of cardiovascular diseases despite the systematic use of the drug in prophylactic doses. In this study, both in the group of patients diagnosed as aspirin-resistant before the procedure (n = 17) and in the entire study group on the day after the procedure (n = 38), the percentage of patients with coexisting diabetes was nearly 40%, which does not coincide with the majority of previous studies, suggesting that a patient with diabetes is more often drug-insensitive. In diabetic patients, increased activity with a tendency to aggregation of platelets was found, and therefore a higher incidence of thromboembolic complications [43, 44]. However, according to some reports, diabetes does not affect the development of aspirin resistance and the percentage of this phenomenon among dia-

betics is comparable to the group of patients without diagnosed diabetes [45, 46]. The clinical importance of biochemically determined aspirin resistance in the development of cardiovascular complications has been confirmed [13, 35]. For example, in the study of Gum et al. [33], it was suggested that about 10% of recurrent adverse vascular events may be caused by resistance to ASA. This confirms that such prognosis of clinical complications, correlating with laboratory resistance, is extremely important for defining the scope and nature of resistance to antiplatelet drugs. Several studies have shown that patients with a decreased response to clopidogrel, measured *in vitro* using platelet function analyzers have a significantly increased risk of early stent thrombosis after percutaneous coronary angioplasty (PTCA) compared to patients with sufficient platelet function blocking [23]. Most of the studies on clopidogrel resistance concerned the study of platelet function after a loading dose of 300 mg [47]. In our study, the antiplatelet effect of clopidogrel was tested with the first day of 75 mg dose. Such a study was designed to determine whether the applied dose is effective in this group of patients, or whether it is worth considering using a higher dose on the day of surgery. Resistance to clopidogrel also varied between investigators, but there was a correlation between laboratory resistance and cardiovascular adverse events. In the work of Metzky et al. [48], patients with myocardial infarction treated with angioplasty were monitored for the effect of clopidogrel by the optical aggregation method, using ADP as an agonist. This allowed identification of a group of 25% of patients resistant to the drug effect, and thus more at risk of recurrent cardiovascular events. The only characteristic of this group was the high percentage of tobacco smokers. In the study by Cuisset et al. on patients with acute coronary syndrome, there was described a higher frequency of periprocedural infarctions in the group with a poor laboratory response to clopidogrel [49, 50]. So far, a small number of studies have been published assessing the antiplatelet efficacy of clopidogrel tested with the PFA-200 analyzer [51]. In our study, the tests were made on the first day of the procedure, so the assessment concerns one dose of 75 mg, confirming its very low effectiveness. Only 10 patients had a correct response to the drug, which is 26.3% in the study group. The remaining patients (73.7%) can be diagnosed with reduced responsiveness to the antiplatelet effect of clopidogrel. In this study, the cytometric test and the Ivy method for the bleeding time were used to compare dual antiplatelet therapy with ASA monotherapy. P-selectin and CD63 are established markers of thrombocyte activity measured by flow cytometry [52, 53]. According to E. McKenzie et al. [53], a significant decrease in the expression of these glycoproteins was described only after a high dose of ASA, which suggests the use of higher doses in patients treated endovascularly. The expression of P-selectin and GP53 was examined in all patients included in the study (n = 72) both before and after surgery. It was found that P-selecting expression was higher in patients who underwent stenting and received two antiplatelet drugs compared to those who had only balloon angioplasty and received ASA.

As for CD63 expression, its level after PTA was comparable in both groups, regardless of the therapy used. Thus, stenting causes a greater activation of platelets, assessed by this marker, than balloon angioplasty itself. The inhibitory effect of ASA and clopidogrel on the expression of these markers of platelet activity (mainly P-selectin) described so far is weaker than the effect of endovascular treatment causing the increase in expression. The assessment of the bleeding time using the Ivy method was found to be normal in 13 patients in the group that received dual antiplatelet therapy after stent implantation (n = 38). This means that 34.2% of the study group was not responsive to the effects of these drugs. On the other hand, in the group of patients after balloon angioplasty and receiving 75 mg of acetylsalicylic acid (n = 34), 41.2% were resistant after the procedure. Moreover, the mean bleeding time is also higher in patients treated with ASA and clopidogrel (477 vs 408 seconds). The above results, despite the lack of statistical significance, allow us to observe that dual antiplatelet therapy is associated with better inhibition of thrombocyte function resulting in prolonged bleeding time. It is worth paying attention to the fact that the implementation of such therapy is more effective even in relation to patients who have had a stent implanted, which is also associated with a higher activation of platelets than after balloon angioplasty only.

In this study, an increase in P-selectin expression after surgery, and thus in platelet activation, was found, assessed on a group of patients receiving ASA permanently (n = 45). In the preoperative ASA group (n = = 27), a significant increase in the mean percentage of activation of CD61/62p antibodies was observed. This difference is greater than in patients using ASA before the procedure, so it can be concluded that the treating patient with aspirin before the procedure results in a lower activation of platelets, and thus a lower risk of developing thrombotic complications in the first days after PTA. Some studies do not describe that aspirin impacts the level of P-selectin expression [54]. According to studies [53] with the use of flow cytometry, in which several markers of platelet activation were used, a decrease in P-selectin expression was found already at the dose of 1.0 g of ASA. On the other hand, after a higher dose of 4.0 g, a statistically significant decrease

in the expression of CD63 antibodies, while after a small dose, a slight increase in the expression of CD63. After a week of using ASA at a dose of 81 mg/day, Valdes et al. [55] found a decrease in the concentration of soluble P-selectin (sP-selectin) in the blood. The studies carried out on a group of healthy people who were administered ASA in a dose of 81 mg showed that there was a decrease in the expression of thrombocyte surface receptors, including P-selectin [56]. In this study, it was shown that the percentage of antibody activation before PTA was lower than after PTA, which means that in patients with PAD, angioplasty causes an increased activation of platelets, which is insufficiently prevented by the drugs used. The search for an effective antiplatelet therapy for patients with PAD is extremely important, also because these patients clearly have an increased risk of myocardial infarction or ischemic stroke [11]. In this study, in the group of patients permanently receiving ASA in a daily dose of 75 mg (n = 45), the level of aspirin resistance confirmed by two methods — PFA-200 and the Ivy method was found in 5 patients, which makes 11% of this group. The above group of patients can be described as "true" aspirin-resistant, because they present the features of resistance in both biochemical and in the *in vivo* test. Moreover, studies evaluating aspirin resistance in relation to the development of thromboembolic complications in patients undergoing antiplatelet therapy estimate the prevalence of resistance at a very similar level. In the analysis of Gum et al. [33], the importance of aspirin resistance in thrombotic complications was estimated at 10%. Similar results were presented by Saunders et al. [57], where in a group of 80 patients with PAD using the PFA-100, persistent aspirin resistance was detected in 9.9% of patients.

Despite many recent studies, it has not been possible to clearly define which group of patients should be diagnosed for aspirin resistance. Though the number of available, relatively simple and quick tests for determining the activity of platelets is increasing, the cost of the equipment and the tests themselves will not allow such extensive diagnostics in the near future. A definition of a patient resistant to aspirin and clopidogrel should be created, which will also enable the development of new or specification of already used tests independent of additional factors modifying the action of these drugs.

Conclusions

Based on the own research presented above, it was found that among patients with peripheral arterial disease treated with endovascular methods, the level of laboratory aspirin resistance is about 40%. An additional factor that increases the resistance to antiplatelet drugs is tobacco smoking. Previous PTA procedure results in increased resistance to antiplatelet drugs. As a result of PTA, the expression of P-selectin and CD63 increases, and thus the activation of platelets also increases, which is insufficiently prevented by the antiplatelet drugs used in the periprocedural period: ASA and clopidogrel. Dual antiplatelet therapy reduces the activation of platelets to a greater extent compared to acetylsalicylic acid monotherapy.

Conflict of interest

None.

References:

1. Baigent C, Blackwell L, Collins R, et al. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. The Lancet. 2009; 373(9678): 1849–1860, doi: 10.1016/s0140-6736(09)60503-1.
2. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. BMJ. 2002; 324(7329): 71–86, doi: 10.1136/bmj.324.7329.71, indexed in Pubmed: 11786451.
3. van Gijn J, Algra A, Kappelle J, et al. Dutch TIA Trial Study Group. A comparison of two doses of aspirin (30 mg vs. 283 mg a day) in patients after a transient ischemic attack or minor ischemic stroke. N Engl J Med. 1991; 325(18): 1261–1266, doi: 10.1056/NEJM199110313251801, indexed in Pubmed: 1922220.
4. Derry S, Loke YK. Risk of gastrointestinal haemorrhage with long term use of aspirin: meta-analysis. BMJ. 2000; 321(7270): 1183–1187, doi: 10.1136/bmj.321.7270.1183, indexed in Pubmed: 11073508.
5. Zimmermann N, Wenk A, Kim U, et al. Functional and biochemical evaluation of platelet aspirin resistance after coronary artery bypass surgery. Circulation. 2003; 108(5): 542–547, doi: 10.1161/01.CIR.0000081770.51929.5A, indexed in Pubmed: 12874188.
6. Bem D, Dretzke J, Stevens S, et al. Investigating the effectiveness of different aspirin dosing regimens and the timing of aspirin intake in primary and secondary prevention of cardiovascular disease: protocol for a systematic review. Syst Rev. 2015; 4: 88, doi: 10.1186/s13643-015-0078-3, indexed in Pubmed: 26088608.
7. Tendera M, Aboyans V, Bartelink ML, et al. European Stroke Organisation, ESC Committee for Practice Guidelines. ESC Guidelines on the diagnosis and treatment of peripheral artery diseases: Document covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal, upper and lower extremity arteries: the Task Force on the Diagnosis and Treatment of Peripheral Artery Diseases of the European Society of Cardiology (ESC). Eur Heart J. 2011; 32(22): 2851–2906, doi: 10.1093/eurheartj/ehr211, indexed in Pubmed: 21873417.
8. Perk J, De Backer G, Gohlke H, et al. European Association for Cardiovascular Prevention & Rehabilitation (EACPR), ESC Committee for Practice Guidelines (CPG). European Guidelines

on cardiovascular disease prevention in clinical practice (version 2012). The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts). Eur Heart J. 2012; 33(13): 1635–1701, doi: 10.1093/eurheartj/ehs092, indexed in Pubmed: 22555213.
9. Mazur P, Frołow M, Niżankowski R, et al. Impaired responsiveness to clopidogrel and aspirin in patients with recurrent stent thrombosis following percutaneous intervention for peripheral artery disease. Platelets. 2013; 24(2): 151–155, doi: 10.3109/09537104.2012.676220, indexed in Pubmed: 22497730.
10. Linnemann B, Thalhammer A, Wolf Z, et al. Late peripheral stent thrombosis due to stent fracture, vigorous exercise and hyporesponsiveness to clopidogrel. Vasa. 2012; 41(2): 136–144, doi: 10.1024/0301-1526/a000177, indexed in Pubmed: 22403133.
11. Matsagas MI, Geroulakos G, Mikhailidis DP. The role of platelets in peripheral arterial disease: therapeutic implications. Ann Vasc Surg. 2002; 16(2): 246–258, doi: 10.1007/s10016-001-0159-8, indexed in Pubmed: 11972262.
12. Hiatt WR. Preventing atherothrombotic events in peripheral arterial disease: the use of antiplatelet therapy. J Intern Med. 2002; 251(3): 193–206, doi: 10.1046/j.1365-2796.2002.00947.x, indexed in Pubmed: 11886478.
13. Grotemeyer KH. Effects of acetylsalicylic acid in stroke patients evidence of nonresponders in a subpopulation of treated patients. Thrombosis Research. 1991; 63(6): 587–593, doi: 10.1016/0049-3848(91)90085-b.
14. Doroszko A, Podgórska K, Drożdż K, et al. Resistance to acetylsalicylic acid — pathophysiology and clinical implications. Acta Angiologica. 2008; 14(3): 79–87.
15. Patrono C. Aspirin resistance: definition, mechanisms and clinical read-outs. J Thromb Haemost. 2003; 1(8): 1710–1713, doi: 10.1046/j.1538-7836.2003.00284.x, indexed in Pubmed: 12911581.
16. Spiliopoulos S, Kassimis G, Hatzidakis A, et al. High on-treatment platelet reactivity in peripheral endovascular procedures. Cardiovasc Intervent Radiol. 2014; 37(3): 559–571, doi: 10.1007/s00270-013-0707-y, indexed in Pubmed: 23897511.
17. Oh MiS, Yu KH, Lee JH, et al. Aspirin resistance is associated with increased stroke severity and infarct volume. Neurology. 2016; 86(19): 1808–1817, doi: 10.1212/WNL.0000000000002657, indexed in Pubmed: 27060166.
18. Mrdovic I, Čolić M, Savic L, et al. Clinical Significance of Laboratory-determined Aspirin Poor Responsiveness After Primary Percutaneous Coronary Intervention. Cardiovasc Drugs Ther. 2016; 30(2): 151–158, doi: 10.1007/s10557-016-6643-8, indexed in Pubmed: 26843365.
19. Michelson AD, Cattaneo M, Eikelboom JW, et al. Platelet Physiology Subcommittee of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis, Working Group on Aspirin Resistance. Aspirin resistance: position paper of the Working Group on Aspirin Resistance. J Thromb Haemost. 2005; 3(6): 1309–1311, doi: 10.1111/j.1538-7836.2005.01351.x, indexed in Pubmed: 15892858.
20. Cattaneo M. Aspirin and clopidogrel: efficacy, safety, and the issue of drug resistance. Arterioscler Thromb Vasc Biol. 2004; 24(11): 1980–1987, doi: 10.1161/01.ATV.0000145980.39477.a9, indexed in Pubmed: 15388526.
21. Snoep JD, Hovens MMC, Eikenboom JCJ, et al. Clopidogrel nonresponsiveness in patients undergoing percutaneous coronary intervention with stenting: a systematic review and meta-analysis. Am Heart J. 2007; 154(2): 221–231, doi: 10.1016/j.ahj.2007.04.014, indexed in Pubmed: 17643570.
22. Yi X, Lin J, Zhou Q, et al. Clopidogrel Resistance Increases Rate of Recurrent Stroke and Other Vascular Events in Chinese Population. J Stroke Cerebrovasc Dis. 2016; 25(5): 1222–1228, doi: 10.1016/j.jstrokecerebrovasdis.2016.02.013, indexed in Pubmed: 26935114.
23. Liu R, Zhou ZY, Chen YB, et al. Associations of CYP3A4, NR1I2, CYP2C19 and P2RY12 polymorphisms with clopidogrel resistance in Chinese patients with ischemic stroke. Acta Pharmacol Sin. 2016; 37(7): 882–888, doi: 10.1038/aps.2016.41, indexed in Pubmed: 27133299.
24. van Velzen JF, Laros-van Gorkom BAP, Pop GAM, et al. Multicolor flow cytometry for evaluation of platelet surface antigens and activation markers. Thromb Res. 2012; 130(1): 92–98, doi: 10.1016/j.thromres.2012.02.041, indexed in Pubmed: 22424855.
25. Rubak P, Nissen PH, Kristensen SD, et al. Investigation of platelet function and platelet disorders using flow cytometry. Platelets. 2016; 27(1): 66–74, doi: 10.3109/09537104.2015.1032919, indexed in Pubmed: 25901600.
26. Chakroun T, Addad F, Abderazek F, et al. Screening for aspirin resistance in stable coronary artery patients by three different tests. Thromb Res. 2007; 121(3): 413–418, doi: 10.1016/j.thromres.2007.04.010, indexed in Pubmed: 17553552.
27. Ochei J. Medical laboratory science: theory and practice. 2nd edition ed. Tata McGraw-Hill Education, New Delhi 2000.
28. Schilling McCann JA. Nursing: deciphering diagnostic tests. Lippincott Williams & Wilkins, Philadelphia 2007.
29. Brunner LS. Brunner & Suddarth's handbook of laboratory and diagnostic tests. Wolters Kluwer/Lippincott Williams & Wilkins, Philadelphia 2010.
30. Lev EI, Patel RT, Maresh KJ, et al. Aspirin and clopidogrel drug response in patients undergoing percutaneous coronary intervention: the role of dual drug resistance. J Am Coll Cardiol. 2006; 47(1): 27–33, doi: 10.1016/j.jacc.2005.08.058, indexed in Pubmed: 16386660.
31. Feher G, Feher A, Pusch G, et al. Clinical importance of aspirin and clopidogrel resistance. World J Cardiol. 2010; 2(7): 171–186, doi: 10.4330/wjc.v2.i7.171, indexed in Pubmed: 21160749.
32. Gurbel PA, Becker RC, Mann KG, et al. Platelet function monitoring in patients with coronary artery disease. J Am Coll Cardiol. 2007; 50(19): 1822–1834, doi: 10.1016/j.jacc.2007.07.051, indexed in Pubmed: 17980247.
33. Gum P, Kottke-Marchant K, Poggio E, et al. Profile and prevalence of aspirin resistance in patients with cardiovascular disease. The American Journal of Cardiology. 2001; 88(3): 230–235, doi: 10.1016/s0002-9149(01)01631-9.
34. Shantsila E, Watson T, Lip* G. Aspirin resistance: What, why and when? Thrombosis Research. 2007; 119(5): 551–554, doi: 10.1016/j.thromres.2006.08.009.
35. Grundmann K, Jaschonek K, Kleine B, et al. Aspirin non-responder status in patients with recurrent cerebral ischemic

attacks. J Neurol. 2003; 250(1): 63–66, doi: 10.1007/s00415-003-0954-y, indexed in Pubmed: 12527994.
36. Linnemann B, Prochnow S, Mani H, et al. Variability of non-response to aspirin in patients with peripheral arterial occlusive disease during long-term follow-up. Ann Hematol. 2009; 88(10): 979–988, doi: 10.1007/s00277-009-0708-8, indexed in Pubmed: 19247655.
37. Pulcinelli FM, Pignatelli P, Celestini A, et al. Inhibition of platelet aggregation by aspirin progressively decreases in long-term treated patients. J Am Coll Cardiol. 2004; 43(6): 979–984, doi: 10.1016/j.jacc.2003.08.062, indexed in Pubmed: 15028353.
38. Maree AO, Curtin RJ, Dooley M, et al. Platelet response to low-dose enteric-coated aspirin in patients with stable cardiovascular disease. J Am Coll Cardiol. 2005; 46(7): 1258–1263, doi: 10.1016/j.jacc.2005.06.058, indexed in Pubmed: 16198840.
39. van der Loo B, Braun J, Koppensteiner R. On-treatment function testing of platelets and long-term outcome of patients with peripheral arterial disease undergoing transluminal angioplasty. Eur J Vasc Endovasc Surg. 2011; 42(6): 809–816, doi: 10.1016/j.ejvs.2011.08.014, indexed in Pubmed: 21917489.
40. Snoep JD, Hovens MMC, Eikenboom JCJ, et al. Association of laboratory-defined aspirin resistance with a higher risk of recurrent cardiovascular events: a systematic review and meta-analysis. Arch Intern Med. 2007; 167(15): 1593–1599, doi: 10.1001/archinte.167.15.1593, indexed in Pubmed: 17698681.
41. Ichiki K, Ikeda H, Haramaki N, et al. Long-term smoking impairs platelet-derived nitric oxide release. Circulation. 1996; 94(12): 3109–3114, doi: 10.1161/01.cir.94.12.3109, indexed in Pubmed: 8989117.
42. Blache D. Involvement of hydrogen and lipid peroxides in acute tobacco smoking-induced platelet hyperactivity. Am J Physiol. 1995; 268(2 Pt 2): H679–H685, doi: 10.1152/ajpheart.1995.268.2.H679, indexed in Pubmed: 7864194.
43. Bhatt DL. What makes platelets angry: diabetes, fibrinogen, obesity, and impaired response to antiplatelet therapy? J Am Coll Cardiol. 2008: 1060–1061.
44. Angiolillo DJ, Suryadevara S. Aspirin and clopidogrel: efficacy and resistance in diabetes mellitus. Best Pract Res Clin Endocrinol Metab. 2009; 23(3): 375–388, doi: 10.1016/j.beem.2008.12.001, indexed in Pubmed: 19520310.
45. Habizal NH, Abdul Ha, Bhaskar S, et al. Prevalence of aspirin resistance in diabetic patients and its associated factors. Malays J Med Sci. 2015;22(1):50-7. Epub 2015/04/22. PubMed PMID: 25892950; PubMed Central PMCID: PMCPMC4390774.
46. Homoródi N, Kovács EG, Leé S, et al. The lack of aspirin resistance in patients with coronary artery disease. J Transl Med. 2016; 14: 74, doi: 10.1186/s12967-016-0827-7, indexed in Pubmed: 26980433.
47. Matsagas M, Jagroop IA, Geroulakos G, et al. The effect of a loading dose (300 mg) of clopidogrel on platelet function in patients with peripheral arterial disease. Clin Appl Thromb Hemost. 2003; 9(2): 115–120, doi: 10.1177/107602960300900204, indexed in Pubmed: 12812379.
48. Matetzky S, Shenkman B, Guetta V, et al. Clopidogrel resistance is associated with increased risk of recurrent atherothrombotic events in patients with acute myocardial infarction. Circulation. 2004; 109(25): 3171–3175, doi: 10.1161/01.CIR.0000130846.46168.03, indexed in Pubmed: 15184279.
49. Kuliczkowski W, Zembala M, Polonski L, et al. Monitoring of antiplatelet drug effects - fashion or necessity? Kardiol Pol. 2008; 66(1): 119–124.
50. Frere C, Quilici J, Morange PE, et al. High post-treatment platelet reactivity is associated with a high incidence of myonecrosis after stenting for non-ST elevation acute coronary syndromes. Thromb Haemost. 2017; 97(02): 282–287, doi: 10.1160/th06-07-0362.
51. Choi JL, Li S, Han JY. Platelet function tests: a review of progresses in clinical application. Biomed Res Int. 2014; 2014: 456569, doi: 10.1155/2014/456569, indexed in Pubmed: 24895576.
52. Leytin V, Mody M, Semple JW, et al. Quantification of platelet activation status by analyzing P-selectin expression. Biochem Biophys Res Commun. 2000; 273(2): 565–570, doi: 10.1006/bbrc.2000.2977, indexed in Pubmed: 10873646.
53. McKenzie ME, Malinin AI, Bell CR, et al. Aspirin inhibits surface glycoprotein IIb/IIIa, P-selectin, CD63, and CD107a receptor expression on human platelets. Blood Coagul Fibrinolysis. 2003; 14(3): 249–253, doi: 10.1097/01.mbc.0000046182.72384.ab, indexed in Pubmed: 12695747.
54. Silverstein RL, Febbraio M. Identification of lysosome-associated membrane protein-2 as an activation-dependent platelet surface glycoprotein. Blood. 1992; 80(6): 1470–1475, doi: 10.1182/blood.v80.6.1470.bloodjournal8061470.
55. Valdes V, Nardi MA, Elbaum L, et al. Reproducibility over time and effect of low-dose aspirin on soluble P-selectin and soluble CD40 ligand. J Thromb Thrombolysis. 2015; 40(1): 83–87, doi: 10.1007/s11239-015-1179-5, indexed in Pubmed: 25648873.
56. Serebruany VL, Malinin AI, Hanley DF. Magnitude and time course of platelet inhibition with extended release dipyridamole with or without aspirin in healthy Japanese volunteers. The AGgrenox versus Aspirin Therapy Evaluation (AGATE-Japan). Thromb Haemost. 2008; 99(1): 116–120, doi: 10.1160/TH07-09-0563, indexed in Pubmed: 18217142.
57. Saunders J, Nambi V, Kimball KT, et al. ELIMIT Investigators. Variability and persistence of aspirin response in lower extremity peripheral arterial disease patients. J Vasc Surg. 2011; 53(3): 668–675, doi: 10.1016/j.jvs.2010.08.029, indexed in Pubmed: 21227624.


Praca pt.: „Ocena funkcji płytek krwi oraz odporności na aspirynę i klopidogrel u pacjentów z chorobą tętnic obwodowych poddawanych leczeniu wewnątrznaczyniowemu", którą w wersji angielskiej zamieszczono w niniejszym numerze „Acta Angiologica" zdobyła pierwszą nagrodę im. Prof. R. Węgłowskiego. Redakcja serdecznie gratuluje Autorom.

POLSKIE TOWARZYSTWO ANGIOLOGICZNE

Kapituła Nagrody im. Prof. R. Węgłowskiego przyznaje I miejsce w Konkursie

Panu Grzegorzowi Borowskiemu i Pani Aleksandrze Nowaczyńskiej

za pracę zatytułowaną

„Ocena funkcji płytek krwi oraz oporności na aspirynę i klopidogrel u pacjentów z chorobą tętnic obwodowych poddawanych leczeniu wewnątrznaczyniowemu"

Przewodniczący Kapituły

Dr hab. med. Piotr Terlecki

Prezes Polskiego Towarzystwa Angiologicznego

Lublin, 6 listopada 2020

VIA MEDICA

ORIGINAL PAPER

Acta Angiol
Vol. 26, No. 4, pp. 129–139
Doi: 10.5603/AA.2020.0025

ISSN 1234–950X
e-ISSN: 1644–3276

Deep-vein thrombosis detection rates and consideration of the living environment in a tsunami disaster area during the disaster reconstruction phase: A cross-sectional study

Hidenori Onishi[1], Osamu Yamamura[2], Shinsaku Ueda[3], Muneichi Shibata[4], Soichi Enomoto[5], Fumie Maeda[6], Hiromasa Tsubouchi[7],Takeshi Hirobe[8], Sadao Shimizu[9], Takahiro Kishimoto[10], Hiroshi Chiba[11], Kazuhiro Sasaki[12], Kazuhiko Hanzawa[13], Tadanori Hamano[14], Yasunari Nakamoto[15], Bunji Kaku[16], Hidekazu Terasawa[17]

[1]Department of Community Medicine, Faculty of Medical Science, University of Fukui, Fukui, Japan
[2]Department of Community Medicine, Faculty of Medical Science, University of Fukui and Second Department of Internal Medicine, Faculty of Medical Science, University of Fukui, Fukui, Japan
[3]Department of Thoracic Surgery, Ishinomaki Red Cross Hospital, Miyagi, Japan
[4]Department of Cardiology, Mackay Base Hospital, Queensland, Australia
[5]Second Department of Internal Medicine, Faculty of Medical Science, University of Fukui, Japan
[6]Department of Clinical Laboratory, University of Fukui, Fukui, Japan
[7]Department of Radiotechnology, Fukui Ken Saiseikai Hospital, Fukui, Japan
[8]Department of Clinical Laboratory, Fukui Prefectural Hospital, Fukui, Japan
[9]Department of Medical Laboratory, National Hospital Organization Kanazawa Medical Center, Ishikawa, Japan
[10]Department of Radiology, University of Fukui Hospital, Fukui, Japan
[11]Division of Clinical Laboratory, Morioka Municipal Hospital, Iwate, Japan
[12]Department of Neurology, Morioka Municipal Hospital, Iwate, Japan
[13]Department of Respiratory Surgery, Graduate School of Medicine, University of Niigata, Niigata, Japan
[14]Second Department of Internal Medicine, Faculty of Medical Science, University of Fukui, Fukui, Japan
[15]Second Department of Internal Medicine, Faculty of Medical Science, University of Fukui, Fukui, Japan
[16]Department of Cardiology, Toyama Red Cross Hospital, Toyama, Japan
[17]Department of Community Medicine, Faculty of Medical Science, University of Fukui, Fukui, Japan

Abstract

Introduction: *Tsunami victims of the Great East Japan Earthquake were screened for deep-vein thrombosis (DVT) in order to compare the DVT incidence rates between temporary and non-temporary housing resident groups.*

Material and methods: *Lower extremity venous ultrasonography was performed on 290 subjects (64 men and 226 women; mean age = 71.9 ± 7.9 years) at 44 months after the disaster. All subjects completed questionnaires to gather information about their background factors which included the Kessler Psychological Distress Scale: K6.*

Results: *The DVT detection rate was 10.7% in the temporary group. In the non-temporary group, it was 11.3% among the subjects who previously lived in temporary housing. For the subjects who were living in their own homes,*

Address for correspondence: Osamu Yamamura, Department of Community Medicine, Faculty of Medical Science, University of Fukui and Second Department of Internal Medicine, Faculty of Medical Science, University of Fukui, 23-3 Matsuokashimoaizuki Yoshida-gun Eihei-ji-cho Fukui 910–1104 Japan, +81 776-61-8264, e-mail: kapi@u-fukui.ac.jp

it was 9.2%. Psychological distress levels measured by K6 were significantly higher in the temporary housing group than in the non-temporary housing group. The multivariate analysis showed that the background factor associated with DVT risk was SV (soleal vein) dilatation in all subjects as well as in the non-temporary housing group, while hypertension and use of sleeping pills were found to be the factors in the temporary housing group.
Conclusions: *DVT detection rates were similar between the temporary and non-temporary housing groups, and were higher than that in the Japanese general population. The psychological distress level of the tsunami victims measured by K6 was also higher in the temporary housing group than in the non-temporary housing group. It is necessary to establish a long-term and awareness-raising disaster victim support system.*

Key words: Great East Japan Earthquake, tsunami disaster area, temporary housing, disaster-related diseases, psychological distress survey

Acta Angiol 2020; 26, 4: 129–139

Introduction

After a major disaster, the risk of cardiovascular disease, infection and psychological disorders increases among survivors under stressful conditions [1]. Deep vein thrombosis (DVT), one of the disaster-related diseases, has been attracting public attention since the Mid Niigata Prefecture Earthquake in 2004 [2]. An increased risk of developing DVT was reported among evacuees in emergency shelters and temporary housing in disaster areas [2–6]. Post-disaster DVT is assumed to occur at a high rate due to poor living conditions in shelters and temporary housing, under which evacuees dehydrate because they try to refrain from water intake to reduce their frequency of urination, face low levels of physical activity and sleep in vehicles [2–6].

In Ishinomaki City, Miyagi Prefecture, another area affected by a tsunami after the Great East Japan Earthquake, an increased risk of developing DVT over a long period of time was reported among residents in temporary housing and houses in the affected area even after their living environment was improved [4]. Our study was conducted in Watari-gun, Miyagi Prefecture (Watari-town and Yamamoto-town), an area which was also severely affected by the tsunami. In our study area, the temporary housing was gradually removed as reconstruction progressed from the third year after the disaster, and the living conditions for survivors were improved. DVT screening was performed for the purpose of prevention and to raise awareness among disaster survivors. Temporary housing residents are more likely to develop DVT because of their low activity levels. This study reports on the comparison of DVT detection rates between temporary housing residents (temporary housing group) and non-temporary housing residents (non-temporary housing group) and also on the identified risk factors.

Material and methods

Disaster situation in our study area

Watari-gun, Miyagi Prefecture (Watari-town and Yamamoto-town) is located approximately 40 km south of Sendai City and is an industrial area focusing on agriculture and fishing with a population of approximately 50,000. In the Great East Japan Earthquake, there were 885 people who died or were missing, 13,000 people were forced to evacuate from their homes, and 7,075 houses were destroyed or partially destroyed. In September 2011, the number of evacuees living in temporary housing reached 6,050. These temporary housing complexes were however mostly removed as reconstruction progressed.

Study subjects

A total of 290 subjects who were living in temporary housing and houses in neighboring areas in Watari-gun, Miyagi Prefecture (64 men, 226 women; mean age = = 71.9 ± 7.9 years) participated in our screening activity. The subjects were divided into two groups: 149 in the temporary group (33 men, 116 women; mean age = 73.4 ± 8.4 years) and 141 in the non-temporary group (31 men, 110 women; mean age = 70.3 ± ± 7.0 years). Of the 141 subjects in the non-temporary housing group, 44 were those who previously lived in temporary housing (9 men, 35 women; mean age = = 70.8 ± 9.4 years), and 97 were those who continued living in their own homes (22 men, 75 women; mean age = 70.0 ± 5.6 years). There were 179 subjects who previously underwent DVT screenings (including screenings conducted by other organizations). The screening was performed at 44 months after the disaster for a total of 2 days (November 1 and 2, 2014). Two subjects in the temporary housing group and four in the non-temporary housing group were excluded because

of inadequacies in the Kessler Psychological Distress Scale (K6) questionnaire, resulting in the temporary housing group having 147 and the non-temporary housing group having 137. Our targeted number of participants was approximately 300.

Setting and examination team

DVT screening was undertaken at meeting places located in temporary housing, healthcare centers and public halls in Yamamoto-town, Watari-gun, Miyagi Prefecture. The medical examination team was organized mainly by the University of Fukui School of Medical Sciences with cooperation from volunteer healthcare providers (doctors, nurses, laboratory medical technologists, etc.) and medical students.

Examination items

Our DVT screening activity was performed in temporary housing in cooperation with the local authority of Watari-town and Yamamoto-town. Posters to raise awareness about DVT prevention were displayed one month prior to the screening. Participation in the screening was on a voluntary basis. All subjects provided written informed consent, and the examination was conducted in the following order: a questionnaire (age, sex, lifestyle, K6, underlying disease, life after a disaster), blood pressure measurement, lower-extremity venous ultrasonography and explanation of the result. The underlying diseases (dyslipidemia, diabetes mellitus, heart disease, hypertension) of the subjects were reported based on their answers to the self-report questionnaire. When subjects answered in the questionnaire that the time spent walking was reduced in comparison with before the disaster, they were classified as having reduced walking hours. The ultrasonography was performed by several medical technologists, each with more than five years of experience [5, 6]. To improve uniformity, the evaluation criteria were discussed prior to the screening [5, 6]. Screening was undertaken using portable ultrasound machines (LOGIQe, GE Healthcare with a 3.3–10.0 MHz linear probe; Noblus, Hitachi Medical Corporation with a 5–18 MHz linear probe; CX50, Philips Japan, Ltd., with a 3–12 MHz linear probe; Viamo, Canon Medical Systems Corporation with a 6.2–11.0 MHz linear probe; NanoMaxx, SonoSite Inc., with a 6–13 MHz linear probe). Ultrasound examinations were performed from the calf to the popliteal veins in the sitting position [5, 6]. Only screening of the calf to the popliteal veins was conducted due to the large number of participants as well as the limitations in our screening setting and time [5, 6]. The presence of thrombus was confirmed using a combination of the color Doppler and the compression technique, where there was a lack of compressibility [5–8]. Thrombi were classified as organized or fresh [6, 9–11]. Inner diameters (short-axis) of the soleal vein (SV) were measured in the sitting position with the lower extremity muscles relaxed, and maximum diameter was used in our analysis. When measuring the diameters, the probe was placed so as not to put pressure on the SV and measurements were not made on the venous valves. The maximum diameter of the soleal vein (SV) was examined, and a diameter ≥ 8 mm was defined as dilatation [6, 12]. Subjects who were found to be DVT-positive received a patient referral document and were encouraged to visit their local medical institutions. K6 was also used to measure the psychological distress levels of the subjects. K6 consisted of six items measuring depression and anxiety over the past month on a five-point scale [13]. The Japanese version of the K6 has also been developed and the reliability and validity have been confirmed [14]. Because the levels of psychological distress caused by the tsunami disaster were assumed to be high in our study area, subjects who scored more than 13 points were classified as having a psychological disorder [15].

Statistical analysis

Age, systolic blood pressure, diastolic blood pressure, K6 and SV diameter are reported as means ± standard deviations, and categorical variables are reported as frequency and percentage (%). R commander version 1.28 was used for the statistical analysis. Mann-Whitney U test and the χ^2 test (including Yates' continuity correction) were used for comparisons between the two groups. To identify risk factors for DVT, multivariate logistic regression analysis (stepwise method) was performed. In all comparative tests, a p-value of < 0.05 was considered statistically significant.

Results

DVT was diagnosed in 30 of the 290 subjects screened (10.3%), of whom 13 were fresh thrombi (4.4%) and 17 were organized thrombi (5.8%).

Comparison of demographic characteristics in all subjects with or without DVT is shown in Tables 1, 2 and Figure 1.

Univariate analysis showed that SV dilatation (43.3% vs 19.2%; $p < 0.01$) and a previous history of DVT screening (83.3% vs 59.2%; $p < 0.05$) were significantly higher in the DVT-positive group than in the negative group. Multivariate analysis showed that SV dilatation was the background factor associated with DVT risk in all subjects (odds ratio 3.21; 95% confidence interval 1.460–7.040; $p = 0.0035$).

Comparison of demographic characteristics of subjects with or without DVT in the temporary housing group is shown in Tables 1, 2, and Figure 1.

Table 1. Demographic characteristics and ultrasonographic findings (univariate analysis)

	all 290 cases			Temporary housing group 149 cases			Non-temporary housing group 141 cases		
	DVT Present n = 30	DVT Absent n = 260	p-value	DVT Present n = 16	DVT Absent n = 133	p-value	DVT Present n = 14	DVT Absent n = 127	p-value
Age(years)	72.0 ± 8.3	71.8 ± 7.8	0.905	74.1 ± 8.6	73.3 ± 8.4	0.6787	69.6 ± 7.6	70.3 ± 6.9	0.712
Gender (male/female)	6/24	58/202	0.955	2/14	31/102	0.506	4/10	27/100	0.774
Blood pressure									
SBP (mm Hg)	141.6 ± 16.6	137.8 ± 19.5	0.308	143.3 ± 14.9	137.0 ± 20.1	0.1186	139.6 ± 18.8	138.5 ± 18.8	0.567
DBP (mm Hg)	82.2 ± 14.7	80.3 ± 13.5	0.484	83.7 ± 15.2	79.2 ± 14.4	0.07426	80.5 ± 14.5	81.6 ± 12.4	0.8685
Lifestyle									
Exercises n (%)	19 (63.3)	179 (68.8)	0.684	8 (50)	86 (64.7)	0.382	11 (78.6)	93 (73.2)	0.911
Smoker n (%)	2 (6.7)	20 (7.7)	1	1 (6.2)	15 (11.3)	0.852	1 (7.1)	5 (3.9)	1
Use of sleeping pills n (%)	14 (46.7)	81 (31.2)	0.131	10 (62.5)	46 (34.6)	0.057	4 (28.6)	35 (27.6)	1.000
Underlying disease									
DL n (%)	19 (63.3)	142 (54.6)	0.474	10 (62.5)	65 (48.9)	0.444	9 (64.3)	77 (60.6)	1
DM n (%)	5 (16.7)	36 (13.8)	0.886	4 (25)	21 (15.8)	0.564	1 (7.1)	15 (11.8)	0.937
Heart disease n (%)	10 (33.3)	71 (27.3)	0.63	7 (43.89	34 (25.6)	0.214	3 (21.4)	37 (29.1)	0.768
HT n (%)	20 (66.7)	138 (53.1)	0.222	13 (81.2)	66 (49.6)	0.033	7 (50)	72 (56.7)	0.845
Insomnia n (%)	1 (43.3)	107 (41.2)	0.973	8 (50)	59 (44.4)	0.871	5 (35.7)	48 (37.8)	1
Life after a disaster									
Reduced urination (Acute phase of the disaster) n (%)	9 (30.0)	76 (29.2)	1	5 (31.2)	40 (30.1)	1.000	4 (28.6)	36 (28.3)	1.000
Sleeping in a vehicle (Acute phase of the disaster) n (%)	6 (20.0)	53 (20.4)	1	2 (12.5)	25 (18.8)	0.784	4 (28.6)	28 (22.0)	0.828
Lower limb symptoms (Acute phase of the disaster) n (%)	11 (36.7)	105 (40.4)	0.844	6 (37.5)	61 (45.9)	0.712	5 (35.7)	44 (34.6)	1
Reduction of walking hours n (%)	16 (53.3)	129 (49.6)	0.847	13 (81.2)	83 (62.4)	0.226	3 (21.4)	46 (36.2)	0.419
Temporary housing resident n (%)	16 (53.3)	133 (51.2)	0.973						
Previous history of DVT screening n (%)	25 (83.3)	154 (59.2)	0.0176	14 (87.5)	113 (85.0)	1	11 (78.6)	41 (32.3)	0.00184
Ultrasonographic findings									
Maximum diameter of the soleal vein (mm)	7.5 ± 1.7	6.6 ± 1.74	0.0157	7.7 ± 1.6	6.5 ± 1.5	0.00689	7.2 ± 1.8	6.8 ± 1.9	0.458
Soleal veindilatation (≥ 8 mm)	13 (43.3)	50 (19.2)	0.0051	6 (37.5)	23 (17.3)	0.111	7 (50)	27 (21.3)	0.040

Mean ± standard deviation. Nominal variables are shown as frequency(%); ns: non–significant difference
SBP: systolic blood pressure; DBP: diastolic blood pressure; DL: dyslipidemia; DM: diabetes mellitus; HT: hypertension; DVT: deep vein thrombosis
continuous variables: Mann–Whitney U test (between each pair of two groups); nominal variables: χ^2 test(between each pair of two groups)

Table 2. Risk factor analysis of deep vein thrombosis (multivariate analysis)

	All 290 cases			Temporary housing group 149 cases			Non-temporary housing group 141 cases		
	Odds ratio	95% CI	p-value	Odds ratio	95% CI	p-value	Odds ratio	95% CI	p-value
Age (years)	0.994	0.943–1.05	0.816	1.01	0.93–1.09	0.853	0.986	0.895–1.09	0.772
Gender (male)	0.758	0.294–2.100	0.628	0.37	0.071–1.9	0.237	1.34	0.363–4.97	0.659
Lifestyle									
Exercises n (%)	0.937	0.386–2.27	0.88	0.713	0.213–2.39	0.58	1.45	0.335–6.3	0.618
Smoker n (%)	0.876	0.177–4.34	0.854	0.725	0.0071–7.32	0.758	1.82	0.164–20.2	0.626
Use of sleeping pills n (%)	1.96	0.901–4.270	0.872	3.270	1.09–9.81	0.034	1.310	0.337–5.08	0.697
Underlying disease									
DL n (%)	1.29	0.557–2.84	0.58	1.180	0.36–3.85	0.788	1.300	0.392–5.05	0.642
DM n (%)	1.16	0.393–3.43	0.786	1.670	0.45–6.19	0.443	0.992	0.095–10.3	0.995
Heart disease n (%)	1.18	0.507–2.74	0.704	1.700	0.534–5.38	0.37	0.572	0.145–2.26	0.426
HT n (%)	1.8	0.795–4.060	0.159	4.550	1.22–17.0	0.024	0.782	0.243–2.52	0.680
Reduction of walking hours n (%)	1.01	0.441–2.3	0.989	2.64	0.663–10.5	0.169	0.438	0.113–1.7	0.232
Temporary housing resident n (%)	1.13	0.509–2.490	0.77						
Soleal vein dilatation (≥ 8 mm)	3.21	1.46–7.040	0.00359	2.850	0.868–9.33	0.084	3.700	1.2–11.5	0.023

multiple logistic regression analysis (risk factors associated with deep vein thrombosis)
SBP: systolic blood pressure; DBP: diastolic blood pressure; DL: dyslipidemia; DM: diabetes mellitus; HT: Hypertension; DVT: deep vein thrombosis

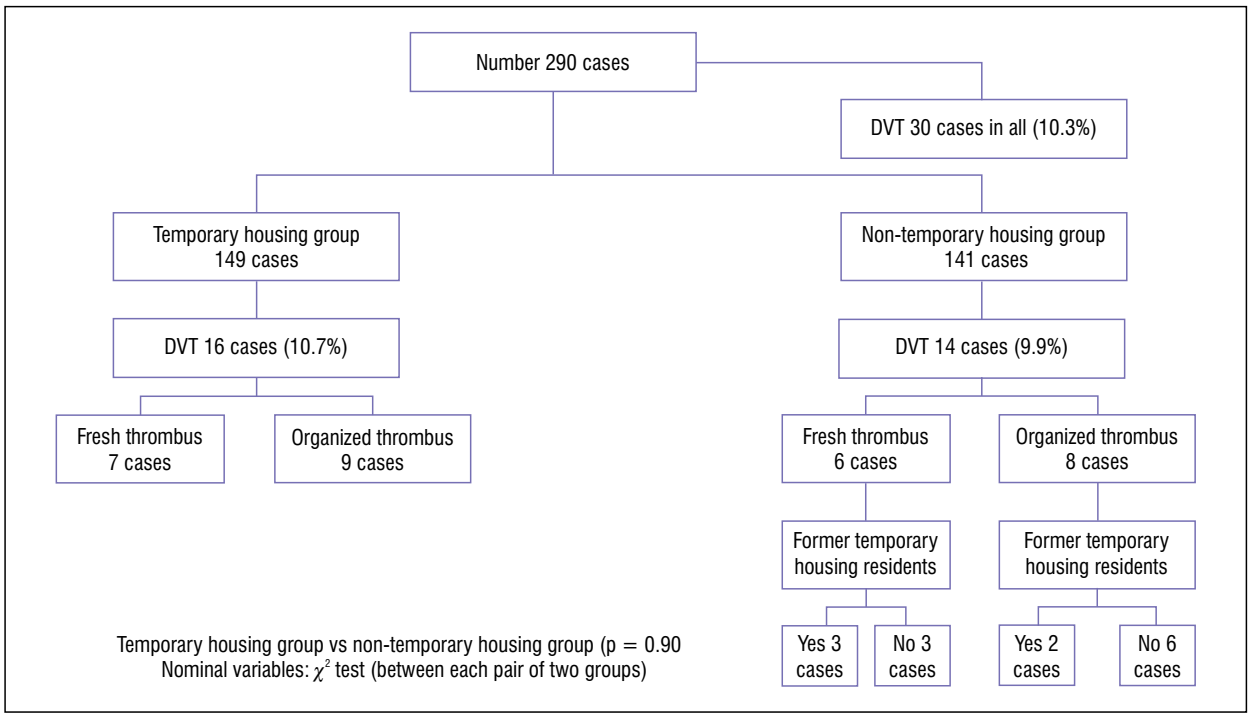


Figure 1. Flow diagram of subject selection

Univariate analysis showed that the rate of subjects with hypertension (81.2% vs 49.6%; $p < 0.05$) was significantly higher in the DVT-positive group than in the negative group. Multivariate analysis showed that hypertension (odds ratio 4.4; 95% confidence interval 1.200–16.100; $p = 0.025$) and use of sleeping pills (odds ratio 3.27; 95% confidence interval 1.090–9.810; $p = 0.034$) were the risk factors for DVT in the temporary housing group.

Comparison of demographic characteristics of subjects with or without DVT in the non-temporary housing group is shown in Tables 1, 2, and Figure 1.

Univariate analysis showed that SV dilatation (50.0% vs 21.3%; $p < 0.05$) and previous history of DVT screening (78.6% vs 32.3%; $p < 0.01$) were significantly higher in the DVT-positive group than in the negative group. Multivariate analysis showed that SV dilatation (odds ratio 3.7; 95% confidence interval 1.200–11.500; $p = 0.023$) was the background factor associated with DVT risk in the non-temporary housing group.

Comparison of DVT detection rates and background factors between temporary and non-temporary housing groups is shown in Table 3 and Figure 1.

The DVT detection rates in the temporary and non-temporary housing groups were 10.7% (16 of 149) and 9.9% (14 of 141), respectively, Therefore, no significant difference was observed ($p = 0.90$). Of the 16 DVT-positive subjects in the temporary housing group, seven had fresh thrombi and nine had organized thrombi. The DVT detection rate for the former temporary housing residents in the non-temporary housing group was 11.3% (5 of 44). Of the five, three had fresh thrombi and two had organized thrombi. The DVT detection rate among those who continued living in their homes in the non-temporary group was 9.2% (9 of 97). Of the nine, three had fresh thrombi and six had organized thrombi. In the comparison of background factors, age (73.4 ± 8.4 years vs 70.3 ± 7.0 years; $p < 0.005$), reduction of walking hours (64.4% vs 34.8%; $p < 0.0001$) and previous history of DVT screening (85.2% vs 36.9%; $p < 0.0001$) were significantly higher in the temporary housing group than in the non-temporary housing group.

Comparison of psychological distress levels of subjects between temporary and non-temporary housing groups is shown in Table 4.

Univariate analysis showed that age (73.3 ± 8.4 years vs 70.3 ± 7.0 years; $p < 0.005$), K6 (11.2 ± 5.9 vs 9.7 ± 4.9; $p < 0.05$) and psychological disorder (38.1% vs 22.6%; $p < 0.01$) were significantly higher in the temporary housing group than in the non-temporary housing group.

Table 3. Comparison of temporary housing and non-temporary housing group (characteristics of individuals studies)

	Temporary housing n = 149	Non-temporary housing n = 141	p-value
Age (years)	73.4 ± 8.4	70.3 ± 7.0	0.00276
Gender (male/female)	33/116	31/110	1
Blood pressure			
SBP (mm Hg)	137.7 ± 19.7	138.7 ± 18.7	0.6483
DBP (mm Hg)	79.7 ± 14.5	81.4 ± 12.6	0.1243
Lifestyle			
Exercises n (%)	94 (63.1)	104 (73.8)	0.0679
Smoker n (%)	16 (10.7)	6 (4.3)	0.0626
Use of sleeping pills n (%)	56 (37.6)	39 (27.7)	0.094
Underlying disease			
DL n (%)	75 (50.3)	86 (61)	0.0878
DM n (%)	25 (16.8)	16 (11.3)	0.247
Heart disease n (%)	41 (27.5)	40 (28.4)	0.976
HT n (%)	79 (53.0)	79 (56)	0.692
Insomnia n (%)	67 (45)	53 (37.6)	0.871
Life after a disaster			
Reduced urination (Acute phase of the disaster) n (%)	45 (30.2)	40 (28.4)	0.831
Sleeping in a vehicle (Acute phase of the disaster) n (%)	27 (18.1)	32 (22.7)	0.412
Lower limb symptoms (Acute phase of the disaster) n (%)	67 (45)	49 (34.8)	0.098
Reduction of walking hours n (%)	96 (64.4)	49 (34.8)	< 0.0001
Previous history of DVT screening n (%)	127 (85.2)	52 (36.9)	< 0.0001
Ultrasonographic findings			
DVT n (%)	16 (10.7)	14 (9.9)	0.973
Maximum diameter of the soleal vein (mm)	6.6 ± 1.5	6.9 ± 1.9	0.185
Soleal vein dilatation (≥ 8 mm)	29 (19.5)	34 (24.1)	0.414

Mean ± standard deviation. Nominal variables are shown as frequency (%).
SBP: systolic blood pressure; DBP: diastolic blood pressure; DL: dyslipidemia; DM: diabetes mellitus; HT: hypertension; DVT: deep vein thrombosis
Continuous variables: Mann-Whitney U test (between each pair of two groups); nominal variables: χ^2 test (between each pair of two groups)

Table 4. Comparison of temporary housing and non-temporary housing group (Kessler Psychological Distress Scale K6)

	Temporary housing group n = 147	Non-temporary housing group n = 137	p-value
Age (years)	73.3 ± 8.4	70.1 ± 6.9	0.0028
Gender (male/female)	33/114	31/106	1
K6	11.2 ± 5.9	9.7 ± 4.9	0.0264
K6 (≥ 13)	56 (38.1)	31 (22.6)	0.007

Mean ± standard deviation. Nominal variables are shown as frequency (%)
Continuous variables: Mann-Whitney U test (between each pair of two groups) nominal variables χ^2 test (between each pair of two groups)

Discussion

DVT detection rates and risk factors in all subjects

A high incidence of DVT detected by the lower extremity venous ultrasonography was also reported in a study conducted among residents in the affected areas after the Mid Niigata Prefecture Earthquake in 2004, and the incidence rate remained higher compared with that in the non-disaster area in Japan even eight years after the disaster [16]. The high detection rate (13.5%) was also reported in the temporary housing resident population

in the case of Iwate Prefecture even four years after the Great East Japan Earthquake. Therefore, the risk of DVT is assumed to increase after a major disaster regardless of the type of evacuation, and is likely to remain high for a long period of time [5]. In this study, the overall DVT detection rate at 44 months after the disaster was 10.3%, which was still much higher than that of the general Japanese population (1.8–2.3%) [4]. Our screening program has also identified that SV dilatation is a background factor associated with DVT risk in all subjects. SV dilatation is a known risk factor for DVT in post-disaster settings. The SV was found to be the most important as the initial site of DVT caused by blood flow stasis [17]. The incidence of DVT associated with SV dilatation has also been reported in several studies [12, 18, 19]. Many cases of idiopathic DVT were observed among Japanese people who had a SV diameter ≥ 7 mm. In the disaster affected areas after the Kumamoto Earthquake, DVT was diagnosed more in survivors (staying in disaster shelters) who had an SV diameter ≥ 8 mm than those with a smaller diameter. In the survivor population of the Great East Japan Earthquake, SV dilatation (≥ 9 mm) in the DVT-positive group was reported to be significantly higher than that in the DVT-negative group (≥ 9 mm) [6, 12, 18]. In the patients who underwent arthroplasty, SV dilation (≥ 10 mm) was reported to be an independent positive predictor of DVT [19]. SV dilatation has not only been reported as a risk factor for DVT, but also as a factor for sustained DVT [20]. SV dilatation contributes to thrombus formation and results in the development of DVT. This may suggest that people with SV dilatation are more likely to suffer from sustained DVT. When physicians treat patients with DVT, they should note that SV dilation is a typical factor in ultrasound imaging that indicates a history of DVT.

In the disaster area, it has been shown that disuse syndrome can diminish calf muscle pump functionality, which causes venous congestion, and people are more likely to develop DVT. In the case of tsunami victims in Ishinomaki City, low levels of physical activity due to their inconvenient lifestyle were observed and this might have contributed to the development of disuse syndrome regardless of living in temporary housing or in their own homes [4]. To avoid having low levels of physical activity, exercise classes were therefore carried out mainly at temporary housing locations. These classes were effective in improving their sense of well-being, but it did not have a substantial impact on the disaster victims [21]. Our study population might have had exercise habits, but we assume that the reduced levels of physical activity were unable to be prevented. In our walking-hour survey, half of the disaster victims stated that their walking time per day was reduced compared to what it was before the earthquake. SV dilatation caused by reduced levels of physical activity after the disaster may have contributed to the development of DVT.

Our high detection rate of DVT may be due to the fact that this study was conducted in a disaster-affected area and included disaster victims with underlying diseases (hypertension, diabetes mellitus and dyslipidemia). Metabolic syndrome (MetS), the clustering of hypertension, hyperlipidemia, diabetes mellitus, and obesity, is a known factor for increasing the risk of venous thromboembolism (VTE) [22]. In addition, an increased risk of recurrent VTE following the accumulation of MetS components, including hypertension, diabetes mellitus, dyslipidemia and obesity, was reported [23]. The VTE recurrence rate was 14% in patients with one component, followed by 21% with two components, 30% with three components, and 37% with all four components [23]. The higher the number of MetS components, the higher the risk of VTE.

Disaster-related DVT was not found to disappear even after several years in many people who developed it immediately after the disaster [5, 16]. The reason for this may be because disaster victims with organized thrombi are more likely to suffer from recurrent DVT over a long period of time [6, 16]. SV dilatation has been shown to be a risk factor for DVT in our study, but it was also reported to be a risk factor for sustained DVT. In addition to this, our study has included subjects who developed DVT immediately after the disaster as well as those who had underlying diseases. This may have contributed the high DVT detection rates in our study.

Addressing self-selection and non-respondent biases is necessary in disaster area studies. In this study, there were many subjects who were concerned about disaster-related diseases, which might have introduced self-selection bias, and thus the actual prevalence of DVT might have been lower than that shown in our study. On the other hand, in order to avoid non-respondent bias, it is particularly important to take measures to encourage all survivors to participate in social activities, including screening activities, in the disaster affected areas.

Comparison of background factors between temporary and non-temporary groups

In the comparison of background factors including those related to living conditions during the disaster reconstruction phase, age, reduction of walking hours and psychological disorders were found to be significantly higher in the temporary housing group than in the non-temporary housing group. In the psychological distress level survey using K6, the prevalence of psychological disorders in both the temporary housing group

(38.1%) and non-temporary housing group (22.6%) were remarkably higher than in the general Japanese population (2.3%) [24]. A post-disaster survey in Miyagi Prefecture (18 years and older) reported that the prevalence of psychological disorders was 8.6% in disaster public housing and 7.5% in temporary housing [25]. The prevalence was higher in our study subjects both in temporary and non-temporary housing groups. The rate in another survey (35.9%), which was conducted one year after the disaster among residents (40 years and older) in Iwanuma City, Miyagi Prefecture, shows a percentage similar to that of the temporary housing group rate in our study [26]. There may be a gap between the regions within the same prefecture. Because the majority of our subjects belong to the elderly population, the increase in the number of psychological disorders may have been a change specific to the elderly. In the disaster reconstruction phase, stress reactions are likely to cause solitary deaths and social withdrawal among elderly people, and these changes are more common among women [27–29]. However, more than 70% of the subjects in our study were women in both groups, and this suggests that no difference due to gender may have been observed in the detection rates. Although the risk factors for DVT differ between temporary and non-temporary housing groups, there is no significant difference in the DVT detection rates, which were high in both groups even three years after the disaster. Although there are some differences in terms of support for survivors and their living conditions between the temporary and non-temporary housing groups, it can be assumed that the onset and sustaining of DVT is a health problem related to the lifestyle of individual survivors. In contrast, the risk factors for DVT differ between the temporary and non-temporary groups. Because a previous study reported that risk factors for DVT could change over time after the disaster, the difference in environmental improvement levels might have led to the variation of risk factors [4, 5, 16, 30]. The risk factors for DVT in this study differ between the temporary and non-temporary groups depending on the support system and their living conditions, which might have contributed to the high incidence of DVT in both groups.

Risk factors for DVT in the temporary housing group

In our study, the risk factors for DVT in the temporary housing group were hypertension and the use of sleeping pills. The association between hypertension and DVT was reported in a study conducted six years after the Mid Niigata Prefecture Earthquake [31]. After a major disaster, the risk of cardiovascular disease, infection and psychological disorders increases among survivors under stressful conditions, and hypertension was the most common incidence [1, 32]. The temporary housing group can be referred to as a high-stress population as they scored 19.1 ± 9.1 in the K6. The use of drugs, such as antipsychotics, and alcohol that depress the central nervous system and cause muscle relaxation of the lower extremity may also contribute to the development of DVT [33, 34]. The longer the evacuation period lasts, the more people complain of mental health problems and insomnia, and they want to take sleeping pills. The use of sleeping pills was reported as one of the risk factors for DVT in a previous study conducted after the Kumamoto Earthquake in 2016 [35]. Because some types of sleeping pills have muscle relaxation effects [36], special attention needs to be paid to prevent the development of DVT. Given these, risk factors for DVT (hypertension and the use of sleeping pills) can be applied to disaster-affected areas in common regardless of the type of disaster. For example, an earthquake directly above its epicenter, tsunami disaster or others.

This study has several limitations. First, this was a cross-sectional study and causality was therefore not determined. Second, a detailed assessment for the stage when our subjects were staying in the disaster shelters was not made. Third, a detailed assessment regarding previously reported common risk factors for DVT was not made. Fourth, because many subjects in the temporary housing group had a history of DVT screening, the awareness of DVT was possibly high in this population. Fifth, it was impossible to target all disaster victims living in temporary housing. Sixth, because medical history and lifestyle were judged using a self-report questionnaire, considerations based on the actual influence were not made. Seventh, those with underlying diseases were also included in our study. Eighth, elderly women tended to participate in community health and social welfare programs more than elderly men. Therefore, less elderly men participated in our study. Future studies that take these eight limitations into consideration are therefore necessary.

Conclusions

DVT detection rates were similar between the temporary and non-temporary housing groups, and were higher than that in the general Japanese population. The Psychological distress levels of the tsunami victims measured by K6 were higher in the temporary housing group than in the non-temporary housing group. It is necessary to establish a long-term and awareness--raising disaster victim support system to prevent disaster-related diseases.

Acknowledgments

This study was conducted in cooperation with — in no particular order — the medical staff, office workers and students of Yamamoto-cho, Watari-cho, Watari-gun Medical Association, Tohoku Fukushi University, the Sendai University Sports Health Science Research and Practice Organization, Fukui Prefectural Hospital, Fukui Kosei Hospital, Fukui-ken Saiseikai Hospital, Takamura Hospital, Fukui Cardiovascular Center, Nakamura Hospital, National Hospital Organization Fukui Hospital, Fukui General Clinic, Tanaka Hospital, Takano Hospital, National Hospital Organization Awara Hospital, National Hospital Organization Tsuruga Medical Center, National Hospital Organization Miyagi National Hospital, Kyoto University Hospital, Harue Hospital, Kaga Medical Center, Anamizu General Hospital, Ishikawa National Hospital, Kanazawa Medical University Hospital, Jouhoku Hospital, Hiroshima City Hiroshima Citizens Hospital, Toyama Rosai Hospital, Toyama City Hospital, Ishinomaki Red Cross Hospital, Morioka Municipal Hospital, Oshu City Mizusawa Hospital, Doijiri Clinic, Fukui University, and the Nippon Dental University. We would like to express our gratitude to them.

Funding details

This study was funded in 2012 by the Japan Society for the Promotion of Science through the JSPS KAKENHI Grant-in-Aid for Scientific Research Project/Basic Research (C) under Grant [Number 24590685], "Study on the Findings by Lower Limbs Venous Ultrasonography and Hemostatic Test in the Tsunami Disaster Area as a Field."

Conflict of interest

None.

References:

1. Kario K. Disaster hypertension — its characteristics, mechanism, and management. Circ J. 2012; 76(3): 553–562, doi: 10.1253/circj.cj-11-1510, indexed in Pubmed: 22327030.
2. Inoue K. Venous thromboembolism in earthquake victims. Disaster Manag Response. 2006; 4(1): 25–27, doi: 10.1016/j.dmr.2005.09.001, indexed in Pubmed: 16360637.
3. Ueda S, Hanzawa K, Shibata M, et al. High prevalence of deep vein thrombosis in tsunami-flooded shelters established after the great East-Japan earthquake. Tohoku J Exp Med. 2012; 227(3): 199–202, doi: 10.1620/tjem.227.199, indexed in Pubmed: 22728376.
4. Ueda S, Hanzawa K, Shibata M. One-year overview of deep vein thrombosis prevalence in the ishinomaki area since the great East Japan earthquake. Ann Vasc Dis. 2014; 7(4): 365–368, doi: 10.3400/avd.oa.14-00106, indexed in Pubmed: 25593620.
5. Shibata M, Chiba H, Sasaki K, et al. The utility of on-site ultrasound screening in population at high risk for deep venous thrombosis in temporary housing after the great East Japan Earthquake. J Clin Ultrasound. 2017; 45(9): 566–574, doi: 10.1002/jcu.22505, indexed in Pubmed: 28556184.
6. Onishi H, Yamamura O, Kosugi I. Comparison of development of deep vein thrombosis detection rates between groups of people in the general shelters and welfare-type shelters in the Kumamoto earthquake area. J Natl Inst Public Heal. 2017; 66: 620–629.
7. Konstantinides SV, Meyer G, Becattini C, et al. ESC Scientific Document Group, The Task Force for the diagnosis and management of acute pulmonary embolism of the European Society of Cardiology (ESC), Authors/Task Force Members, Authors/ /Task Force Members, Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology (ESC). 2014 ESC guidelines on the diagnosis and management of acute pulmonary embolism. Eur Heart J. 2014; 35(43): 3033–69, 3069a, doi: 10.1093/eurheartj/ehu283, indexed in Pubmed: 25173341.
8. American Institute of Ultrasound in Medicine, American College of Radiology, Society of Radiologists in Ultrasound. Practice guideline for the performance of peripheral venous ultrasound examinations. J Ultrasound Med. 2011; 30(1): 143–150, doi: 10.7863/jum.2011.30.1.143, indexed in Pubmed: 21193718.
9. Murphy TP, Cronan JJ. Evolution of deep venous thrombosis: a prospective evaluation with US. Radiology. 1990; 177(2): 543––548, doi: 10.1148/radiology.177.2.2217798, indexed in Pubmed: 2217798.
10. Ohgi S, Ito K, Tanaka K, et al. Echogenic Types of Venous Thrombi in the Common Femoral Vein by Ultrasonic B-Mode Imaging. Vascular Surgery. 2016; 25(4): 253–258, doi: 10.1177/153857449102500401.
11. Meissner MH, Moneta G, Burnand K, et al. The hemodynamics and diagnosis of venous disease. J Vasc Surg. 2007; 46 Suppl S: 4S–424S, doi: 10.1016/j.jvs.2007.09.043, indexed in Pubmed: 18068561.
12. Ohgi S, Tachibana M, Ikebuchi M, et al. Pulmonary embolism in patients with isolated soleal vein thrombosis. Angiology. 1998; 49(9): 759–764, doi: 10.1177/000331979804901008, indexed in Pubmed: 9756428.
13. Kessler RC, Andrews G, Colpe LJ, et al. Short screening scales to monitor population prevalences and trends in non-specific psychological distress. Psychol Med. 2002; 32(6): 959–976, doi: 10.1017/s0033291702006074, indexed in Pubmed: 12214795.
14. Furukawa TA, Kawakami N, Saitoh M, et al. The performance of the Japanese version of the K6 and K10 in the World Mental Health Survey Japan. Int J Methods Psychiatr Res. 2008; 17(3): 152–158, doi: 10.1002/mpr.257, indexed in Pubmed: 18763695.
15. Kessler RC, Barker PR, Colpe LJ, et al. Screening for serious mental illness in the general population. Arch Gen Psychiatry. 2003; 60(2): 184–189, doi: 10.1001/archpsyc.60.2.184, indexed in Pubmed: 12578436.
16. Hanzawa K, Ikura M, Nakajima T, et al. Pulmonary embolism or ischemic stroke increase 8-year after mid Niigata Prefecture earthquake 2004 in the residents with asymptomatic below-the-knee deep vein thrombosis. International Angiology. 2013; 32(Suppl 1): 78.
17. Lohr JM, Kerr TM, Lutter KS, et al. Lower extremity calf thrombosis: to treat or not to treat? J Vasc Surg. 1991; 14(5): 618–623, doi: 10.1067/mva.1991.33057, indexed in Pubmed: 1942369.

18. Maeda F, Yamamura O, Ueda S. Relevant factors for soleal vein dilatation obtained from screening activities in disaster areas. Jap J Med Technol. 2016; 65(1): 25–30.
19. Abe K, Yuda S, Yasui K, et al. Soleal vein dilatation assessed by ultrasonography is an independent predictor for deep vein thrombosis after major orthopedic surgery. J Cardiol. 2017; 69(5): 756–762, doi: 10.1016/j.jjcc.2016.07.004, indexed in Pubmed: 27484506.
20. Shimizu S, Yamamura O, Okamoto H, et al. Study of factors perpetuating deep vein thrombosis in areas affected by the Great East Japan Earthquake. Neurosonology. 2017; 30(2): 43–48, doi: 10.2301/neurosonology.30.43.
21. Tomata Y, Sato N, Kogure M, et al. [Health effects of interventions to promote physical activity in survivors of the 2011 Great East Japan Earthquake. A longitudinal study]. Nihon Koshu Eisei Zasshi. 2015; 62(2): 66–72, doi: 10.11236/jph.62.2_66, indexed in Pubmed: 25865402.
22. Ageno W, Prandoni P, Romualdi E, et al. The metabolic syndrome and the risk of venous thrombosis: a case-control study. J Thromb Haemost. 2006; 4(9): 1914–1918, doi: 10.1111/j.1538-7836.2006.02132.x, indexed in Pubmed: 16848878.
23. Stewart LK, Kline JA. Metabolic syndrome increases risk of venous thromboembolism recurrence after acute deep vein thrombosis. Blood Adv. 2020; 4(1): 127–135, doi: 10.1182/bloodadvances.2019000561, indexed in Pubmed: 31917844.
24. Sakurai K, Nishi A, Kondo K, et al. Screening performance of K6/K10 and other screening instruments for mood and anxiety disorders in Japan. Psychiatry Clin Neurosci. 2011; 65(5): 434–441, doi: 10.1111/j.1440-1819.2011.02236.x, indexed in Pubmed: 21851452.
25. Miyagi Prefectural Office, Health Promotion. Section: disaster public housing resident health findings; 2015. (in Japanese). https://www.pref.miyagi.jp/uploaded/attachment/366321.pdf (1.04.2019).
26. Koyama S, Aida J, Kawachi I, et al. Social support improves mental health among the victims relocated to temporary housing following the Great East Japan Earthquake and Tsunami. Tohoku J Exp Med. 2014; 234(3): 241–247, doi: 10.1620/tjem.234.241, indexed in Pubmed: 25382281.
27. Jia Z, Tian W, Liu W, et al. Are the elderly more vulnerable to psychological impact of natural disaster? A population-based survey of adult survivors of the 2008 Sichuan earthquake. BMC Public Health. 2010; 10: 172, doi: 10.1186/1471-2458-10-172, indexed in Pubmed: 20353554.
28. Zhang Y, Ho SMY. Risk factors of posttraumatic stress disorder among survivors after the 512 Wenchuan earthquake in China. PLoS One. 2011; 6(7): e22371, doi: 10.1371/journal.pone.0022371, indexed in Pubmed: 21799838.
29. Farooqui M, Quadri SA, Suriya SS, et al. Posttraumatic stress disorder: a serious post-earthquake complication. Trends Psychiatry Psychother. 2017; 39(2): 135–143, doi: 10.1590/2237-6089-2016-0029, indexed in Pubmed: 28700042.
30. Hasegawa K, Yoshino H, Yanagi U, et al. Indoor environmental problems and health status in water-damaged homes due to tsunami disaster in Japan. Building and Environment. 2015; 93: 24–34, doi: 10.1016/j.buildenv.2015.02.040.
31. Hanzawa K, Okamoto T, Sato K, et al. DVT in residents in mid Niigata Prefecture earthquake after 6 years: relationship between DVT and hypertention. The Japanese Journal of Phlebology. 2012; 23(4): 315–320, doi: 10.7134/phlebol.23.315.
32. Kario K, Matsuo T, Kobayashi H, et al. Earthquake-induced potentiation of acute risk factors in hypertensive elderly patients: possible triggering of cardiovascular events after a major earthquake. J Am Coll Cardiol. 1997; 29(5): 926–933, doi: 10.1016/s0735-1097(97)00002-8.
33. Jönsson AK, Schill J, Olsson H, et al. Venous Thromboembolism During Treatment with Antipsychotics: A Review of Current Evidence. CNS Drugs. 2018; 32(1): 47–64, doi: 10.1007/s40263-018-0495-7, indexed in Pubmed: 29423659.
34. Karino T, Motomiya M. Flow through a venous valve and its implication for thrombus formation. Thromb Res. 1984; 36(3): 245–257, doi: 10.1016/0049-3848(84)90224-x, indexed in Pubmed: 6515603.
35. Sato K, Sakamoto K, Hashimoto Y, et al. KEEP Project. Risk Factors and Prevalence of Deep Vein Thrombosis After the 2016 Kumamoto Earthquakes. Circ J. 2019; 83(6): 1342–1348, doi: 10.1253/circj.CJ-18-1369, indexed in Pubmed: 30956268.
36. Gaillard. JM. Comparison of two muscle relaxant drugs on human sleep: diazepam and parachlorophenylgaba. Acta Psychiatr Belg. 1977; 77(3): 410–425.

VIA MEDICA

CASE REPORT

Acta Angiol
Vol. 26, No. 4, pp. 140–143
Doi: 10.5603/AA.2020.0021

ISSN 1234–950X
e-ISSN: 1644–3276

Primary intestinal lymphangiectasia with lymphedema of lower extremities

Kamil Klimas, Katarzyna Drożdż, Angelika Chachaj, Andrzej Szuba

Department of Angiology, Hypertension and Diabetology, Wroclaw Medical University, Wroclaw, Poland

Abstract

Primary intestinal lymphangiectasia (PIL), also known as Waldmann's disease, is a rare disorder manifested by the presence of dilated intestinal lymphatic ducts and leading to protein-losing enteropathy. PIL usually presents early in childhood; however, rarely may be also diagnosed in adults. Suggestive laboratory findings include hypoproteinemia, hypoalbuminemia, and hypogammaglobulinemia. Peripheral pitting edema due to hypoalbuminemia is the main clinical feature. Peripheral lymphedema is a less common symptom. We present a case of a 23-year-old woman with lymphedema of lower extremities and PIL diagnosed in childhood.

Key words: lymphatics, lymphedema, protein-losing entheropathy, hypoalbuminemia

Acta Angiol 2020; 26, 4: 140–143

Introduction

Primary intestinal lymphangiectasia (PIL), also known as Waldmann's disease, is a rare disorder, resulting from the presence of dilated intestinal lymphatic ducts and leading to protein-losing enteropathy. Dilated intestinal lymphatics lead to lymph leakage into the lumen of the small intestine and consequently, to hypoalbuminemia, hypogammaglobulinemia, lymphopenia, and in severe cases to generalized edema. PIL usually occurs in children before 3 years of age and adolescents, but rarely may be also diagnosed in adults [1, 2]. We described a case of a 26-year-old woman with lymphedema of lower extremities and PIL diagnosed in childhood.

Case report

A 26-year-old woman was referred to the Department of Angiology, Hypertension and Diabetology at Wroclaw Medical University because of edema of lower extremities. The lower limb edema was observed for the first time at the age of six months and has gradually progressed. The medical history of the patient revealed a very typical course of primary intestinal lymphangiectasia (PIL). Shortly after birth, temporary swelling of the labia appeared. The edema of the lower extremities was the next symptom. Until the age of five, the patient was repeatedly hospitalized due to recurrent respiratory infections accompanied by hypoalbuminemia (21 g/L), hypoproteinemia (42 g/L), hypogammaglobulinemia (IgG: 2–3.5 g/l; IgA: 0.16 g/l) and lymphopenia (10%). The endoscopic examination of the gastrointestinal tract and albumin scintigraphy did not clearly confirm the PIL. The abdominal computed tomography (CT) and magnetic resonance imaging (MRI) have shown small intestine thickening with slight ascites. Finally, at the age of five, the patient underwent a laparotomy, which revealed the presence of intestinal lymphangiectasia. Histopathological examination of biopsy specimens taken during laparotomy established the suspected diagnosis of PIL. Since childhood the patient did not suffer from any recurrent abdominal pain, nausea, vomiting, weight loss, obstructive ileus, or steatorrhea. The lower extremity edema during the current hospitalization was the dominant clinical symptom, which significantly affected the everyday life of the patient (Fig. 1). Diet therapy with medium-chain triglycerides (MCT) has been applied since the diagnosis of PIL. In the past, the

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

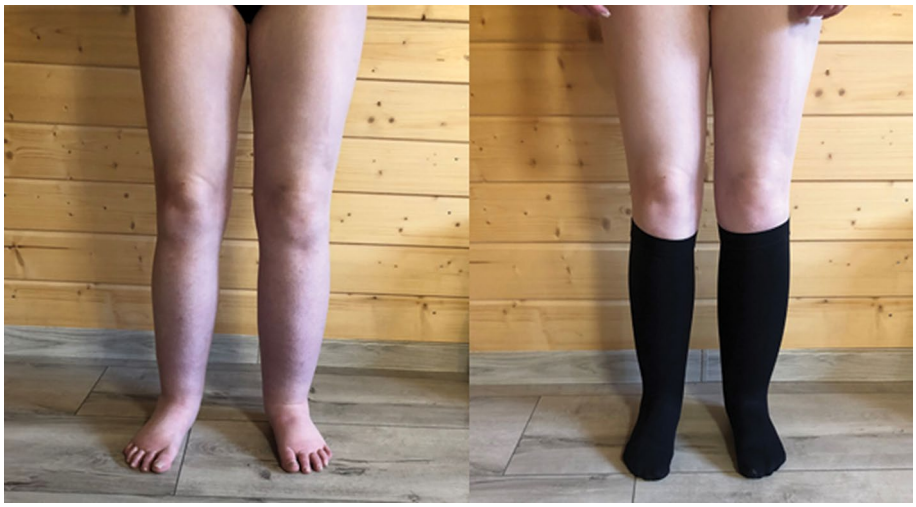


Figure 1. Lymphedema of the lower extremities in our patient. In the second photo the patient is wearing the compression stockings, which are the basic treatment of lymphedema

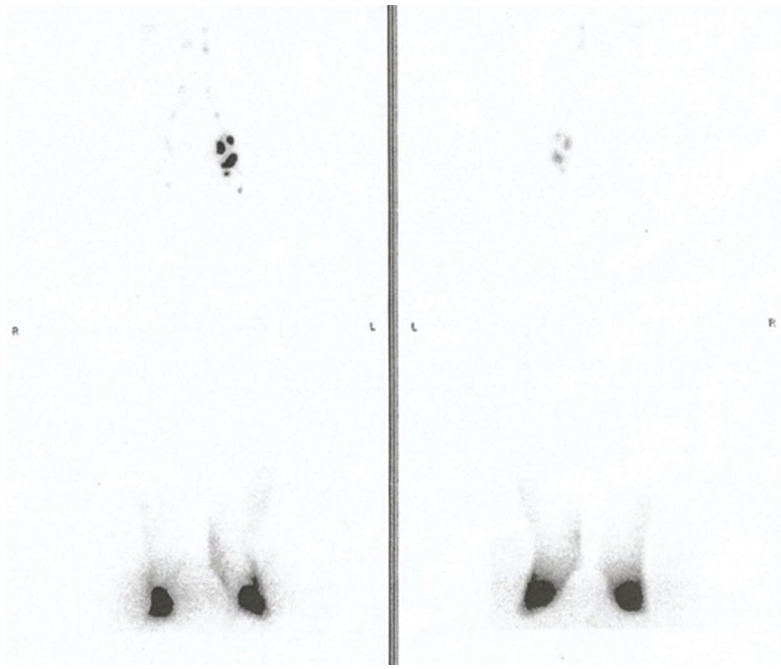


Figure 2. Lymphoscinthigraphy showing the lack of visualization of the lymphatic trunks in both legs and of the inguinal lymph nodes on the right side. Dermal backflow is also visible within the calves

patient was also treated with intravenous immunoglobulins, intravenous fresh frozen plasma, and octreotide. However, these therapies resulted in only temporary improvement of hematological and scintigraphy findings. The patient has never been treated with compression therapy because of the leg lymphedema.

On a physical examination performed during the current hospitalization, the scar after laparotomy and moderate peripheral edema of lower extremities, with Stemmer's sign and skin thickening, was noted. The laboratory studies revealed hypoalbuminemia and hypogammaglobulinemia. The lymphoscintigraphy of the lower extremities revealed the lack of visible lymphatic trunks in both legs and of the inguinal lymph nodes on the right side. Dermal backflow was also noticeable within the calves (Fig. 2). The compression therapy,

firstly with low-stretch bandages and secondly with compression stockings, has been started with the good clinical effect of lymphedema reduction. The sirolimus, a mammalian target of rapamycin (mTOR) inhibitor and/or intestine microsurgery has been considered for further treatment.

Discussion

Primary intestinal lymphangiectasia (PIL) is a rare protein-losing enteropathy of unknown prevalence. Less than 200 cases have been reported since 1961 when Waldmann et al. described the first 18 cases of the disease [1]. The etiology of PIL is unknown. It is caused by congenital malformation or obstruction of intestine lymphatics with concomitant increased intraluminal pressure. The disease can affect all small intestine or maybe segmental. It leads to dilatation of lymphatic vessels in mucosa, submucosa, and subserosa and lymph leakage into the small bowel lumen resulting in hypoalbuminemia, hypogammaglobulinemia, and lymphopenia [1, 2]. The basic clinical feature is peripheral pitting edema of variable degree, usually symmetrical, due to low oncotic pressure usually involving lower limbs, face, external genitalia, scrotum, or vagina. Serous effusions in more severe cases are also common — pleural effusion, chylous ascites, and pericarditis may be present in patients and may be life-threatening. Other concomitant symptoms are abdominal pain, nausea, vomiting, moderate diarrhea, fat-soluble vitamin deficiencies, and weight loss [2–5]. In our patient, there were no digestive symptoms all the time. However, diet therapy was applied just after the diagnosis of PIL. The swelling of the labia was the earliest symptom of the disease in our patient. Lymphedema of lower extremities was the next clinical feature. Lymphedema of lower limbs is a rarer symptom in PIL [1]. Lymphedema of upper extremities, breast, and external genitalia were also noted [6]. At the age of 26, lymphedema of lower limbs affected our patient's quality of life the most. However, compression therapy was started scarcely during hospitalization in our Department.

The diagnosis of PIL in our patient was based on the clinical course, laparotomy, and histopathological findings of intestine specimens taken during laparotomy. At present, endoscopy with histopathological assessment of intestine biopsy is the most important tool in PIL diagnostics [1]. The laboratory findings of hypoproteinemia, hypoalbuminemia, hypogammaglobulinemia, and lymphocytopenia may be suggestive. The macroscopic abnormalities which may be found during small bowel endoscopy include scattered whitish spots (snowflake appearance), thickened villi, and edematous mucosa of the small intestine [7]. Although capsule endoscopy cannot be used to perform a biopsy, it is a comfortable method to examine mucosa of the small intestine [1, 7, 8]. Radiologic examinations also can be useful. Ultrasonography has the potential to show dilation of the intestinal loops, regular and diffuse thickening of the walls, plical hypertrophy and mesenteric edema [9]. CT may reveal thickening and edema of small intestine wall, as a consequence of the dilated lymphatics [10, 11]. Moreover, Sun et al. documented a new diagnostic method of multiple-detector computed tomography (MDCT) after direct lymphangiography in 55 patients with PIL. In this study, intra- and extraintestinal abnormalities, especially regarding the morphology and the extent of lymphatic vessel involvement were observed. Therefore, it can be a significant tool for the diagnosis of PIL [12]. Lymphoscintigraphy is a useful diagnostic tool for identifying abnormal lymphatics within the upper and lower extremities [1, 13].

The rarity of PIL is the reason for the lack of treatment guidelines in this disorder. Dietary intervention is the gold standard in PIL management. A low-fat and high-protein diet supplemented with medium-chain triglycerides (MCT) is usually recommended [7, 8]. The majority of PIL children respond to dietary therapy and according to Prasal et al. only 20% need additional therapy [14]. Lipid elements in food provoke lymphatic pressure increase and lymphatic leakage into the small bowel lumen. A low-fat diet reduces lymphatic flow and lacteal dilation and thus helps to prevent lymph loss. MCTs are absorbed directly in portal venous circulation by passing the lymphatic system and thus provide nutrient fat and lessens lacteal engorgement [2]. Other treatment methods can be used in the combination with a low-fat diet with MCT supplementation, mostly in severe cases. These are as follows: octreotide (150–200 ug twice a day or slow-release formulation), tranexamic acid (1 g, 3 times a day), antiplasmin, corticosteroids, vitamin D supplementation, albumin infusion (applied in patients with significant serous effusion) [1, 15] . In the cases with segmental lesions within intestine, surgical procedures as small bowel resection may be recommended [16]. Recently, the successful use of mTOR inhibitors (sirolimus, everolimus) in the treatment of a small collection of vascular anomalies and PIL has also been reported [17, 18]. Lymphedema of upper and lower extremities should be treated with standard compression therapy, including complex physical therapy and compression garments [19].

Conflict of interest

None.

References

1. Vignes S, Bellanger J. Primary intestinal lymphangiectasia (Waldmann's disease). Orphanet J Rare Dis. 2008; 3: 5, doi: 10.1186/1750-1172-3-5, indexed in Pubmed: 18294365.
2. Ingle SB, Hinge Ingle CR. Primary intestinal lymphangiectasia: Minireview. World J Clin Cases. 2014; 2(10): 528–533, doi: 10.12998/wjcc.v2.i10.528, indexed in Pubmed: 25325063.
3. Lopez RN, Day AS. Primary intestinal lymphangiectasia in children: A review. J Paediatr Child Health. 2020; 56(11): 1719–1723, doi: 10.1111/jpc.14837, indexed in Pubmed: 32463559.
4. Abramowsky C, Hupertz V, Kilbridge P, et al. Intestinal lymphangiectasia in children: a study of upper gastrointestinal endoscopic biopsies. Pediatr Pathol. 1989; 9(3): 289–297, doi: 10.3109/15513818909037733, indexed in Pubmed: 2748490.
5. Lee WS, Boey CC. Chronic diarrhoea in infants and young children: causes, clinical features and outcome. J Paediatr Child Health. 1999; 35(3): 260–263, doi: 10.1046/j.1440-1754.1999.00356.x, indexed in Pubmed: 10404446.
6. Goktan C, Pekindil G, Orguc S, et al. Bilateral breast edema in intestinal lymphangiectasia. Breast J. 2005; 11(5): 360, doi: 10.1111/j.1075-122X.2005.21578.x, indexed in Pubmed: 16174162.
7. Wen J, Tang Q, Wu J, et al. Primary intestinal lymphangiectasia: four case reports and a review of the literature. Dig Dis Sci. 2010; 55(12): 3466–3472, doi: 10.1007/s10620-010-1161-1, indexed in Pubmed: 20198428.
8. Lee SJ, Song HJ, Boo SJ, et al. Primary intestinal lymphangiectasia with generalized warts. World J Gastroenterol. 2015; 21(27): 8467–8472, doi: 10.3748/wjg.v21.i27.8467, indexed in Pubmed: 26217101.
9. Maconi G, Molteni P, Manzionna G, et al. Ultrasonographic features of long-standing primary intestinal lymphangiectasia. Eur J Ultrasound. 1998; 7(3): 195–198, doi: 10.1016/s0929-8266(98)00037-8, indexed in Pubmed: 9700215.
10. Mazzie J, Maslin P, Moy L, et al. Congenital intestinal lymphangiectasia. Clinical Imaging. 2003; 27(5): 330–332, doi: 10.1016/s0899-7071(02)00588-0.
11. Yang DMo, Jung DH. Localized intestinal lymphangiectasia: CT findings. AJR Am J Roentgenol. 2003; 180(1): 213–214, doi: 10.2214/ajr.180.1.1800213, indexed in Pubmed: 12490507.
12. Sun X, Shen W, Chen X, et al. Primary intestinal lymphangiectasia: Multiple detector computed tomography findings after direct lymphangiography. J Med Imaging Radiat Oncol. 2017; 61(5): 607–613, doi: 10.1111/1754-9485.12606, indexed in Pubmed: 28345300.
13. Szuba A, Shin WS, Strauss HW, et al. The third circulation: radionuclide lymphoscintigraphy in the evaluation of lymphedema. J Nucl Med. 2003; 44(1): 43–57, indexed in Pubmed: 12515876.
14. Prasad D, Srivastava A, Tambe A, et al. Clinical profile, response to therapy, and outcome of children with primary intestinal lymphangiectasia. Dig Dis. 2019; 37(6): 458–466, doi: 10.1159/000499450, indexed in Pubmed: 31030202.
15. Sari S, Baris Z, Dalgic B. Primary intestinal lymphangiectasia in children: is octreotide an effective and safe option in the treatment? J Pediatr Gastroenterol Nutr. 2010; 51(4): 454–457, doi: 10.1097/MPG.0b013e3181d1b162, indexed in Pubmed: 20512058.
16. Chen CP, Chao Y, Li CP, et al. Surgical resection of duodenal lymphangiectasia: a case report. World J Gastroenterol. 2003; 9(12): 2880–2882, doi: 10.3748/wjg.v9.i12.2880, indexed in Pubmed: 14669360.
17. Hammill AM, Wentzel M, Gupta A, et al. Sirolimus for the treatment of complicated vascular anomalies in children. Pediatr Blood Cancer. 2011; 57(6): 1018–1024, doi: 10.1002/pbc.23124, indexed in Pubmed: 21445948.
18. Ozeki M, Hori T, Kanda K, et al. Everolimus for primary intestinal lymphangiectasia with protein-losing enteropathy. Pediatrics. 2016; 137(3): e20152562, doi: 10.1542/peds.2015-2562, indexed in Pubmed: 26908672.
19. Szuba A, Rockson SG. Lymphedema: classification, diagnosis and therapy. Vasc Med. 1998; 3(2): 145–156, doi: 10.1177/1358836X9800300209, indexed in Pubmed: 9796078.

VIA MEDICA

CASE REPORT

Acta Angiol
Vol. 26, No. 4, pp. 144–146
Doi: 10.5603/AA.2020.0020

ISSN 1234–950X
e-ISSN: 1644–3276

Clavicular non-union as an undiagnosed cause of progressive limb-threatening upper extremity ischemia

Łukasz Dzieciuchowicz, Arkadiusz Krzemiński

Department of Vascular Surgery and Vascular Diseases, University of Zielona Góra, Poland

Abstract

A rare case of progressive upper limb-threatening ischemia is presented. The ischemia was caused by the chronic embolization from the axillary artery that was compressed by the clavicular pseudoarthrosis due to the remote in time fracture.

Key words: clavicular pseudoarthrosis, upper limb ischemia, arterio-arterial embolism

Acta Angiol 2020; 26, 3: 144–146

Introduction

In comparison to lower extremity, upper limb is less often affected by both acute and chronic limb ischemia. Also, the progression of disease to limb-threatening ischemia is less frequent. The etiology is also different, while the atherosclerosis prevails in lower limb, the upper limb ischemia is most commonly caused by vascular trauma and cardiogenic embolism [1]. That is why the limb-threatening ischemia and its etiology may be misdiagnosed and adequate treatment delayed. The purpose of this report is to present a case of progressive upper limb-threatening ischemia due to chronic intermittent compression of the axillary artery by the clavicular pseudoarthrosis.

Case report

A sixty-two-year old male was referred to the Department of Vascular Surgery because of severe rest pain and gangrene of stumps of the fingers of the right upper limb. He was a retired truck driver and heavy cigarette smoker. Four months earlier he presented to the general surgery department because of infected necrosis of the fingers of right hand. At that time the infected and necrotic fingers were incised and drained. Due to lack of improvement and progression of necrosis ischemia was suspected, and the patient was referred to a vascular surgeon. The ischemia was confirmed. Thromboembolectomy of brachial and forearm arteries was performed together with the forearm fasciotomy. Good inflow and outflow were obtained and a remarkable improvement of perfusion of the limb was observed. At that time no atrial fibrillation was observed, and cardiogenic embolism was excluded. The patient was referred back to general surgery department for the amputations of the necrotic phalanges.

At the present hospitalization the limb was critically ischemic and axillary, brachial and distal pulses were absent. A resilient bulge was noted in the supraclavicular area (Fig. 1). Thorough history-taking revealed fractures of the right clavicle at three occasions at the age of 12 that is 50 years earlier. Plain X-ray showed the presence of clavicular non-union with its deformation (Fig. 2). Computed Tomography Angiography (CTA) showed patent and free of stenosis brachio-cephalic trunk and subclavian artery, severe stenosis of the proximal portion of axillary artery with patency of its distal segment, brachial artery was stenosed in its proximal segment and occluded distally and the take-off of deep brachial artery was also occluded. The stenosis of the axillary artery

Address for correspondence: Arkadiusz Krzemiński, Department of Vascular Surgery and Vascular Diseases, University of Zielona Góra, ul. Zyty 26, 65–046 Zielona Góra, Poland, e-mail: arekkrzeminski@icloud.com

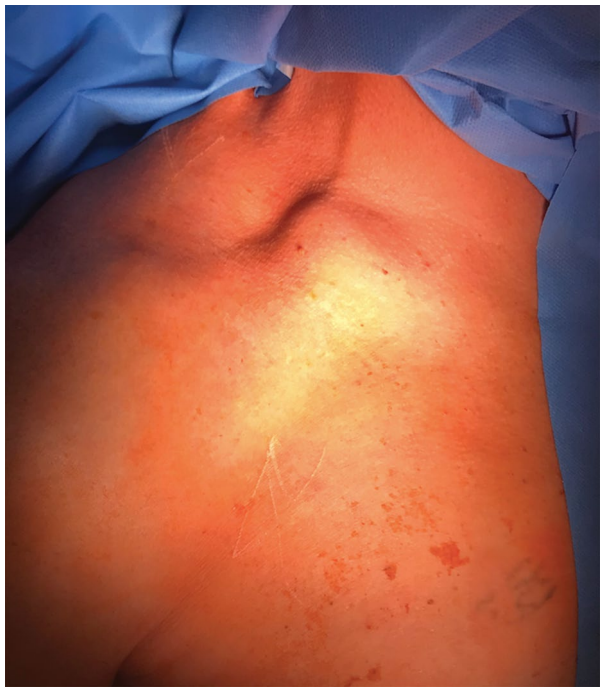


Figure 1. A resilient bulge was observed in the supraclavicular area

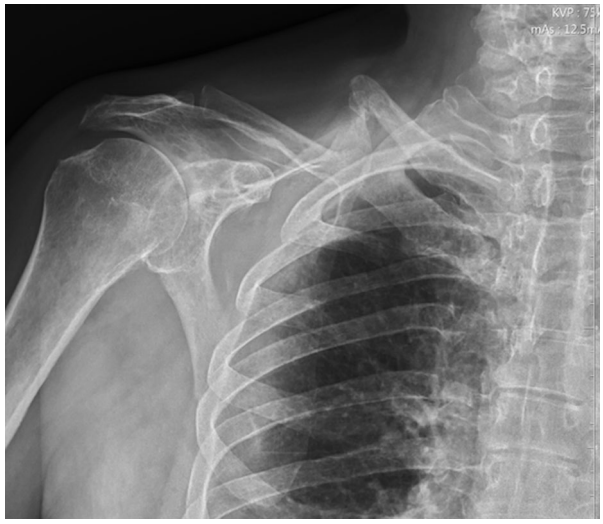


Figure 2. A clavicular non-union with its deformation seen on plain X-ray

was exactly at the site of the clavicular pseudoarthrosis (Fig. 3). The patient was qualified for an urgent surgery. Through an S-shape incision the deformed clavicle together with the pseudoarthrosis was removed. That allowed a good exposure of the axillary artery which was dilated. After longitudinal arteriotomy a thickening of arterial wall and the presence of old thrombi were observed. The lumen was not dilated. With Fogarty

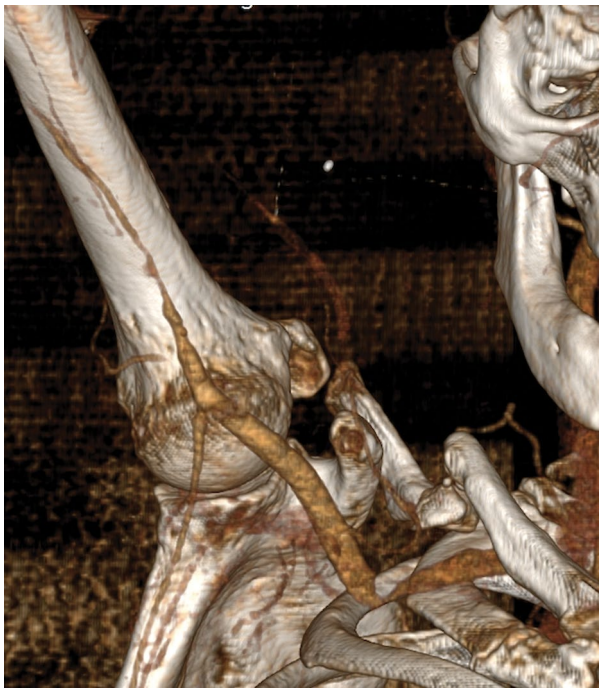


Figure 3. The stenosis of the axillary artery at the site of the clavicular pseudoarthrosis and occlusion of brachial artery seen on the pre-operative CTA

catheter similar old thrombi were removed from the distal axillary artery and proximal brachial artery and a good inflow and outflow were observed (Fig. 5). It was not possible to advance the Fogarty catheter more distally. The arteriotomy was closed with a continuous 5/0 polypropylene suture and the wound was drained and sutured in a layered fashion. Postoperatively, the rest pain subsided and a marked improvement of the perfusion of the limb was observed. A CTA showed widely patent subclavian, axillary and proximal brachial and profunda brachial arteries, the middle portion of brachial artery was occluded and the flow in its distal portion and forearm arteries was reconstituted through collaterals from profunda brachial artery (Fig. 4). The necrotic portions of stumps of the fingers were reamputated and primary healing was achieved. In the six months follow-up no recurrence of limb-threatening ischemia was observed.

Discussion

This report presents a case of a misdiagnosed upper chronic limb-threatening ischemia. Initially the infected gangrene of the fingers was not associated with limb ischemia and then though the ischemia was diagnosed and treated its cause was not established that led to its recurrence. In the absence of cardiogenic cause of

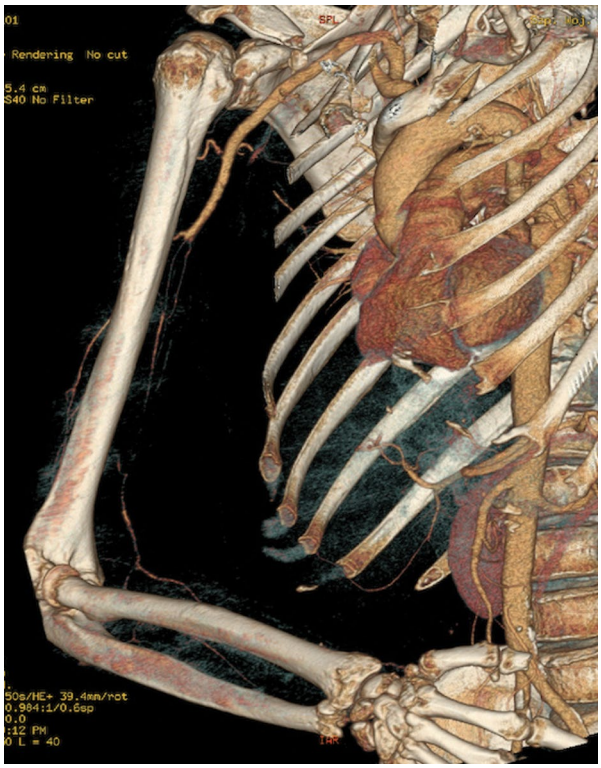


Figure 4. A post-operative angiography

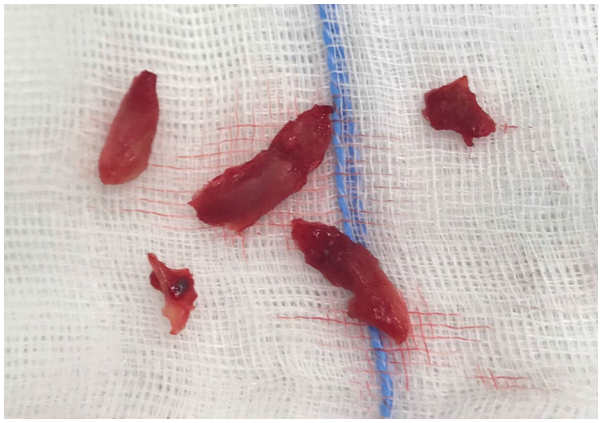


Figure 5. Old thrombotic material removed from the axillary artery and proximal part of brachial artery

emboli, a post embolectomy angiography should have been performed to look for a non-cardiogenic source. The arterial compression by the pseudoarthrosis of the clavicle is a rare but already described cause [2, 3]. Interestingly, there was a 50-year interval between clavicular fracture and the occurrence of limb threatening ischemia. Similarly, in recent single case reports limb ischemia developed 43 and 30 years after fracture of the clavicle [2, 3]. That long interval may have contributed to a failure to associate the symptoms with the presence of clavicular pseudoarthrosis. In the described case, a chronic repetitive compression of the axillary artery by the clavicular pseudoarthrosis lead to its inflammation, as reflected by the thickening of its wall and thrombosis, which was the cause of progressive embolization of the brachial artery. The chronicity is supported by the presence of very well-developed collateral circulation from the profunda brachial artery as well as by the impossibility of thrombus removal from the middle portion of the brachial artery. It may somehow resemble an arterial thoracic outlet syndrome. However, in the latter case typically a post-stenotic aneurysm is the source of emboli. That was not the case in presented patient that points to an intermittent and not permanent compression of axillary artery.

The thrombectomy of axillary artery and proximal portion of brachial artery removed a source of potential emboli, restored good inflow and re-perfused the deep brachial artery that resulted in a significant improvement in the blood flow to the limb. In case when limb perfusion was unsatisfactory a bypass to the distal brachial artery should be considered.

One of the drawbacks that limit the interpretation of angiographic finding is lack of the preoperative angiography with the upper limb in an anatomical position and of the postoperative angiography with the elevated limb. To prevent the exposure of the patient to the iodinated contrast media and ionizing radiation in a short period of time an additional angiography was not performed. However, we believe that stenosis of axillary artery observed with limb elevation is always pathological.

In conclusions, in case of upper limb ischemia its causes should be thoroughly investigated. Failure to establish the etiology of ischemia will result in recurrence and further deterioration of the condition of the extremity. History of the fracture of the clavicle, even if remote, should draw attention to the possible arterial compression syndrome.

Conflict of interest

None.

References:

1. Deguara J, Ali T, Modarai B, et al. Upper limb ischemia: 20 years experience from a single center. Vascular. 2005; 13(2): 84–91, doi: 10.1258/rsmvasc.13.2.84, indexed in Pubmed: 15996362.
2. Miyamotto M, Sanvido LV, Brendolan LF, et al. Late presentation of critical upper limb ischemia caused by pseudarthrosis of the clavicle. J Vasc Bras. 2018; 17(2): 174–177, doi: 10.1590/1677-5449.009617, indexed in Pubmed: 30377431.
3. Stella M, Santolini E, Briano S, et al. Late recurrent peripheral upper limb ischemia after non-union of a clavicle fracture. Injury. 2015; 46: S3–S7, doi: 10.1016/s0020-1383(15)30035-8.

VIA MEDICA

CASE REPORT

Acta Angiol
Vol. 26, No. 4, pp. 147–149
Doi: 10.5603/AA.2020.0022

ISSN 1234–950X
e-ISSN: 1644–3276

Non-traumatic ulnar artery aneurysm in a middle-aged male

Nalaka Gunawansa, Prasath Subramaniyam

National Institute of Nephrology and Transplantation, Colombo, Sri Lanka

Abstract

Aneurysms in the extremity arteries are rare and usually occur as pseudoaneurysms secondary to trauma or iatrogenic interventions. True spontaneous non-traumatic aneurysms in the extremities are extremely rare with no consensus on their aetiology or optimum management strategy. Here, we discuss a case of a young man with an isolated spontaneous non-traumatic ulnar artery aneurysm presenting with acute pain and discomfort.

Key words: aneurysm, ulnar artery aneurysm, Marfan syndrome, pseudoaneurysm

Acta Angiol 2020; 26, 4: 147–149

Introduction

Upper extremity arterial aneurysms (UEAA) are rare in clinical practice. Even when encountered, they are primarily pseudoaneurysms often following direct trauma or iatrogenic interventions such as arterial catheterization. True spontaneous aneurysms in the upper extremities are very uncommon and offer unique challenges in their management. While spontaneous aneurysms in the brachial artery have been reported sporadically, aneurysms arising in the forearm arteries distal to the brachial artery bifurcation are extremely uncommon [1]. Santis and colleagues (2013) in a systematic review covering 20 years (1990–2011), reported just 28 cases of non-traumatic forearm aneurysms, the majority of which were distal palmar aneurysms [2]. We report a rare case of a non-traumatic ulnar artery aneurysm in a 39-year-old active male who presented with acute pain and tenderness in the forearm.

Case report

A thirty-nine-year-old male presented to the Emergency Department with sudden onset pain and swelling of the right forearm, with gradual worsening of symptoms over a 7-day period. He denied any history of direct trauma to the region preceding the onset of pain. On clinical examination, he had a tender swelling in the proximal 1/3 of the right forearm with no clinical evidence of cellulitis or compartment syndrome. There was a mild ecchymotic patch over the proximal forearm. The proximal brachial artery pulse at the cubital fossa and distal radial and ulnar pulses at the wrist were present and clinically equivalent to the left side. Allen test of the right hand confirmed radial artery dominance. He had no major co-morbidities other than being on regular steroidal inhalers for chronic obstructive airway disease. He had no history of substance abuse or self-injection. He was quite active and independent, being employed as a computer programmer.

The blood biochemistry results were unremarkable with no evidence of infection or inflammation. An initial ultra-sound scan of the forearm suggested a muscular haematoma. An arterial duplex ultra-sound (DUS) assessment of the forearm revealed a possible aneurysmal dilatation of the proximal ulnar artery with normal distal arterial flow pattern. Abdominal, lower limb and carotid duplex imaging did not reveal any further aneurysmal change elsewhere. An echocardiogram did not reveal any cardiac valvular or intra-mural pathology. A computerized tomographic angiogram (CTA) was done to further visualize the region of interest.

The CTA confirmed an elongated aneurysmal segment of the proximal ulnar artery with no intramural

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

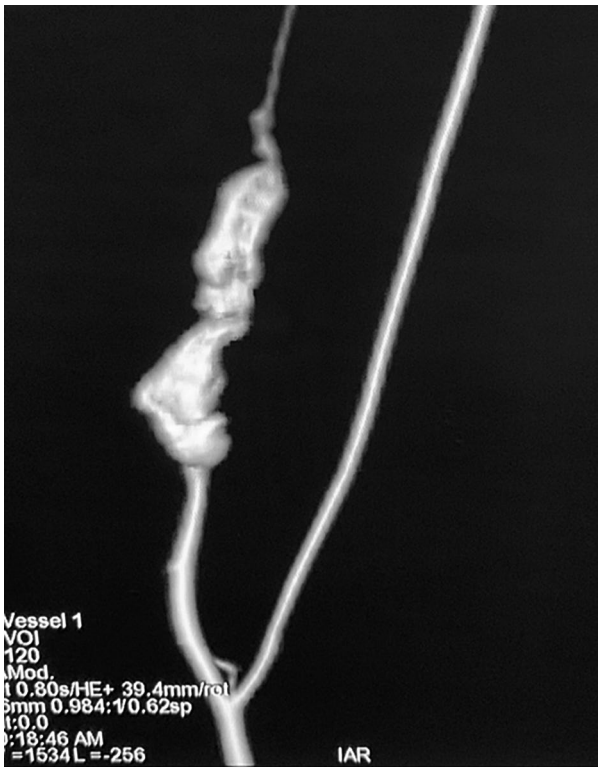


Figure 1. Reconstructed CTA image showing the elongated aneurysmal segment in the proximal ulnar artery

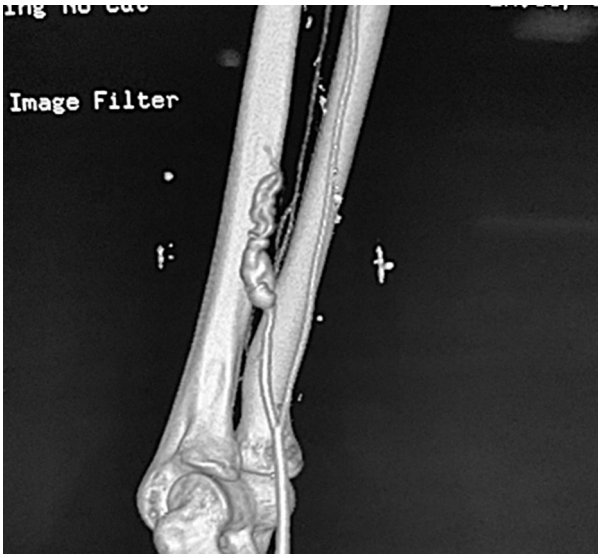


Figure 2. CT Angiogram with bone window

thrombi (Figs 1, 2). There was no venous filling to indicate any possibility of arterio-venous malformation. The remaining arterial architecture appeared pristine. There was no extravasation to suggest rupture.

The images were studies with regards to a possible radiological intervention with insertion of a covered stent. However, technical limitations and lack of local expertise in stenting the ulnar artery were prohibitive in the management planning. Hence, given the progressively worsening symptoms and the extent of the lesion, a decision was taken to proceed with surgical exploration.

The aneurysmal region was approached with a liner incision extending from the cubital fossa to mid forearm under a regional nerve block. Proximal and distal control was achieved by atraumatic vascular tapes. During exploration, the proximal ulnar artery was found to be extremely friable and not amenable to an arterial anastomosis or reconstruction. The ulnar artery was ligated proximal and distal to the diseased segment and the aneurysmal component was excised. The segment was sent for histological confirmation and tissue culture while the wound was closed over a vacuum drain.

The recovery from surgery was uneventful. The swelling and pain subsided rapidly, and his distal palmar and digital perfusion remained excellent. Currently, 9 months after surgery, he remains well without symptoms, fully active and back at his usual employment. The resected segment of aneurysmal artery was examined by histology and confirmed a true aneurysm with thinned out arterial wall and no evidence of infection or inflammation. There was no evidence of atheromatous deposits, fibrinoid necrosis or arteritis. The related specimens sent for bacterial and tuberculous culture were negative. A repeat DUS examination of all extremities and neck vessels showed no similar pathology or local recurrence.

Discussion

Background

UEAA are rather uncommon compared to abdominal, visceral or lower limb artery aneurysms. Even when they do occur, it is usually secondary to repetitive trauma or direct injury resulting in pseudoaneurysms. Distal radial and ulnar artery aneurysms have been reported due to repetitive trauma to the hand among manual labourers [3, 4]. More recently with increasing incidence of endovascular interventions through radial artery approach, iatrogenic pseudoaneurysms of the distal radial artery have also been reported. Proximal forearm non-traumatic aneurysms are extremely rare and reported only as case reports in sporadic publications [1, 5].

Diagnosis

Accurate diagnosis requires imaging confirmation. This patient was initially evaluated with a DUS. In similar situations, DUS is the first investigation of choice. It is

non-invasive, readily available and can demonstrate as well as localise the aneurysm. However, DUS remains highly operator dependent and may not be accurate for finer details in terms of size, extent and associated minor pathologies in the adjacent arterial tree. CTA or magnetic resonance angiogram (MRA) would be required as the gold standard imaging modality to confirm the diagnosis. Compared to CTA, MRA is more sensitive and specific for diagnosing AV malformations whereas in UEAA, MRA does not provide any significant advantage over CTA [6].

Aetiology

One of the reported aetiologies of non-traumatic peripheral aneurysms is infection, leading to mycotic aneurysms. In this index patient, inflammatory markers were normal and repeated blood cultures were negative. The tissue culture taken from the excised artery was also negative for standard bacterial survey and mycobacteria. Another possible rare aetiology is primary vasculitis or auto-immune disease affecting the arterial wall. This too was unlikely in the index patient who was found negative for the complete auto-immune survey, had normal level inflammatory markers and lacked any suggestive finding on histology.

Treatment

Even in the current endovascular era there is no consensus on the ideal management of UEAA. Given the uncertain aetiology as well as complex morphological pattern of the aneurysmal segment, endovascular stenting was not possible in this patient. There are reported cases of pseudoaneurysms treated with covered stent and coil embolization [7]. We did not consider coil embolization due to the absence of a clear aneurysm neck and possibility of distal embolization in the dominant arm. Open surgical exploration gives an opportunity to excise the entire diseased segment and evaluate for histological confirmation [8]. Furthermore, if carefully performed, it allows immediate decompression of the forearm and hence relief of symptoms in addition to the definitive treatment of the aneurysm. Surgical options include complete ligation or end-to-end repair using a venous segment. While end-to-end reconstruction is preferred in the absence of any obvious infection, complete ligation is also a viable option where the distal perfusion can be reliably sustained.

Conclusion

True aneurysms of the proximal forearm arteries are very rare. Accurate diagnosis requires imaging by either CTA or MRA. Due to the uncertain nature of their natural history and associated symptomatology, definitive treatment is often required either by endovascular stenting, embolization or open surgical repair. The actual treatment modality depends on anatomy, morphological nature, availability of stents and expertise as well as adequacy of collateral distal perfusion. If further investigations confirm infective or inflammatory aetiology, long-term treatment of such primary pathology is required to prevent recurrence or occurrence of new disease elsewhere.

Conflicts of interest

None.

Consent

Specific informed written consent of the index patient was obtained for publication of above details and images for the purpose of medical education.

References:

1. Clark ET, Mass DP, Bassiouny HS, et al. True aneurysmal disease in the hand and upper extremity. Ann Vasc Surg. 1991; 5(3): 276–281, doi: 10.1007/BF02329386, indexed in Pubmed: 2064922.
2. De Santis F, Martini G, Mani G, et al. Forearm and hand arteries' aneurysms – a case report of bilateral true ulnar artery aneurysm in the hypothenar eminence and systematic review of the literature. Vascular. 2013; 21(3): 169–176, doi: 10.1177/1708538113478732, indexed in Pubmed: 23493282.
3. Johnston K, Rutherford R, Tilson M, et al. Suggested standards for reporting on arterial aneurysms. Journal of Vascular Surgery. 1991; 13(3): 452–458, doi: 10.1067/mva.1991.26737.
4. Kubo N, Murase T, Moritomo H, et al. Giant aneurysm of the ulnar artery in the palm treated by resection and microvascular reconstruction. Scand J Plast Reconstr Surg Hand Surg. 2009; 43(2): 113–116, doi: 10.1080/02844310701384066, indexed in Pubmed: 19308863.
5. Sekino S, Takagi H, Kato T, et al. Nontraumatic pseudoaneurysm of the proximal ulnar artery with eosinophilia. J Vasc Surg. 2005; 42(6): 1233–1235, doi: 10.1016/j.jvs.2005.08.019, indexed in Pubmed: 16376222.
6. Wu G, Yang J, Zhang T, et al. The diagnostic value of non-contrast enhanced quiescent interval single shot (QISS) magnetic resonance angiography at 3T for lower extremity peripheral arterial disease, in comparison to CT angiography. J Cardiovasc Magn Reson. 2016; 18(1): 71, doi: 10.1186/s12968-016-0294-6, indexed in Pubmed: 27760564.
7. Buda SJ, Johanning JM. Brachial, radial, and ulnar arteries in the endovascular era: choice of intervention. Semin Vasc Surg. 2005; 18(4): 191–195, doi: 10.1053/j.semvascsurg.2005.09.004, indexed in Pubmed: 16360575.
8. Igari K, Kudo T, Toyofuku T, et al. Surgical treatment of aneurysms in the upper limbs. Ann Vasc Dis. 2013; 6(3): 637–641, doi: 10.3400/avd.cr.13-00024, indexed in Pubmed: 24130621.

VIA MEDICA

CASE REPORT

Acta Angiol
Vol. 26, No. 4, pp. 150–154
Doi: 10.5603/AA.2020.0023

ISSN 1234–950X
e-ISSN: 1644–3276

Technique of endovascular repair of iatrogenic subclavian artery injury following subclavian vein catheterization

Marek Kazibudzki[1], Jerzy Wojciech Krzywoń[1], Tomasz Kwiatkowski[1], Katarzyna Zbierska- Rubinkiewicz[1], Elżbieta Dobrowolska[2], Mariusz Trystuła[1]

[1]Department of Vascular Surgery, John Paul II Hospital, Krakow, Poland
[2]Department of Anesthesiology and Intensive Care, John Paul II Hospital, Krakow, Poland

Abstract

The iatrogenic subclavian artery injury is a rare but potentially serious complication of subclavian vein cannulation. The use of endovascular techniques is an alternative to surgical repair especially in patients with concomitant diseases in whom immediate, potentially large surgery would be associated with a high risk of perioperative complications. This article discusses technical aspects of endovascular repair of iatrogenic injury of subclavian artery with implantation of covered stents based on two cases. Author's experience and data from literature suggests that endovascular management including covered stent implantation is safe and effective treatment and should be considered as a method of choice especially among patients in poor general condition and/or major comorbidities.

Key words: subclavian artery, covered stents, central catheters, iatrogenic injury

Acta Angiol 2020; 26, 4: 150–154

Introduction

Central venous catheter (CVC) insertion is a frequently performed procedure. The most commonly cannulated vessels are the internal jugular, subclavian and femoral vein. The iatrogenic subclavian artery injury described in this paper is a rare but potentially serious complication of large vein catheterization, especially when large diameter dialysis catheters are used. The outflow of arterial blood from the cannula is the evidence of an incorrect position of the catheter in the artery. X-ray, ultrasound and Angio CT are helpful in confirming the diagnosis. Considering relatively difficult surgical approach to subclavian artery and frequently poor general condition of patients undergoing central veins cannulation, endovascular repair of injured artery seems reasonable.

Cases report

The paper presents two cases (a 62-year-old male and a 44-year-old female) of iatrogenic injury of the subclavian artery following the attempt of subclavian vein cannulation with a central venous catheter. In both cases, the catheter was misplaced in the subclavian artery. Artery injury did not cause a significant deterioration of patient's clinical condition. However, due to the underlying diseases and comorbidities, it was necessary to choose the least burdensome method of catheter removal and local repair of the vessels,

Address for correspondence: Tomasz Kwiatkowski, Department of Vascular Surgery, John Paul II Hospital, Krakow, Poland, Prądnicka 80, 31–202 Kraków, Poland; e-mail: tomkwiatkowski@go2.pl

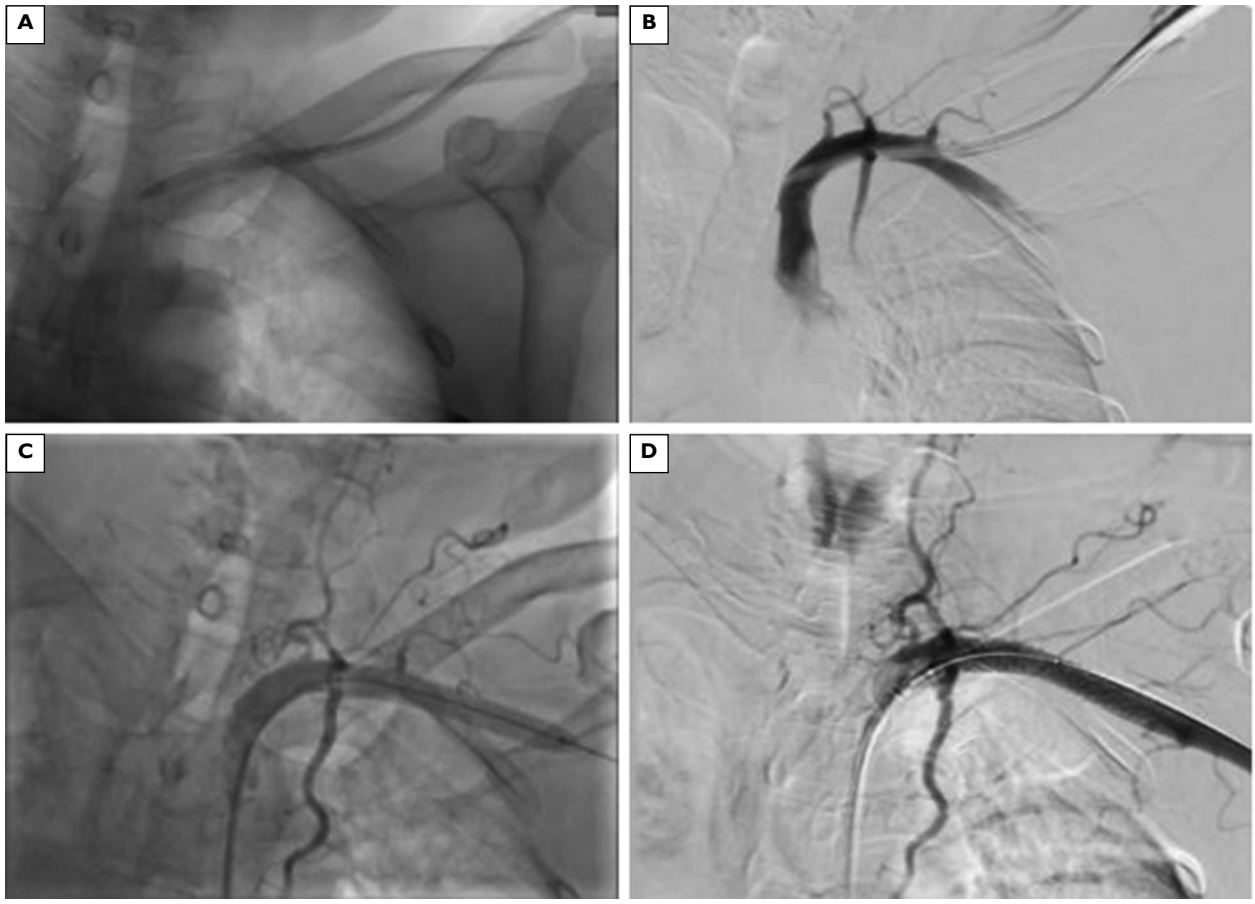


Figure 1. Case 1: A — location of the catheter using angiography; B — subclavian artery with a catheter; C — stent positioning; D — after stent implantation

preferably avoiding open surgery. In both cases, the procedure consisted of catheter removal under fluoroscopic control and endovascular repair of the damaged artery with a covered stent. Another possible method of treatment would be hybrid operation with use of balloon for temporary occlusion of the vessel and surgical repair or open vascular repair, a very complicated and risky procedure in both patients.

Surgical technique

Local anesthesia with 1% lignocaine solution was used at the CVC puncture site and access site to the common femoral artery in both cases and additionally at the right brachial artery in the second patient. In both cases puncture and insertion of the 7F sheath into the common femoral artery (CFA) was performed under ultrasound guidance. Next, guidewire supported with diagnostic catheter was introduced through injured subclavian artery (SA) to peripheral part of brachial artery. Subsequently, the previously used short sheath was replaced with a long one, introduced to the proximal part of the SA. Injury of the vessel was precisely localized in fluoroscopy and diameter of artery was measured to select appropriate balloon expandable covered stent.

In both cases an additional leakage test was performed using the balloon catheter with a nominal diameter 1 mm larger than the diameter of the vessel at the site of injury. Absence of both contrast flow to the peripheral part of the artery and it's extravasation after simultaneous central catheter removal and balloon inflation in the injury site confirmed appropriate choice of covered stent diameter. In the first case stent was introduced via femoral access. The same way was used for angiography. In the second case (due to different vessels anatomy) stent was introduced through brachial access, and angiographic control was performed with femoral access for better landing precision. CVC removal and implantation of a covered stent under fluoroscopic control were performed simultaneously to minimize bleeding from artery perforation. Angiographic control of the stent tightness revealed no leakage. In the second case, it was necessary to cover the ostium

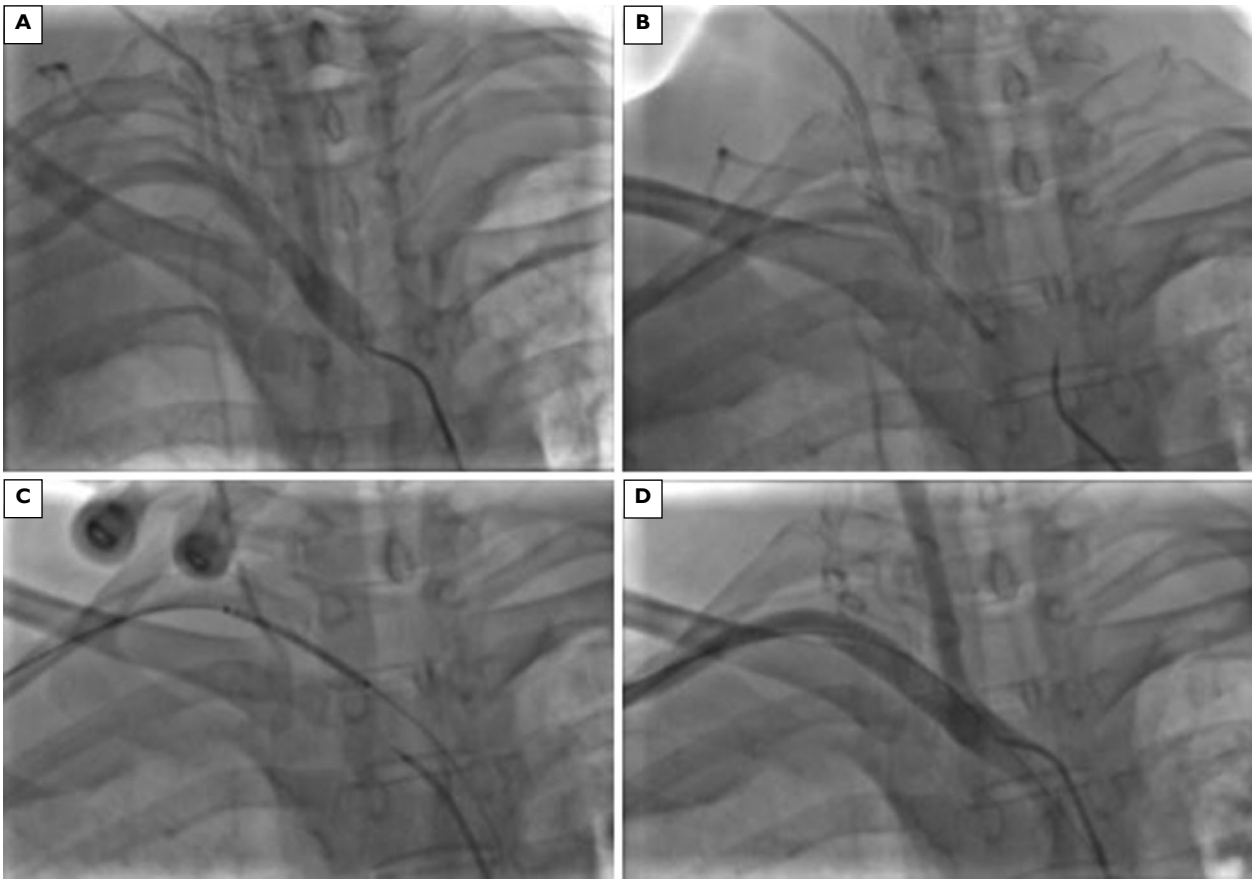


Figure 2. Case 2: A, B — location of the catheter in the vessel; C — stent positioning; D — after stent implantation

of the right vertebral artery (VA), due to its proximity of the puncture site. No neurological deficits associated with the VA coverage were observed. In both cases, the access site to CFA was closed using AngioSeal system. Both patients were discharged to their primary hospitals with no signs of leakage (bleeding) or hemoglobin level decrease.

Procedure — step by step:

1. Ultrasound-guided puncture of CFA and introduction of short sheath 7F.
2. Introduction of hydrophilic guide wire 0.035" (Terumo) and diagnostic catheter Bern 4F (Boston Scientific) to the injured SA. Exchange of wire for the Supra Core 35 Guide Wire (Abbott).
3. Exchange of the short sheath 7F for the long 7F Destination (Terumo) (with a diameter guaranteeing contrast application when positioning the stent in the case of using this sheath as a working channel as in case 1) or performing access to brachial artery for retrograde stent delivery as in case 2. In the second case, diagnostic catheter previously introduced via femoral access was used for angiographic control during positioning and implantation of the stent.
4. Measurement of the vessel diameter and the use of a balloon catheter (Armada 35, Abbott) inflated in the site of future stent implantation to confirm proper stent diameter.
5. Simultaneous removal of a foreign body and expansion of the PTFE covered stent Advanta V12 (Atrium) on the balloon to minimize bleeding from the site of damage.
6. Angiographic control, removal of the catheter and sheath, access site closure with Angio-Seal.

Discussion

Central access is obtained using anatomical landmarks or with ultrasound/ fluoroscopy guidance. The first technique is characterized by a high percentage of failures and complications of 30% and 18.8%, respectively [1]. The use of ultrasound significantly reduced the number of failures, and attempts needed to gain central vein access as well as the frequency of complications such as accidental puncture of the artery, hematoma, pneumothorax, etc. Ultrasound-guided access to the subclavian vein is more difficult (compared to the

internal jugular and femoral vein) due to anatomical conditions. Consequently, the risk of complications is higher in this access site, especially because the subclavian artery, due to its anatomical location, cannot be effectively compressed and the catheters used have a significantly higher diameter [2]. Therefore, the injury to the subclavian artery by erroneous puncture may result in pseudoaneurysm, arteriovenous fistula or uncontrolled bleeding, especially that puncture attempts are often performed several times [3–5]. It seems that insertion into the jugular vein under ultrasound control is a more reliable and safer alternative to subclavian access, although damage at this level is more frequently reported. Mortality of up to 30% was reported as a result of damage of SA and proximal part of the axillary artery [6]. For this reason as well as due to technical difficulties of open surgery, techniques of endovascular repair of these vessels injuries are currently preferred. They can be used separately or as part of a hybrid method involving prior endovascular bleeding control using balloon catheter followed by open surgical repair.

If the catheter is accidentally positioned in the artery, the best way of action is to secure it with dressing and contact the vascular center. Because in most cases the catheter alone allows to maintain local hemostasis, it gives time to prepare for surgery. The use of endovascular techniques, such as covered stent implantation, temporary balloon closure, embolization, and the use of thrombin, is an alternative to surgical repair, especially in patients with concomitant diseases in whom immediate, potentially large surgery would be associated with a high risk of perioperative complications. Due to large diameter of implanted catheters in our patients, the use of closure device was expected to be inefficient. In these cases endovascular repair with precise damage control seems to be optimal choice. In cases in which catheter was already removed with subsequent pseudoaneurysm, bare metal stent with additional embolization can be considered. If endovascular repair fails and active bleeding is still present, open surgical repair is inevitable, but was never necessary in our experience.

The open surgical reconstruction is the treatment of choice for extensive vascular injury, active arterial bleeding and pleural damage [7, 8]. In our opinion in other cases, the use of a covered stent, if possible, should be the treatment of choice. Generally in case of SA lesion, self-expandable stents are preferred especially in case of variable vessel diameter ant it's tortuosity. In these particular cases of artery injury, balloon expandable stents were used due to the possibility of precise implantation, avoidance of additional maneuvers (stent postdilatation) connected with potential blood loss. Furthermore, both patients were in severe medical condition (with short life expectancy); thus, risk of future stent damage caused by limb movements (mechanism of the clavicle-ribbed scissors) was considered acceptable. It is important to accurately verify the size, both diameter and length of a stent, to avoid leakage and necessity of implantation of additional stents [9]. In the technique described above, it was helpful to pre-seal the vessel with a balloon catheter of diameter 1 mm greater than the vessel measured under fluoroscopy and length equal to pre-selected stent in order to confirm proper stent selection. It is important to use a single stent with a length and diameter that guarantees hemostasis. Simultaneous expansion of the stent and removal of a foreign body (CVC) under fluoroscopic control minimizes the possibility of uncontrolled blood loss. In the case of difficult anatomy or proximity of the puncture site to the ostium of the vertebral artery (VA) like in the second case or other important anatomical structure, additional access from the brachial artery should be considered to optimize visualization of stent deployment.

Conclusions

Iatrogenic injury of the subclavian artery following an attempt of subclavian vein cannulation can be effectively and safely treated with endovascular techniques. In our opinion, endovascular management should be considered as a method of choice especially among patients in poor general condition and/or with major comorbidities. The key points for successful procedure are precise localization of artery injury site with high quality angiogram and proper selection of covered stent length and diameter. Depending on vessels anatomy and injury localization, simultaneous use of both femoral and brachial accesses may be required. In case of extensive vascular injury, when open surgery may be inevitable, prior endovascular bleeding control using balloon catheter is strongly recommended.

Conflict of interest

None.

References

1. Sznajder JI, Zveibil FR, Bitterman H, et al. Central vein catheterization. Failure and complication rates by three percutaneous approaches. Arch Intern Med. 1986; 146(2): 259–261, doi: 10.1001/archinte.146.2.259, indexed in Pubmed: 3947185.
2. Rossi UG, Petrocelli F, Ferro C. Subclavian artery pseudoaneurysm complicating central venous catheterization: endovascular treatment with Amplatzer Vascular Plug 4 and covered stent. Catheter Cardiovasc Interv. 2013; 82(7): E906–E910, doi: 10.1002/ccd.24796, indexed in Pubmed: 23359531.
3. Wheeler SC, Zinn KM, Hughes TW. Endovascular covered stent repair of an iatrogenic subclavian artery-to-pulmonary artery

fistula and pseudoaneurysm. J Vasc Interv Radiol. 2007; 18(6): 775–779, doi: 10.1016/j.jvir.2007.02.029, indexed in Pubmed: 17538141.
4. Stoica SC, Fleet M, Howd A. Subclavian artery injury following percutaneous insertion of dialysis catheter. Rev Med Chir Soc Med Nat Iasi. 1998; 102(3-4): 194–197, indexed in Pubmed: 10756874.
5. Cox CS, Allen GS, Fischer RP, et al. Blunt versus penetrating subclavian artery injury: presentation, injury pattern, and outcome. J Trauma. 1999; 46(3): 445–449, doi: 10.1097/00005373-199903000-00017, indexed in Pubmed: 10088848.
6. Waller CJ, Cogbill TH, Kallies KJ, et al. Contemporary management of subclavian and axillary artery injuries — A Western Trauma Association multicenter review. J Trauma Acute Care Surg. 2017; 83(6): 1023–1031, doi: 10.1097/TA.0000000000001645, indexed in Pubmed: 28715360.
7. Tawfic QA, Bhakta P, Mohammed AK, et al. Subclavian vein injury and massive hemothorax requiring thoracotomy following insertion of tunneled dialysis catheter--a case report and review of literature. Middle East J Anaesthesiol. 2010; 20(6): 861–864, indexed in Pubmed: 21526674.
8. Maciejewski DR, Tekieli Ł, Machnik R, et al. Simultaneous vertebral and subclavian artery stenting. Postepy Kardiol Interwencyjnej. 2017; 13(2): 142–149, doi: 10.5114/pwki.2017.68052, indexed in Pubmed: 28798785.

Forum Medycyny Rodzinnej — Konferencja Czasopisma Forum Medycyny Rodzinnej

2–3 lipca 2021 roku

Przewodniczący Komitetu Naukowego:
prof. dr hab. n. med. Janusz Siebert

VIRTUAL MEETING

Szczegółowe informacje oraz bezpłatna rejestracja:
www.medycynarodzinna.viamedica.pl

Virtual Meeting jest skierowany tylko do osób uprawnionych do wystawiania recept lub osób prowadzących obrót produktami leczniczymi — podstawa prawna: Ustawa z dnia 6 września 2001 r. Prawo farmaceutyczne (t. j. Dz.U. z 2019 r. poz. 499).

PATRONAT

Polskie Towarzystwo Medycyny Rodzinnej

ORGANIZATOR

VIA MEDICA

20-0857.001.017

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