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RECOMMENDATIONS

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Thrombolytic therapy using recombinant tissue plasminogen activator (r-tPA): the position of the Polish Society for Vascular Surgery

developed by the expert team including Tomasz Jakimowicz*, Zbigniew Krasiński, Maciej Niewada, Grzegorz Borowski, Włodzimierz Hendiger*, Arkadiusz Jawien, Tomasz Zubilewicz*, Zbigniew Gałązka*, Michał Goran Stanisic*, Wacław Kuczmik*, Stanisław Przywara*, Paweł Wierzchowski*, Andrzej Wojtak*, Piotr Andziak*, **

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1. Introduction

Thrombolytic therapy is currently used to treat coronary thrombosis, cerebral artery thrombosis, and massive hemodynamically unstable pulmonary embolism. For many years, thrombolytic therapy has also been used in patients with acute limb ischemia and deep vein thrombosis. While fibrinolytic medications can be administered intravenously in the first three indications, the latter two require them being targeted directly into thrombus or its vicinity by means of a catheter.

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For many years, alteplase — a recombinant tissue plasminogen activator (r-TPA) — has been the only fibrinolytic medication available in Poland. However, the treatment of limb ischemia is not a registered indication as per the summary of product characteristics.

2. Indications for fibrinolytic therapy in peripheral arterial and venous diseases

This work is aimed at presenting the off-label uses of recombinant tissue plasminogen activator (r-TPA). Registered indications and uses in line with these indications will not be discussed.

2.1. Acute limb ischemia (ALI)

Acute limb ischemia (ALI) and deep vein thrombosis (DVT) are sudden-onset disorders requiring urgent treatment due to their potential for causing serious complications directly threatening the limbs and even the lives of patients.

ALI is characterized by a sudden stop of blood flow to tissues and is associated with a risk of limb loss as well as a risk to patient life. Most commonly, ALI is caused by an embolism or a thrombus within the arteries. Thrombosis may occur within an atherosclerotically remodeled artery, a peripheral arterial aneurysm, previously implanted stent or vascular bypass or, less frequently, within a region of arterial delamination or injury. The disorder requires emergency diagnostics and treatment. ALI is diagnosed if symptoms have been observed for less than 2 weeks.

Clinical classification of acute limb ischemia as proposed by Rutherford (TASC II) [1] consists of four categories:

I — limb survival not directly at risk,

IIa — limb survival at borderline risk, limb salvation possible upon timely treatment, IIb — limb survival at immediate danger, immediate intervention required III — irreversible ischemia. The rate of amputations due to ALI is 10 to 15%, and the associated 30-day mortality rate ranges from 15 to 25% [2].

In the case of category IIa or IIb ischemia , revascularization must be undertaken immediately (within 6 hours) [3, 4] to reduce the risk of progression to category III. Thrombolysis may also be a preliminary procedure for arterial bridging operations, e.g. in the case of popliteal or crural aneurysm thrombosis.

2.2. Deep vein thrombosis (DVT)

Deep vein thrombosis within the iliofemoral segment poses an exceptional risk of both early and distant complications. The most serious early complication of DVT is pulmonary embolism which is a direct threat to patient's life. The prevalence of pulmonary embolism is estimated at 50–100/100,000, and fatal pulmonary embolism is detected in 50/100,000 autopsies each year. Almost 1/3 of pulmonary embolism cases have been shown to lead to death within the first few hours from the onset of symptoms. This is usually a period when proper treatment cannot be given. However, in cases where proper diagnosis had been made early and proper treatment was initiated, the mortality rate is only about 7% [5]. Chronic thromboembolic pulmonary hypertension (CTEPH) is a severe distant complication of pulmonary embolism. It is a rare yet potentially fatal complication. It is observed in approximately 4% of patients with the history of PE. Another significant distant complication of deep venous thrombosis within the iliofemoral segment if the post-thrombotic syndrome observed in 20–30% of patients with the history of DVT. An increasing number of reports suggest that post-thrombotic syndrome is more common if the thrombosis affects the iliofemoral segment and the patient is treated with oral anticoagulants alone. Targeted thrombolysis should be considered as a means to reduce the risk of early and distant complications in these cases [5].

Indications for thrombolytic therapy of DTV include:

1. Phlegmasia cerulea dolens.
2. Acute, proximal, massive and symptomatic deep lower limb vein thrombosis in all patients.
3. Iliofemoral segment thrombosis in young patients at low risk of bleeding and high risk of distant complications resulting from vessel obstruction or post-thrombotic syndrome.
4. Acute symptomatic thrombosis of the axillary and/or subclavian vein associated with the thoracic outlet syndrome (TOS).

3. Contraindications for thrombolytic therapy

Thrombolysis is contraindicated in patients with increased risk of bleeding. Since cancer and old age have not been clearly identified as treatment exclusion criteria, they do not constitute a definite contraindication for thrombolysis, but an increased risk of bleeding should always be considered. Contraindications for thrombolysis were categorized into absolute, major, and minor contraindications (see Table 1) [5, 6].

4. Methods and techniques for fibrinolytic therapy of peripheral arterial and venous thrombosis

Treatment of patients with AIL may consist in surgical thromboembolectomy or catheter-directed thrombolysis (CDT) and/or thromboaspiration. The selected

Table 1. Contraindications for thrombolytic therapy of acute limb ischemia

Absolute
History of cerebrovascular incident [including TIA (transient ischaemic attack)] within the last two months
Active hemorrhagic diathesis
Recent history of gastrointestinal bleeding (< 10 days)
History of neurosurgical (intracranial, cortical) procedure within the last three months History of craniocerebral trauma within the last three months
Movable left heart thrombus
Irreversible limb ischemia (severe sensory disorders and muscle stiffness)
Major
History of CPR within the last 10 days History of major non-vascular surgery or trauma within the last 10 days
History of biopsy within the last 10 days
Uncontrolled hypertension: systolic pressure > 180 mm Hg or diastolic pressure > 110 mm Hg.
Puncture of a non-susceptible vessel Intracranial tumor
Recent history of eye surgery
Minor
Hepatic insufficiency, particularly with coagulopathy
Severe renal insufficiency
Bacterial endocarditis
Pregnancy
Diabetic hemorrhagic retinopathy
Thrombocyte count < 100,000/mm^3, prothrombin index < 50%

technique should ensure the most rapid restoration of arterial flow at the lowest risk to the patient. Catheter-directed thrombolysis can ensure rapid restoration of blood supply to the affected limb, particularly in the case of fresh thrombotic lesions, bypass graft or stent thrombosis [7, 8]. A great advantage of thrombolysis consists in that in contrast surgical thrombectomy where thrombi can be removed only from large arteries, lysis can be achieved in both large and small arteries as well as within the arterial capillary bed.

4.1. Methods for thrombolytic therapy

1. Pharmacological thrombolysis consists in administration of thrombolytic drugs without the use of mechanical thrombectomy devices; it is divided into the following sub-categories:

a) systemic thrombolysis — thrombolytic medication being administered through an IV catheter away from the affected limb (currently abandoned and hence not discussed in this document);

b) flow-directed thrombolysis — thrombolytic medication being administered through an IV catheter placed within the peripheral part of the ischemic limb, with or without compression bands to deliver the medication to the deep venous system;

c) catheter-directed thrombolysis (CDT) — thrombolytic medication being administered through an infusion catheter placed inside the thrombus (arterial or venous). After the catheter is in place, medication is slowly infused into the thrombus (via a catheter, usually featuring multiple side holes, such as fountain catheter). Ultrasound-assisted CDT consists in the medication being administered through an infusion catheter which simultaneously emits ultrasound wave energy into the thrombus (e.g. EkoSonic catheter; EKOS, Bothell, WA, USA).

2. Percutaneous mechanical thrombectomy (PMT) consists in the use of endovascular mechanical devices which facilitate the removal of clots by means of their fragmentation, maceration and/or aspiration without the administration of thrombolytic medication (will not be discussed due to the nature of the document).
3. Pharmacomechanical CDT (PDCT) consists in the thrombus being dissolved and removed by simultaneous pharmacological CDT and PMT. PCDT

involves a combination of techniques, including the use of multiple side-hole infusion catheters, pulsed spraying technique for applying the liquid to the thrombus manually or using a dedicated device (e.g. AngioJet Rheolytic Thrombectomy System; Medrad, Warrendale, PA, USA) with or without segmental isolation by means of catheter-mounted balloons (e.g. Trellis Peripheral Infusion System; Covidien, Mansfield, MA, USA). The commonly used auxiliary intravascular techniques include aspiration thrombectomy (syringe being used to aspirate blood clots from a vein via the catheter, device, or sheath), balloon maceration (angioplasty balloon being used for thrombus maceration or fragmentation), balloon angioplasty, and stenting.

4.2. Thrombolytic medications — a pharmacologist's perspective

In the past, an indirect, non-fibrin-specific plasminogen activator streptokinase was used as the first fibrinolytic agent. Its use was discontinued due to low efficacy, increased risk of hemorrhagic complications, and highly allergenic nature.

Urokinase is the only non-specific plasminogen activator registered for the treatment of limb ischemia in Poland. However, the drug is currently unavailable in the country which could prevent a large group of patients from receiving thrombolytic treatment of limb ischemia or venous thrombosis.

Alteplase, a recombinant tissue plasminogen activator (r-tPA) is a widely available drug for the treatment of cerebral ischemia, cardiac ischemia, and pulmonary embolism yet not indicated in the treatment of peripheral thromboembolism. Alteplase is widely used worldwide and has been included in the guidelines of many scientific societies despite the lack of formal registration. An additional argument supporting the use of alteplase consists in urokinase being withdrawn from use e.g. in the US. Alteplase is currently the most widely used thrombolytic medication; notably, it is the only medication of this type available in Poland. Alteplase is a fibrin-specific agent which preferentially activates fibrin-bound (i.e. clot-bound) plasminogen. Its higher specificity to fibrin has the advantage consisting in reduced rates of systemic hemorrhagic complications.

Alteplase is a glycoprotein (serine protease) obtained by DNA recombination in Chinese hamster ovary (CHO) cells, its activity being identical to that of the endogenous tissue plasminogen activator (novel, third-generation thrombolytic drugs feature a modified t-PA structure to present with modified pharmacological properties such as longer duration of action) [9]. Alteplase is activated upon fibrin binding and directly activates plasminogen to form plasmin which digests the clot proteins, particularly fibrin. The thrombus is made up of fibrin monomers cross-linked via side lysine chains characterized by high affinity for plasminogen. Alteplase's affinity to fibrin-bound plasminogen determines its being activated mainly within the thrombus and results in a lower risk of hemorrhagic complications as compared to classical fibrinolytic medications with a non-fibrin-specific effect (streptokinase, urokinase). The relative affinity towards fibrin causes alteplase to moderately reduce the blood fibrinogen levels resulting in a minor generalized fibrinolytic effect. Plasminogen deficiency and elevated levels of plasminogen activator inhibitor (PAI) may reduce the activity of alteplase.

Alteplase is the first recombinant plasminogen activator registered for the treatment of fresh myocardial infarction (1987), acute massive pulmonary embolism (1990), acute ischemic stroke (1996), and restoration of patency in central venous or other vascular catheters (2001) [10]. Currently, the medication is registered in Poland in the first three of these indications; it is not registered for use in acute limb ischemia (it is worth noting that the summaries of product characteristics are different in different EU countries, with no unified binding document being available). Alteplase is used in intravenous or intraarterial injections. Pharmacokinetic data are mainly derived from studies in acute myocardial infarction which may be relevant in other patient populations, particularly in the elderly. The pharmacokinetic model is a two-compartmental one. The half-life of the drug is short, amounting to only 3–6 minutes in the alpha phase (corresponding mainly to distribution) and 26–40 minutes in the beta phase (corresponding mainly to elimination) in healthy volunteers [11–13]. This means that plasma alteplase levels following a bolus administration are virtually indeterminable after 40 minutes [14]. Therefore, continuous intravenous infusion is required to sustain the medication effect [15].

Due to its structure, alteplase is metabolized in in the liver with the formation of low molecular weight, water-soluble fractions subsequently excreted with urine. The metabolism largely depends on hepatic blood flow; however, no data are available regarding the consequences of this fact for alteplase dosing. Nitroglycerin bay reduce the efficacy of alteplase by significantly dilating veins and thus increasing hepatic blood flow [16].

Simultaneous anticoagulants, antiplatelet drugs or other agents increasing the risk of coagulation disorders may increase the risk of hemorrhagic complications of alteplase treatment. Contraindications for alteplase treatment are related to indications for use and associated with the severity of clinical condition/prognosis and the expected benefits of treatment in terms of possible adverse reactions and complications. Notably, the use of

this fibrinolytic medication may also have an impact on administration restrictions, i.e. Systemic administration is more dangerous than CDT.

Hemorrhagic complications are the main adverse effects of alteplase treatment; severe adverse effects, including symptomatic intracerebral hemorrhage, are rather rare (about 1%) and obviously dependent on the medication dose as well as numerous factors affecting hemostasis. Anaphylactic reactions are rare (small amounts of gentamycin are produced during the manufacturing process and may also be responsible for allergic reactions) and usually limited to oral edema, including angioedema (probably secondary to a plasmin-dependent kinin release mechanism), and hypotonia. As a rule, all these symptoms respond well to antihistamine and glucocorticosteroid treatments; however, angioedema may be a life threatening condition which requires intubation. No immunological data are available indicating the long-term production of antibodies against recombinant human tissue plasminogen activator molecules. This means that the medication can be used in a repeatable and anaphylaxis-safe manner even in short intervals.

According to the summary of product characteristics for Actylise®, the only product containing alteplase available in Poland, the solution (after mixing all the powder and solvent in provided in the packaging; 10 mg, 20 mg, and 50 mg preparations available) contains 1 mg of alteplase in 1 mL. Further dilution with sterile physiological saline (do not use injection water or carbohydrate solutions for infusions, e.g. glucose, due increased turbidity) is possible down to the minimum concentration of 0,2 mg of alteplase in 1 mL of solution. The medication should not be mixed with other agents (including heparin) vials in the same vial or catheter. Alteplase has a shelf life of 2 to 3 years and should be stored away from direct sunlight. After opening, alteplase can be stored at 2–8°C for up to 24 hours.

Protocols for transcatheter administration of alteplase in peripheral vascular embolism vary [17]. Different durations of infusions are used to sustain the medication's effect. Lower doses of medication are characterized by efficacy similar to the higher ones, additionally reducing the risk of hemorrhagic complications upon longer infusions.

Alteplase dosing

The recommended quantity of r-tPA is 0.5–1.0 mg/h; alternatively, the maximum starting dose 0.01 mg/kg/h is administered via an infusion catheter over 12–24 hours. Upon the administration of r-tPA, subtherapeutic doses of non-fractionated heparin can be delivered simultaneously in 300–500 U/h IV infusion from a peripheral catheter or sheath without initial UFH bolus. Therapeutic aPTT levels should only be reached after CDT has been completed.

5. Fibrinolytic therapy monitoring and safety conditions

During CDT, the patient should remain in the high dependency unit so that vital signs and neurological parameters of the limb can be monitored. The level of fibrinogen should be monitored every 4–6 hours due to its documented direct relationship with hemorrhagic complications. If the fibrinogen level drops below 150 mg/dL, the r-TPA infusion rate should be cut by a half; infusion should be stopped if the fibrinogen level drops below 100 mg/dL. In addition, hemoglobin level as well as activated partial thromboplastin time (APTT, in cases of simultaneous heparin infusion) should be monitored every 4–6 hours. The objective is to reach the subtherapeutic APTT of < 50 seconds during the administration of r-TPA and heparin. Arteriographic/phlebographic follow-up should be performed 12–36 hours after the initiation of thrombolytic therapy to verify its efficacy. The following options are possible depending on the results:

1. Continued infusion of alteplase and another follow-up in 12–36 h.
2. Repositioning/replacement of the catheter (so that the "working part" is located within the remaining thrombus) and follow-up in 12–36 h.
3. Termination of thrombolytic therapy and initiation of causative treatment: angioplasty/stenting of the vessel of origin or a classical surgery to remove the origin (and removal of vascular access).
4. Termination of therapy and removal of vascular access.
5. The procedure rarely requires continuation beyond 48 hours, up to a maximum of 72 hours. After this time, infusion must be interrupted and the catheter must be removed. The total r-tPA dose should not exceed 100 mg [18]. After CDT is completed and vascular access is removed, manual compression or closure systems are used to obtain hemostasis and the patient remains immobilized in bed for 6–24 hours. Therapeutic-level anticoagulation treatment is resumed within 2 hours after hemostasis has been obtained. If UFH was administered during CDT, no bolus is given. In patients receiving LMWH, the previous treatment regimen is continued. Vitamin K or DOAC antagonists are administered as indicated on the day of sheath removal.

6. Complications of fibrinolytic therapy

The main potential complication following the administration of a thrombolytic agent consists in bleeding which may result in discontinuation of treatment. Bleeding occurs in 13–30% of cases, including the most severe intracranial bleeding in 0.4–2.3% [19]. In the case of severe bleeding complications, transfers of blood products, cryoprecipitate, freshly frozen plasma, and platelets are delivered along with antifibrinolytic medications (tranexamic acid).

7. Early and distant outcomes of fibrinolytic therapy of peripheral arterial and venous thrombosis

CDT has the advantage over surgical treatment in grade IIa AIL [20, 21]. Recently, intravascular treatment is also used for grade IIb AIL, including percutaneous mechanical thrombectomy (PMT) being added to local thrombolysis. This approach results in similar revascularization outcomes with lower 30-day mortality rates as compared to open surgery [22–24].

8. Summary

Alteplase is a modern, effective thrombolytic medication and should be used in local treatment of arterial and venous thrombosis. Due to the absence this indication in the summary of product characteristics, a separate patient's consent is necessary for the off-label use of the medication.

Legal aspects and opinions of medical law experts for off label application of Alteplase in Poland are included in the attachement 1 and 2 of Polish version of this Guidelines. Please note, that this legal opinions are only applicable in Poland.

Conflict of interest

None.

References:

1. Jaff MR, White CJ, Hiatt WR, et al. TASC Steering Committee, TASC Steering Committee, TASC II Working Group, TASC II Working Group, TASC II Working Group. Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). Eur J Vasc Endovasc Surg. 2007; 33 Suppl 1(2): S1–75, doi: 10.1016/j.ejvs.2006.09.024, indexed in Pubmed: 17140820.
2. Patel NH, Krishnamurthy VN, Kim S, et al. CIRSE and SIR Standards of Practice Committees. Quality improvement guidelines for percutaneous management of acute lower-extremity ischemia. J Vasc Interv Radiol. 2013; 24(1): 3–15, doi: 10.1016/j.jvir.2012.09.026, indexed in Pubmed: 23273693.
3. Gerhard-Herman MD, Gornik HL, Barrett C, et al. 2016 AHA/ACC Guideline on the Management of Patients With Lower Extremity Peripheral Artery Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2017; 135(12): e726–e779, doi: 10.1161/CIR.0000000000000471, indexed in Pubmed: 27840333.
4. Fluck F, Augustin AM, Bley T, et al. Current Treatment Options in Acute Limb Ischemia. Rofo. 2020; 192(4): 319–326, doi: 10.1055/a-0998-4204, indexed in Pubmed: 31461761.
5. Gloviczki P. Choroby żył i układu limfatycznego. Medipage, Warszawa 2020.
6. Marquis-Gravel G, Tremblay-Gravel M, Lévesque J, et al. Ultrasound guidance versus anatomical landmark approach for femoral artery access in coronary angiography: A randomized controlled trial and a meta-analysis. Journal of Interventional Cardiology. 2018; 31(4): 496–503, doi: 10.1111/joic.12492.
7. Thrombolysis in the management of lower limb peripheral arterial occlusion, a consensus document. J Vasc Interv Radiol 2003;14:S337e49.
8. Comerota AJ, Weaver FA, Hosking JD, et al. Results of a prospective, randomized trial of surgery versus thrombolysis for occluded lower extremity bypass grafts. Am J Surg. 1996; 172(2): 105–112, doi: 10.1016/S0002-9610(96)00129-8, indexed in Pubmed: 8795509.
9. Jongkind V, Earnshaw JJ, Bastos Gonçalves F, et al. Editor's Choice - European Society for Vascular Surgery (ESVS) 2020 Clinical Practice Guidelines on the Management of Acute Limb Ischaemia. Eur J Vasc Endovasc Surg. 2020; 59(2): 173–218, doi: 10.1016/j.ejvs.2019.09.006, indexed in Pubmed: 31899099.
10. Actylise. Summary of Product Characteristics. https://www.boehringer- ingelheim.pl/sites/pl/files/documents/poland_pdf/actilyse_20_chpl2019.pdf (15.10.2020).
11. Acheampong P, Ford GA. Pharmacokinetics of alteplase in the treatment of ischaemic stroke. Expert Opin Drug Metab Toxicol. 2012; 8(2): 271–281, doi: 10.1517/17425255.2012.652615, indexed in Pubmed: 22248305.
12. Tanswell P, Seifried E, Su PC, et al. Pharmacokinetics and systemic effects of tissue-type plasminogen activator in normal subjects. Clin Pharmacol Ther. 1989; 46(2): 155–162, doi: 10.1038/clpt.1989.120, indexed in Pubmed: 2503283.
13. Verstraete M, Bounameaux H, de Cock F, et al. Pharmacokinetics and systemic fibrinogenolytic effects of recombinant human tissue-type plasminogen activator (rt-PA) in humans. J Pharmacol Exp Ther. 1985; 235(2): 506–512, indexed in Pubmed: 4057083.
14. Nilsson T, Wallén P, Mellbring G. In vivo metabolism of human tissue-type plasminogen activator. Scand J Haematol. 1984; 33(1): 49–53, doi: 10.1111/j.1600-0609.1984.tb02209.x, indexed in Pubmed: 6431604.
15. Kane I, Sandercock P. Alteplase: thrombolysis for acute ischemic stroke. Therapy. 2005; 2(5): 709–716, doi: 10.1586/14750708.2.5.709.
16. Tanswell P, Seifried E, Stang E, et al. [Recombinant tissue-type plasminogen activator: pharmacokinetics and effect on the hemostasis system of the human]. Klin Wochenschr. 1988; 66 Suppl 12(3): 40–49, indexed in Pubmed: 2450222.

17. Romeo F, Rosano GM, Martuscelli E, et al. Concurrent nitroglycerin administration reduces the efficacy of recombinant tissue-type plasminogen activator in patients with acute anterior wall myocardial infarction. Am Heart J. 1995; 130(4): 692–697, doi: 10.1016/0002-8703(95)90065-9, indexed in Pubmed: 7572574.
18. Ebben HP, Jongkind V, Wisselink W, et al. Catheter Directed Thrombolysis Protocols for Peripheral Arterial Occlusions: a Systematic Review. Eur J Vasc Endovasc Surg. 2019; 57(5): 667–675, doi: 10.1016/j.ejvs.2018.11.018, indexed in Pubmed: 31005512.
19. Giannakakis S, Galyfos G, Sachmpazidis I, et al. Thrombolysis in peripheral artery disease. Ther Adv Cardiovasc Dis. 2017; 11(4): 125–132, doi: 10.1177/1753944716687517, indexed in Pubmed: 28164744.
20. Grip O, Kuoppala M, Acosta S, et al. Outcome and complications after intra-arterial thrombolysis for lower limb ischaemia with or without continuous heparin infusion. Br J Surg. 2014; 101(9): 1105–1112, doi: 10.1002/bjs.9579, indexed in Pubmed: 24965149.
21. Karnabatidis D, Spiliopoulos S, Tsetis D, et al. Quality improvement guidelines for percutaneous catheter-directed intra-arterial thrombolysis and mechanical thrombectomy for acute lower-limb ischemia. Cardiovasc Intervent Radiol. 2011; 34(6): 1123–1136, doi: 10.1007/s00270-011-0258-z, indexed in Pubmed: 21882081.
22. Kessel DO, Berridge DC, Robertson I. Infusion techniques for peripheral arterial thrombolysis. Cochrane Database Syst Rev. 2004(1): CD000985, doi: 10.1002/14651858.CD000985.pub2, indexed in Pubmed: 14973961.
23. Hage AN, McDevitt JL, Chick JF, et al. Acute Limb Ischemia Therapies: When and How to Treat Endovascularly. Semin Intervent Radiol. 2018; 35(5): 453–460, doi: 10.1055/s-0038-1676321, indexed in Pubmed: 30728661.
24. Valle JA, Waldo SW. Current Endovascular Management of Acute Limb Ischemia. Interv Cardiol Clin. 2017; 6(2): 189–196, doi: 10.1016/j.iccl.2016.12.003, indexed in Pubmed: 28257767.
25. Ebben H, Jongkind V, Wisselink W, et al. Catheter Directed Thrombolysis Protocols for Peripheral Arterial Occlusions: a Systematic Review. European Journal of Vascular and Endovascular Surgery. 2019; 57(5): 667–675, doi: 10.1016/j.ejvs.2018.11.018.

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Proximal vertebral artery surgery. Results of treatment of ischemia of the rhombencephalon (hindbrain). Simultaneous carotid and vertebral artery operating procedures

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Abstract

Introduction: *Surgical treatment of hindbrain ischemia is becoming the accepted surgical procedure in cases of stenosis of extracranial segments of vertebral arteries in the course of advanced atherosclerotic lesions in their initial segments (V1) or caused by external compression of these arteries in the canal formed by the transverse processes of cervical vertebrae. The latter is referred to as vertebrobasilar insufficiency (VBI). The transposition of the left vertebral artery to the common carotid artery in cases where stent graft implantation is necessary with coverage of the subclavian artery and possible blood supply disorders of both the hindbrain and the spinal cord has become important.*

Material and methods: *In the Department of Vascular Surgery at the Medical University in Wrocław, in 58 out of 76 patients treated for ischemia of the hindbrain, the procedures were performed in the distal vertebral artery. The authors present the diagnosis of 18 patients treated surgically for stenosis or kinking of vertebral arteries in their first segment.*

Results: *In 12 cases, the procedure was performed with simultaneous unblocking of significantly narrowed left internal carotid artery. The material includes patients operated on between 1994 and 2018, most of whom had a good or very good outcome with zero mortality.*

Conclusions: *Our results allow for a conclusion that proximal anastomosis of the common carotid and vertebral arteries is an effective method of treatment of vertebrobasilar insufficiency resulting both from atherosclerotic lesions of the vertebral arteries and their kinking. The qualification for the procedure is relatively difficult and must be based on angiography, whereas non-invasive methods are not fully reliable and should be, therefore, treated as auxiliary. We believe, however, that with increasing experience, ultrasound methods will also allow for a proper assessment. Unfavorable results of stenting, especially of vertebral arteries, demonstrated in our study, indicate the necessity to rely on surgical treatment.*

Key words: vertebral artery surgery, diagnosis, concomitant carotid artery endarterectomy procedures

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Introduction

Cerebral ischemia caused by lesions of the vertebral and basilar arteries is much less frequently diagnosed than syndromes originating in the carotid artery vascularization area. Cerebral strokes in the vascularization area of these arteries account for about 15% of all ischemic cerebral strokes and their number shows an increasing trend. The essential role in cerebral blood supply is played by internal carotid arteries supplying 80–85% of the blood, while the remaining portion is supplied by vertebral arteries. The normal cerebral flow is calculated at 700-900 ml of blood per minute, which is 1/5 of the minute stroke volume of the heart. This amount of blood carries approx. 500–600 ml/min of oxygen and 75–100 mg/min of glucose, which allows to supply the brain with about 30 watts of energy per day, obtained from the combustion of glucose [1, 2]. The cerebral blood flow time from the common carotid artery to the jugular vein is calculated at 7–9 sec. The flow velocity in the vertebral arteries is slightly lower — it is about 10 sec. However, the contact time of a given blood volume in the cerebral capillaries is only about 0.5–1.0 sec. [1, 2].

The hindbrain is supplied by two vertebral arteries with a small cross-section of 3 to 5 mm, forming the first branches of the subclavian arteries. The vertebral arteries (VA) run their characteristic winding course starting from the subclavian arteries through the canal opened by the transverse processes of the cervical vertebrae from the height of the 6th vertebra to the 2nd vertebra, which means practically to the height of the skull base.

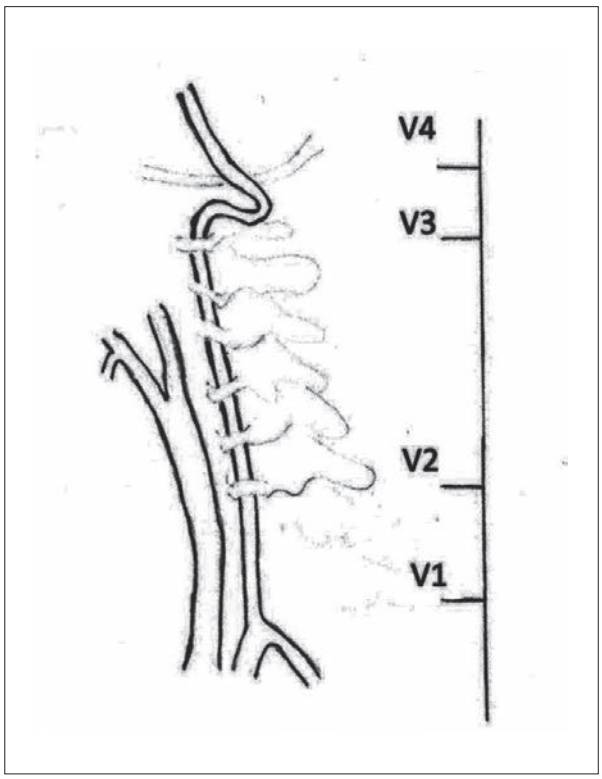

Figure 1. The course of the vertebral artery and its segmentation

Due to the anatomy and from the pathophysiological point of view, the course of each of them is divided into four segments (V1–V4) (Fig. 1). Vertebral arteries are often asymmetric, they narrow gradually, and in 25% of the population they differ in diameter. Hypoplasia in segment V1 is defined as a diameter ≤ 2.5 mm, while ultrasound examination shows a significant decrease in flow velocity compared to the opposite side and an increase in the ipsilateral flow resistance index [3].

Historically, intra-arterial angiography was the "gold standard" in the diagnosis of lesions in both the common carotid (CCA) and internal carotid (ICA) arteries, and in VA. However, because of the potential for angiography-associated stroke, it has been replaced with noninvasive imaging, particularly contrast-enhanced MR (angio MR) and contrast-enhanced CT (angio CT). Both methods allow visualization of the entire vertebrobasilar system. These examination techniques make it possible to detect simultaneously the extracranial and intracranial lesions of the ACC, ACI, and VA, as well as stenosis in the basilar artery. Angio MR provides better visualization of the vertebrobasilar system, especially the proximal VA, than non-contrast MR techniques [4]. A study comparing angio CT, angio MR, and ultrasound for the "gold standard" of endovascular angiography concluded that digital angiography with the use of the new techniques has high sensitivity and specificity and that these methods are superior to ultrasound [5].

The stenotic changes in the form of atherosclerosis or kinking are most common in the first segment, i.e. from the vertebral artery exit to its entry into the canal formed by the transverse processes. In the second segment of VA, stenosis is caused mainly by external compression due to degenerative changes in the vertebrae or disc hernias. The main pathology within the third segment is VA kinks. The terminal segments of VA and the basilar artery are more frequently affected by atherosclerotic lesions. Compared with carotid artery lesions, kinks in these arteries are found in the distal parts of the ICA, whereas atherosclerotic lesions in carotid arteries are most frequent in the CCA division and the proximal segment of the ICA (more than 80%). The posterior and anterior cerebral circulations interconnect in the circle of Willis, which is efficient only in 50% of the population [6].

The vertebrobasilar system supplies blood to centers located in the brainstem, cerebellum, occipital lobes, and (in most patients) inferior temporal lobes and most of the thalamus. When chronic VA stenosis oc-

curs, nonspecific and diverse complaints are diagnosed relatively late [1, 7]. The most common ones include dizziness, binocular visual disturbances, eye movement disturbances, and complete loss of vision (cortical blindness). Less commonly, hemianopia, tinnitus, alternate sensory disturbances, and numbness of the upper extremities are reported. The most characteristic symptoms are sudden, repeated limb movements with falling to the knees with consciousness preserved, so-called "drop attacks", and gait disturbances. The most characteristic symptoms include sudden recurring lower limb floppiness with falling to the knees while maintaining consciousness (so-called "drop attacks") and gait disturbances caused by balance disorders, most often with deviation in the direction in which the hearing is impaired (as under the influence of alcohol). The explanation for these complaints is not simple and often requires the consultation of specialists in ENT, cardiology, and rheumatology [8–10].

In a series of 407 patients with posterior circulation stroke, the most common symptoms included dizziness (47%), unilateral limb weakness (41%), dysarthria (31%), headache (28%), and nausea with vomiting (27%). In another study, the most common symptoms included unilateral limb weakness (38%), gait ataxia (31%), unilateral limb ataxia (30%), dysarthria (28%), and nystagmus (24%) [11]. Chronic vertebrobasilar events may also include symptoms that can be attributed to classic ischemia in terms of anterior cerebral circulation disorders, including unilateral limb weakness or numbness.

Acute incidents in the form of posterior cerebral circulation strokes are much easier to diagnose, though a high percentage ends in death.

In non-invasive diagnostics, a very helpful examination is Doppler ultrasound performed to assess the morphology of lesions and the velocity and direction of flow, as well as to evaluate functional changes in different head positions, especially when the patient may have characteristic symptoms.

Indicators of hemodynamically significant VA stenosis include an increase in flow velocity at the site of stenosis (PSV ≥ 120 cm/s and EDV ≥ 40 cm/s), a marked decrease in velocity downstream of the stenosis, and asymmetry between right and left VA (> 15%), consistent with Doppler imaging. In contrast, retrograde (reflex) flow is indicative of subclavian artery stealth syndrome.

Visualization of the VA outflow from the subclavian artery is not always possible for anatomical reasons. Frequent changes in the caliber of the arteries also make an unambiguous diagnosis difficult. However, VA diameter and flow direction can always be assessed and hypoplasia, stenosis, or vessel occlusion can be distinguished.

On ultrasound, VA is most easily visualized in segment II by initially obtaining a longitudinal section of the CCA and then varying the probe angle toward the anteroposterior plane. The assessment of flow in this segment with head turns provides important information, though it is not always diagnostically sufficient [12].

Magnetic resonance imaging shows greater sensitivity than Computed Tomography without contrast in imaging ischemia and/or infarcts in the lateral segment of the CNS, especially in the brainstem. In identifying infarcts, especially small ones, in the brainstem or cerebellum, the resolution of MRI is higher compared to CT due to its lower susceptibility of the former to artifacts.

Diffusion-weighted imaging (DWI) is recognized as the most sensitive and specific method to observe a stroke minutes after its onset [13].

Indications for treatment

Making a decision regarding invasive treatment in the area of vertebral arteries is difficult. A frequently obscure disease pattern and complex nature of symptoms require detailed multispecialty diagnostics. The risk of stroke in patients with asymptomatic VA stenosis is significantly lower than in patients with symptomatic VA stenosis. The annual risk of stroke was 0.2% in patients with isolated asymptomatic VA stenosis and 0.8% in those with symptomatic VA lesions. The prognosis changes markedly with concomitant carotid artery stenosis.

Indications for treatment are facilitated when lesions are present in both vertebral arteries. It should be noted that blood supply disorders in hindbrain circulation are particularly dangerous and often lead to the patient's death. This has been confirmed by cases of fatal embolism and thrombosis after Blalock surgery.

Conservative treatment

There are virtually no randomized trials regarding the conservative treatment of vertebral arteries. Patients with asymptomatic VA stenosis are routinely given antiplatelet drugs and may be put on statin therapy, similar to patients treated for carotid artery lesions [14].

Surgical treatment

In their 1958 paper, Crawford, DeBakey, and Filds reported four cases of surgical treatment of basilar artery insufficiency. A year later Cate and Scott described the technique of transclavicular access to the vertebral artery for endarterectomy. At the same time, however, reports were dominated by carotid artery surgery and treatment of cases of subclavian artery steal syndrome. The growing experience led to an interesting report by

De Weese in 1973. He discovered that in patients with non-classical symptoms of carotid artery insufficiency, a good surgical result is achieved only in 13% of cases. He put forward a hypothesis that the reason for the lack of good surgical outcome is vertebrobasilar insufficiency. Similar observations began to proliferate and in Polish literature, they were reported by A. Dorobisz.

Even though vertebral artery surgeries are, in a way, challenging, there is a need to perform them in clinical practice. This is a direct result of the increasing number of catastrophic strokes, also in young people after cervical spinal trauma, especially those arising in an overstretched mechanism leading to dissection and thrombotic changes in the vertebral arteries [15].

The first reports on vertebral artery surgery date back to the 19th century: in 1831 Dietrich was the first to propose vertebral artery ligation in the occipital region, whereas in 1833 Velpeau suggested ligation in its proximal segment. In 1853 Maisonneuve ligated the injured vertebral artery at the level of the 6th cervical vertebra. The patient died due to septic embolism one month after the procedure. In 1864, A. Smythe selectively ligated the vertebral artery due to the subclavian artery aneurysm. In 1881 Fenger observed cessation of breathing after ligation of the vertebral artery, and 7 years later, R. Matas successfully ligated the vertebral artery because of an aneurysm between the axis and the atlas vertebrae. In 1882 Alexander from Liverpool ligated vertebral arteries unilaterally and bilaterally to treat epilepsy. In 1946 Elkin and Harris published a report on the ligation of vertebral arteries in 10 cases of arteriovenous fistulas. A year later, However and French reported that ligation of the vertebral artery even on only one side could result in the patient's death due to slowing of blood flow and thrombosis of the basilar artery [16]. In 1959, DeBakey described a method of treating ischemia of the posterior cerebellum, which consisted in inserting a saphenous vein and anastomosing it between the subclavian and vertebral arteries. Technically very difficult, this method allows to achieve good results. VA anastomosis was first performed by Crawford in 1958 and Cate in 1959. However, these procedures led to early thrombosis of the vertebral artery, which can be explained by the small caliber of the vessel. In 1972, Edwards performed a side-to-side anastomosis of the vertebral and common carotid arteries. This procedure is also technically difficult and in clinical follow-up the results were poor, which led to the eventual abandonment of these procedures. In 1976, Cormier described the technique of end-to-side anastomosis of the vertebral artery with the common carotid artery (Fig. 2A). It is now the most commonly performed procedure with very good and durable results [16].

Early post-surgery complication rates are low — up to 2.5% for proximal VA reconstruction, with perioperative mortality rates of 0–4% [16].

Studies suggest the need for early intervention in symptomatic patients. The literature of the subject had often reflected a belief that acute neurological events, such as vertebrobasilar events, had a better prognosis than events in the carotid artery blood supply area. As

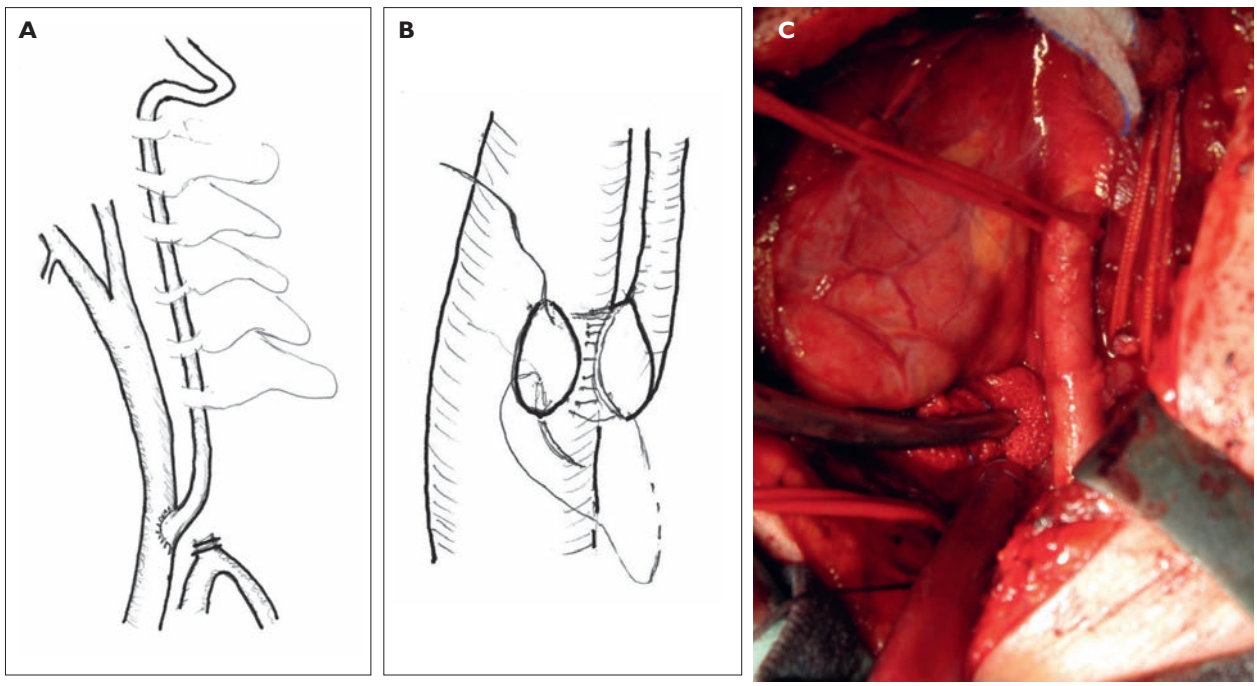

Figure 2A–C. Proximal anastomosis of VA with CCA using P.J. Comier's method

a result, patients were less rigorously screened and did not always receive intensive secondary prevention. However, recent studies suggest that VA stenosis is associated with higher rates of early and recurrent stroke in comparison with symptomatic carotid artery lesions. Evidence from numerous centers suggests that the 90-day risk of recurrent stroke is 7% in patients with no hemodynamically significant VA stenosis, 16% in patients with significant extracranial stenosis in the VA, and 33% in patients with intracranial or basilar artery stenosis. Therefore, the evidence suggests that any intervention in symptomatic patients should be undertaken early after the onset of symptoms [17–19].

Since stenosis of the first vertebral artery segment is most often caused by atherosclerotic lesions or kinking, a detailed morphological and hemodynamic assessment of the carotid arteries is necessary during the qualification for surgery [20, 21].

Material and methods

Between 1994 and 2018, 76 patients diagnosed with vertebrobasilar insufficiency (44 men, 32 women), including 18 patients with vertebral artery stenosis in the first segment, were surgically treated in the Department of Vascular, General, and Transplant Surgery, at Wroclaw Medical University. The remaining patients underwent surgery for a typical vertebrobasilar syndrome with lesions in the 2nd and 3rd segments. The patients' age was between 42 and 65 years (Fig. 3).

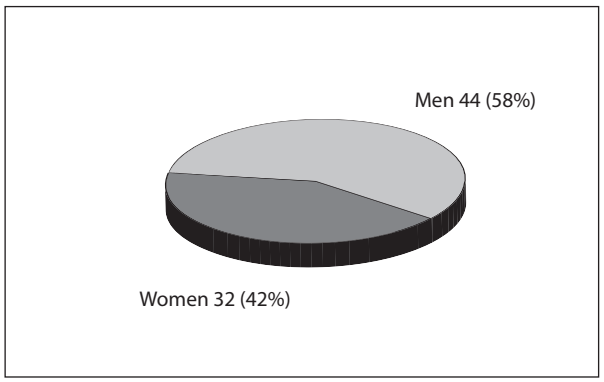

Figure 3. Gender of patients, n (%)

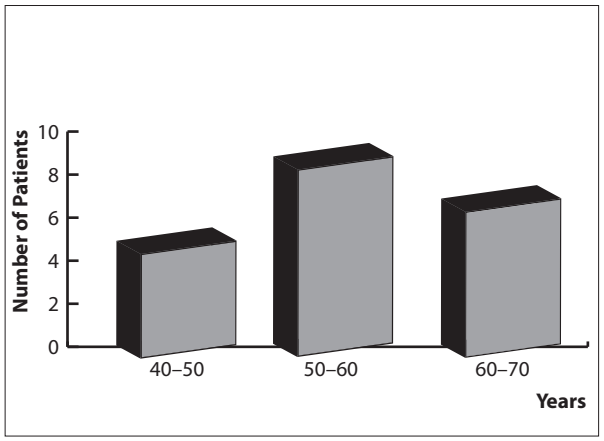

Figure 4. The age of the patients ranged from 42 to 65 years

Results

In the first group of 18 patients, 12 cases revealed coexisting symptomatic stenosis of the internal carotid artery (ICA). In this group, due to concomitant symptoms in the anterior and posterior collateral pathways in the circle of Willis, neurological consultations and an extended panel of examinations resulted in the decision to perform simultaneous surgery to unblock the internal carotid artery and to displace (implant) the vertebral artery into the common carotid artery.

The largest group consisted of patients aged less than 60 years (Fig. 4).

The neurological symptoms presented by the patients are summarized in Table 1.

Table 1. Neurological symptoms presented by patients with proximal VA stenosis

Symptom	n = 18
Dizziness	18
Bilateral visual disturbances	18
Periodic nausea	18
Drop attack	16
Double vision on turning the head	15
Sensory disturbances of the face	10
Visual acuity disorders	12
TIA with unilateral hemiparesis	12

All patients with hemodynamically active internal carotid artery stenosis showed symptoms of transient cerebral ischemic attacks, mostly transient hemiparesis and unilateral visual disturbances.

Angiographic and angio-CT findings in the vertebral and carotid arteries are presented in Table 2.

Table 2. Anatomical changes found in angiography and/or angio-CT

Anatomical changes found	n
Cerebellar stroke	9
Closure of one vertebral artery and stenosis of the other one	10
Bilateral significant vertebral artery stenosis	4
Unilateral lesions on the left vertebral artery	4
Concomitant significant left ICA stenosis	12

All patients reported concomitant multiple neurological symptoms. The most common included headaches, dizziness, balance disorders, periodic nausea, falls with preserved consciousness (drop attacks), skin sensory disturbances, and particularly facial burning and visual disturbances in the form of double vision and

blurred vision. In 9 cases, the patients were treated for a cerebellar stroke and a diagnosed Wallenberg syndrome.

The qualification for surgery was performed in two stages. During the first stage, the general and neurological examination was followed by cervical spine radiography to discover lesions likely to cause compression of the vertebral arteries running in the transverse process channel (degenerative changes, discopathies). This was followed by duplex Doppler examinations carried out to visualize abnormalities of flow through the vertebral arteries (atheromatous stenosis, kinking, occlusions, and abnormalities of flow during head turns). They were performed functionally in the head position in which the patients presented symptoms of insufficiency of the basilar artery and to visualize the carotid arteries. The next examination was meant to determine the blood flow through the vertebral and basilar arteries using the Transcranial Doppler. Measurements were taken in two head positions: straight ahead and in the position in which symptoms of vertebrobasilar insufficiency were present. It was characteristic and significant that during the examination, only half of the patients managed to induce symptoms of hindbrain ischemia [1].

The outpatient evaluation of vertebral artery lesions is not straightforward. Out of 250 patients referred for outpatient diagnostics, 76 were qualified for surgery on the basis of all standard examinations performed. In 18 patients, lesions were found in the first segment of the vertebral artery, while in the remaining patients — in the second and third segments. During hospitalization, the patients underwent Transcranial Doppler, head CT (or MRI), and angiography (including functional CT with head turns). Half of the patients showed changes in head angio-CT in the form of a history of cerebellar stroke and atrophic changes in the posterior cerebellum. Angiographic changes were found in all cases, 21 of which showed occlusion of one vertebral artery and stenotic changes in the other. The remaining cases showed bilateral stenotic lesions, often accompanied by hypoplasia of one of the arteries.

Surgical procedures for the first segment of the vertebral artery are undoubtedly more difficult technically than procedures to revascularize the carotid artery, This is clearly the main reason why surgery to treat symptomatic stenosis is less frequently undertaken. The procedure should be performed with the use of loupes and under general anesthesia. Access is gained from a similar incision as for the carotid artery, i.e. along with the sternocleidomastoid muscle, and often requires its partial transection. The view is obtained between the common carotid artery and the internal jugular vein. Once the lymphatic duct is exposed, it should be carefully ligated to avoid lymphothorax, which is often difficult to treat. After ligation of the vertebral veins, the vertebral artery is exposed as the first shunt of the subclavian artery. Once the common carotid artery (CCA) and internal carotid artery (ICA) (and vertebral and subclavian arteries for safety reasons) are captured in surgical loops, several types of procedures can be performed, including the transposition to the CCA, reimplantation of VA into the subclavian artery, or insertion of a saphenous vein insert from the VA to the subclavian artery. At this stage, the common carotid artery and its division were always palpated for safety reasons after clamping the internal carotid artery. In 12 cases, significant narrowing of the internal carotid artery was confirmed. The ICA was revascularized using the flow shunt. In all patients, the VA was sutured to the side of the CCA.

When significant stenosis of the ICA was discovered, the first procedure involved its revascularization. A long flow drain was inserted from ICA to the aortic arch. This was followed by the revascularization of the division of the CCA into the ICA and this stage of the procedure was completed by suturing the artery and inserting a patch. Subsequently, the vertebral artery was cut off at the subclavian artery and its distal end was sewn end-to-side to the common carotid artery. Towards the end of the suturing procedure, the flow drain was removed and the retrograde outflow from the carotid arteries was controlled following the principles of clamp removal similar to the endarterectomy of the ICA alone. After removing the flow drain, the vascular suture was completed. The blood flow was first directed to the external carotid artery, then to the vertebral artery, and finally to the internal carotid artery to avoid the possibility of microembolism. In procedures limited to the implantation of the VA, the flow drain was also placed in the CCA, although it was shorter and reached distally half of the ACC length.

Table 3. Early results of surgical treatment

	Cessation of symptoms	Improvement	No improvement	Deterioration
No history of stroke		8	1	0
A history of cerebellar stroke	9	8 (90%)	0	0

Table 4. Distant results of surgical treatment

	Cessation of symptoms	Improvement	No improvement	Deterioration
No history of stroke	9	9	0	0
A history of cerebellar stroke	9	7 (80%)	2	0

Treatment outcomes

Early treatment results (up to 4 weeks after surgery) are shown in Table 3.

Nine patients without cerebrovascular lesions and nine patients after an ischemic stroke were operated for insufficient cerebrovascular circulation. Preoperative angiographic examination revealed atherosclerotic lesions of the arteries in 14 patients, while in four patients ischemia was a result of kinking of vertebral arteries (Table 4).

Further follow-up was conducted on an outpatient basis, with the shortest period of follow-up being three years. Follow-up examinations included not only the history and neurological examination but also USG-DD-ultrasound of cephalic arteries. In this group, a very good (complete remission of symptoms) or good (partial remission of symptoms) postoperative effect was achieved in 16 cases. Patients reported complete remission of extremely bothersome symptoms of the disease. Those with previous cerebellar strokes reported partial remission of symptoms, while all patients reported reduced but still persistent dizziness and periodic facial burning as an expression of sensory disturbances. This group of patients showed a significant increase in the comfort of life, with complete resolution of visual disturbances. In two cases, the symptoms persisted. The lack of improvement may be attributed to the established neurological changes. No new neurological symptoms developed as a perioperative complication in any case, nor did any patient die of other causes. In all patients, an ultrasound examination showed normal patency of anastomoses of the vertebral artery with the common carotid artery. There was no evidence of internal carotid artery restenosis.

Conclusions

According to the presented data, the efficacy of arterial revascularization can be described as high. The long-term follow-up (up to nine years) showed a good effect or clinical improvement in almost all cases; a poor early result (no improvement) was obtained in one case. The efficacy of proximal vertebral artery anastomoses, especially the preserved patency, confirms the good surgical outcome. A very good result obtained in 12 patients with concomitant internal carotid artery stenosis indicates the feasibility and high safety of combined procedures. Anastomosis of the common carotid artery and vertebral artery has resulted in the complete remission of neurological symptoms.

Our results allow for a conclusion that proximal anastomosis of the common carotid and vertebral arteries is an effective method of treatment of vertebrobasilar insufficiency resulting both from atherosclerotic lesions of the vertebral arteries and their kinking. The qualification for the procedure is relatively difficult and must be based on angiography, whereas non-invasive methods are not fully reliable and should be, therefore, treated as auxiliary. We believe, however, that with increasing experience, ultrasound methods will also allow for a proper assessment. Unfavorable results of stenting, especially of vertebral arteries, demonstrated in our study, indicate the necessity to rely on surgical treatment [22, 23].

Conflict of interest

None.

References:

1. Huber P. Stenosierende und oblitierende zerebrale Gefässprozesse. In: Diethelm L, Henck F, Olssen S, Strand S, Vieten H, Zuppinger A. ed. Handbuch der medizinischen radiologie. Springer Verlag, Berlin – Heidelberg 1981: 571.
2. Lübbers DW. Physiologie der Gehirndurchblutung. In: Gänschirt HW. ed. Der Hirnkreislauf. Thieme Verlag, Stuttgart 1972.
3. Hua Y, Meng XF, Jia LY, et al. Color Doppler imaging evaluation of proximal vertebral artery stenosis. AJR Am J Roentgenol. 2009; 193(5): 1434–1438, doi: 10.2214/AJR.09.2624, indexed in Pubmed: 19843764.
4. Khan S, Cloud GC, Kerry S, et al. Imaging of vertebral artery stenosis: a systematic review. J Neurol Neurosurg Psychiatry. 2007; 78(11): 1218–1225, doi: 10.1136/jnnp.2006.111716, indexed in Pubmed: 17287234.
5. Yurdakul M, Tola M. Doppler criteria for identifying proximal vertebral artery stenosis of 50% or more. J Ultrasound Med. 2011; 30(2): 163–168, doi: 10.7863/jum.2011.30.2.163, indexed in Pubmed: 21266553.
6. Pitts FW. Variations of collateral circulation in internal carotid occlusion. Comparison of clinical and x-ray findings. Neurology. 1962; 12: 467–471, doi: 10.1212/wnl.12.7.467, indexed in Pubmed: 14038389.
7. Parkinson D. Collateral circulation of cavernous carotid artery. Can J Surg. 1964; 7: 251–268, indexed in Pubmed: 14176972.

8. Piton J, Caille M. Anastomoses carotido–carotidiennes chez l humane. J Radiol Elekreol. 1971; 52: 447.
9. Schechter MM, Zingesser LH. The radiology of basilar thrombosis. Radiology. 1965; 85: 23–32, doi: 10.1148/85.1.23, indexed in Pubmed: 14303067.
10. Szapiro J. Z zagadnienia fizjopatologii krążenia krwi w mózgu. Łódzkie Tow. Nauk. 1960.
11. Searls DE, Pazdera L, Korbel E, et al. Symptoms and signs of posterior circulation ischemia in the new England medical center posterior circulation registry. Arch Neurol. 2012; 69(3): 346–351, doi: 10.1001/archneurol.2011.2083, indexed in Pubmed: 22083796.
12. Khan S, Cloud GC, Kerry S, et al. Imaging of vertebral artery stenosis: a systematic review. J Neurol Neurosurg Psychiatry. 2007; 78(11): 1218–1225, doi: 10.1136/jnnp.2006.111716, indexed in Pubmed: 17287234.
13. Khan S, Rich P, Clifton A, et al. Noninvasive detection of vertebral artery stenosis: a comparison of contrast-enhanced MR angiography, CT angiography, and ultrasound. Stroke. 2009; 40(11): 3499–3503, doi: 10.1161/STROKEAHA.109.556035, indexed in Pubmed: 19762707.
14. Compter A, van der Worp HB, Algra A, et al. Second Manifestations of ARTerial disease (SMART) Study Group. Prevalence and prognosis of asymptomatic vertebral artery origin stenosis in patients with clinically manifest arterial disease. Stroke. 2011; 42(10): 2795–2800, doi: 10.1161/STROKEAHA.110.612903, indexed in Pubmed: 21852605.
15. Carney AL. Vertebral Artery Surgery: Historial Development Basic Concepts of Brain Hemodynamics and Clinical Experiens of 102 cases. In: Advances in Neurology, vol. 30. Diagnosis and Treatment of Brain Ischemia. Raven Press, New York, 1981, 250.
16. Dorobisz A. Badania nad skutecznością chirurgicznego leczenia niedokrwienia mózgu. In: Wrocław, Akad. Med., 1996; 109. Rozprawy Habilitacyjne Akademii Medycznej we Wrocławiu; 4/1996.
17. Gulli G, Marquardt L, Rothwell PM, et al. Stroke risk after posterior circulation stroke/transient ischemic attack and its relationship to site of vertebrobasilar stenosis: pooled data analysis from prospective studies. Stroke. 2013; 44(3): 598–604, doi: 10.1161/STROKEAHA.112.669929, indexed in Pubmed: 23386676.
18. Kieffer E, Praquin B, Chiche L, et al. Distal vertebral artery reconstruction: long-term outcome. J Vasc Surg. 2002; 36(3): 549–554, doi: 10.1067/mva.2002.126092, indexed in Pubmed: 12218980.
19. Berguer R, Morasch M, Kline R. A review of 100 consecutive reconstructions of the distal vertebral artery for embolic and hemodynamic disease. Journal of Vascular Surgery. 1998; 27(5): 852–859, doi: 10.1016/s0741-5214(98)70265-4.
20. Dorobisz AT. Langzeitergebnisse der operativen Behandlung des vertebrobasilären Syndroms. Zentralblatt für Chirurgie. 2006; 131(1): 3–7, doi: 10.1055/s-2006-921406.
21. Writing Group: A.R. Naylor and all, Editor's Choice – Management of Atherosclerotic Carotid and Vertebral Artery Disease: 2017 Clinical Practice Guidelines of the European Society for Vascular Surgery (ESVS). 2018; 55(1): 3–81.
22. Gargiulo G, Sannino A, Stabile E, et al. New cerebral lesions at magnetic resonance imaging after carotid artery stenting versus endarterectomy: an updated meta-analysis. PLoS One. 2015; 10(5): e0129209, doi: 10.1371/journal.pone.0129209, indexed in Pubmed: 26017678.
23. Stayman AN, Nogueira RG, Gupta R. A systematic review of stenting and angioplasty of symptomatic extracranial vertebral artery stenosis. Stroke. 2011; 42(8): 2212–2216, doi: 10.1161/STROKEAHA.110.611459, indexed in Pubmed: 21700936.

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Evaluation of the predictive role of standard laboratory tests for disease severity in patients with deep venous thrombosis

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Abstract

Introduction: *Deep venous thrombosis (DVT) can result in fatal outcomes if it is not timely diagnosed and sufficiently treated. Some laboratory markers were identified in previous reports for predicting the disease with low sensitivity or specificity. We aimed to evaluate the predictive value of serum albumin levels and compare them with conventional laboratory parameters.*

Material *and methods: Fifty patients with acute lower-extremity DVT who has no previous history of malignancy or hematologic disorder were included in the study. The demographical variables and standard biomarkers of the DVT group were compared with the normal population (n:50). Thereafter patients were divided into two groups extensive DVT (thrombosis involves popliteal, femoral, and iliac veins together) and localized DVT (thrombosis involves popliteal vein and below) and biomarkers were compared in patient groups.*

Results: *The demographical variables and white blood cell count (WBC) were found as similar between healthy groups and DVT groups. However, mean platelet volume (MPV), D-Dimer, neutrophil to lymphocyte ratio (NLR), and fibrinogen to albumin ratio (FAR) were found markedly higher in DVT patients. Moreover, statistically incremental FAR and NLR levels were detected ($p < 0.05$) in patients with extensive DVT (involved iliac and femoral veins).*

Conclusion: *Serum NLR and FAR levels seem to be significant predictors for the extensive thrombotic event in patients with DVT.*

Key words: deep venous thrombosis, extensive disease, neutrophil to lymphocyte ratio, fibrinogen to albumin ratio

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Introduction

Deep venous thrombosis (DVT) is an important pathology that can progress with highly mortal and morbid outcomes such as pulmonary thromboembolism (PTE) or post-thrombotic syndrome (PTS). Therefore, timely diagnosis and appropriate treatment are necessary for avoiding adverse outcomes [1, 2]. The most simple and definitive diagnoses of this disorder can be confirmed with Doppler ultrasonography. Ultrasonography is a reliable method but not objective [2]. Thus, researchers tried to determine an objective laboratory marker that

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is highly specific and scientific for venous thrombosis. However, any powerful diagnostic laboratory marker to confirmation and follow up the progression of the disease has not been identified [2, 3]. Fibrinogen and D-dimer are commonly studied laboratory parameters in DVT and its complications. Higher levels of these parameters are useful to determine for uncertain patients with precursor symptoms. Despite, higher sensitivity, fibrinogen, and D-dimer are not sufficiently specific for DVT [3, 4]. New parameters were investigated for serving this purpose. Especially, some recent studies were focused on indicators for the tendency of disease and extensive thrombosis burden such as lower albumin levels [5].

In the current study, we aimed to investigate the standard laboratory parameters in DVT and evaluate the predictive role of these biomarkers in progressive disease.

Material and methods

This prospective study was approved by the local ethical committee of the University (2019-7-17). All protocols of the study were conducted according to Helsinki Declaration and in adherence to local guidelines for good clinical practice. Written informed consent was obtained from each participant. After the designation of the study, 50 healthy control subjects and patients with acute DVT (after major surgery or trauma or etc.) were included in the study. Patients with malignancy, hematologic disorder or previous recurrent DVT were excluded from the study. Totally, 50 DVT patients were enrolled in the study. Patients were divided into two subgroups as extensive DVT [n:26] (thrombosis involves popliteal, femoral, and iliac veins together) and localized DVT [n:24] (thrombosis involves popliteal vein and below) in accordance to Doppler ultrasound findings. Thereafter, Demographic data (age, sex) and some routine blood parameter [Neutrophil to Lymphocyte ratio (%), mean platelet volume [MPV] (fL), white blood cell [WBC] (10^{-3}/uL), Platelet (10^{-3}/uL), D-dimer (ng/L), Fibrinogen to albumin ratio [FAR] (%), Neutrophil to Lymphocyte ratio [NLR] (%)] values compared between healthy and DVT groups. Finally, the same parameters were compared in localized and extensive DVT subgroups.

Statistical analyze

Data analysis was applied SPSS software program (ver. 15.0, Chicago, Illinois). Categorical variables were expressed as percentages and continuous values were given as mean ± SD. Normally distributed variables compared with Kolmogorov Smirnov and Shapiro-Wilk tests. Student T-test was used for single analysis and variables were determined differently in single analyzes compared with univariate and multivariate tests. Receiver operator characteristic (ROC) curve analysis was used to detect the optimal cut-off value for serum biomarkers for identifying extensive thrombosis with expressing maximum sensitivity and specificity. The area under the curve (AUC) was used to determine the accuracy of the test. P-value smaller than 0.05 was considered significant.

Results

Age and sex distributions were similar in the healthy and the DVT groups (Table 1). Similarly, the white blood cell counts (WBC) were insignificant between these groups ($p > 0.05$). Contrarily, platelet count, mean platelet volume (MPV), D-Dimer, neutrophil to lymphocyte ratio (NLR), and fibrinogen to albumin ratio (FAR) were markedly higher in DVT group, when compared with healthy subjects (Table 2). Especially, statistically incremental MPV (9.7 ± 1.3), NLR (3.5 ± 1.6), and FAR (114.8 ± 33.5) values were detected in DVT group ($p = 0.000$). The multiple regression analysis (Table 3) revealed that FAR and MPV values are the most significant parameters in DVT group ($p = 0.000$).

In subgroup analyses, WBC, platelet count, FAR, and NLR values were statistically significant in the extensive DVT group ($p < 0.05$). The comparisons of serum parameters between subgroups were presented in Table 4. The ROC curve analyses of platelet count, WBC, NLR, and FAR values to predict extensive deep venous thrombosis were presented in Figure 1. The optimal cut-off value of NLR levels was found as 3.15% for predicting extensive thrombosis in DVT with 73.1%

Table 1. The demographical comparison of healthy subjects and patient group

	Normal n:50	DVT* n:50	p**
Age mean±SD	58.18 ± 15.81	53.42 ± 11.70	0.68
Sex Male/n:%	26 (52%)	29 (58%)	0.90

*DVT: Deep venous thrombosis; **$p < 0.05$ is considered statistically significant

Table 2. The comparison of biochemical markers between healthy subjects and patient group

	Normal n:50	DVT n:50	p
MPV	9.7 ± 1.3	7.9 ± 1.6	0.000
WBC	8.4 ± 2.89	7.6 ± 2.4	0.137
Platelet	289.9 ± 96.2	241.9 ± 75.4	0.007
D-Dimer	2099.9 ± 5085.2	11.01 ± 11.3	0.005
Fibrinogen to albumin ratio	114.8 ± 33.5	75.8 ± 31.7	0.000
Neutrophil to lymphocyte ratio	3.5 ± 1.6	2.1 ± 1.4	0.000

DVT: deep venous thrombosis; MPV: mean platelet volume; WBC: white blood cell; $p < 0.05$ is considered statistically significant

Table 3. The multiple regression analyze of biochemical markers

	B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
							Lower	Upper
MPV	1.186	.258	21.155	1	.000	3.274	1.975	5.427
Platelet	.011	.005	4.721	1	.030	1.011	1.001	1.021
Fibrinogen to albumin ratio	.050	.012	18.081	1	.000	1.052	1.028	1.077

MPV: mean platelet volume; $p < 0.05$ statistically significant

Table 4. Analyze of biochemical markers in popliteal DVT and extensive (popliteal+femoral+iliac) DVT patients.

	Group	N	Mean	Standard Deviation	p
MPV	Popliteal	24	9.6896	1.50607	0.735
	Extensive	26	9.8185	1.16526	
WBC	Popliteal	24	7.5667	2.36388	0.044
	Extensive	26	9.2065	3.15215	
Platelet	Popliteal	24	259.4583	80.66785	0.030
	Extensive	26	318.1154	102.28209	
Fibrinogen to albumin ratio	popliteal	24	89.4650	19.60465	0.001
	Extensive	26	138.3073	25.62590	
Neutrophil to lymphocyte ratio	popliteal	24	2.8529	1.38346	0.007
	Extensive	26	4.1058	1.74225	
D-Dimer	Popliteal	24	2785	7137	0.985
	Extensive	26	1374	1634	

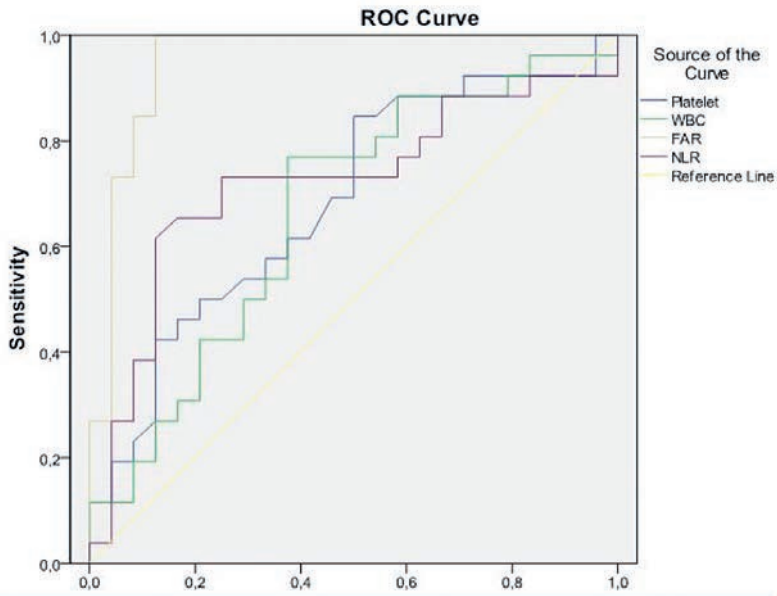
MPV: mean platelet volume; WBC: white blood cell; $p < 0.05$ is considered statistically significant

sensitivity and 75.0% specificity. The optimal cut-off value of FAR levels was found as 110.30 % for predicting extensive thrombosis in DVT with 84.6% sensitivity and 91.7% specificity.

Conclusions

Despite the pro-thrombotic parameters described in many studies in patients with DVT, the routine serum biomarkers were not completely evaluated for detecting the severity of the disease. According to our knowledge, it is the first study that investigated the relationship between extensive DVT and FAR levels. Our findings demonstrated that serum NLR and FAR levels could be related to the burden of disease in a patient with DVT. In another perspective, DVT can be presented with extensive thrombosis in patients with higher NLR and FAR levels. Additionally, serum FAR levels were found as quite sensitive for thrombosis burden in patients with DVT.

Because of the close interaction between thrombosis and inflammation, complete blood counting parameters were investigated the thrombotic cardiovascular events formerly [6, 7]. The determinants



Area Under the Curve

Test Result Variable(s)		Area	Std. Error[a]	Asymptotic Sig.[b]	Asymptotic 95% Confidence Interval	
					Lower Bound	Upper Bound
–	Platelet	,685	,076	,025	,536	,834
	WBC	,665	,078	,045	,512	,818
	FAR	,952	,033	,000	,000	1,000
	NLR	,720	,076	,008	,572	,869

The test result variable(s): Platelet, NLR has at least one tie between the positive actual state group and the negative actual state group. Statistics may be biased.

a. Under the nonparametric assumption

b. Null hypothesis: true area = 0.5

Figure 1. ROC analysis of the serum WBC, platelet, NLR, and FAR levels for prediction of extensive disease in the deep venous thrombosis

of thrombogenesis and thrombus resolution should be completely understood for the protection and treatment of venous thrombosis. It was previously demonstrated that the extravasation of inflammatory agents can provide more quick resolution of thrombi in experimental models with primates [8]. On the other hand, recent reports indicate that classic serum parameters give brief reflections about the acute thrombotic events, as follows; increased MPV was shown as a potential predictor of high platelet activation and reactivity in thrombotic disorders, white blood cells and their subtypes delineates increased atherosclerotic and thrombotic vascular occlusions in cardiovascular events, neutrophil to lymphocyte ratio (NLR) newly identified expression of the inflammatory process was demonstrated as an independent indicator for cardiovascular mortality, and etc. [7]. Higher MPV values were reported in patients with DVT when compared with healthy controls [9]. Moreover, it was claimed that MPV is an independent predictor of thrombus burden in coronary artery thrombosis [10]. However, we could not detect any difference between distal DVT and extensive DVT. Similarly, neutrophil to lymphocyte ratio (NLR), red cell distribution width (RDW), and other inflammatory markers were investigated in the ST-segment elevation myocardial infarction patients with a high thrombus burden. RDW and NLR were detected as potential predictors of coronary thrombus burden [11, 12]. Furthermore, it was claimed that NLR increased could identify the risk population for venous thrombosis as total knee arthroplasty [13]. Despite WBC levels being similar between the healthy control group and DVT patients, MPV, D-Dimer, platelet, NLR values were statistically higher in DVT patients. Incidentally, WBC, platelet, NLR, FAR levels were found as markedly increased in a subgroup with extensive DVT (both iliac and femoral involvement) patients.

D-dimer and fibrinogen are other important predictors for venous thrombosis. D-dimer fibrin degradation product is a quantitative measurement of fibrinolysis

that is commonly investigated in venous thrombosis. Fibrinogen is suspected as a modulator of the structural properties of fibrin gel formation that are presented in DVT. Also, fibrinogen levels were investigated together with D-dimer levels in DVT. However, the specificity of these markers is quite low for the thrombotic process [13, 14]. Even some recent reports claimed that increased fibrinogen levels were not associated with DVT risk, but it can be related to thrombus fragmentations which can be associated with high pulmonary embolism risk [14]. In this context, higher fibrinogen levels may not reflect the burden of disease but it can be associated with thrombi fracture formations [14]. Albumin is another serum marker that can directly associate with blood viscosity and thrombogenesis. Also, lower plasma albumin concentrations were reported with higher venous thrombosis risk [15]. In another view, acute lower albumin levels were suspected as a reflection of inflammatory status which linked with venous thrombosis and embolism like an acute phase reactant [15, 16]. Namely, lower albumin levels were suggested as a predictor of venous thromboembolism [16]. To obtain a more sensitive marker serum fibrinogen to albumin ratio evaluated in other types of cardiovascular events. It was speculated that fibrinogen and albumin as hemorheological markers will have more significant and specific predictive potentials if they are considered together [17, 18]. Karahan et al. [18] indicated that the fibrinogen to albumin ratio might reflect the severity of disease in patients with venous insufficiency. Similarly, we found higher FAR levels in both comparison healthy vs. DVT groups and popliteal vs. extensive DVT subgroups ($p = 0.000$). Moreover, higher D-dimer levels were detected in patients with extensive disease ($p = 0.005$). Additionally, higher FAR levels were demonstrated as highly sensitive (84.6%) and highly specific (91.7%) for the burden of thrombosis with a cut-off point value of 110.30 g/dL.

To sum up, we found higher MPV, platelet, D-Dimer, NLR, and FAR levels in patients with DVT. Furthermore, incremental WBC, platelet, NLR, and FAR values were found as related to extensive disease. Especially, higher NLR and FAR seem to be highly related to extensive disease in DVT. Serum NLR and FAR levels can be related to progressive disease and these markers should be investigated with more detailed studies as a predictor of extensive disease or thrombosis burden.

Conflict of interest

None.

References:

1. Riddle DL, Hillner BE, Wells PS, et al. Diagnosis of lower-ex
2. References:
3. Thachil J. Deep vein thrombosis. Hematology. 2014; 19(5): 309–310, doi: 10.1179/1024533214Z.000000000284, indexed in Pubmed: 24939044.
4. Baglin T. Using the laboratory to predict recurrent venous thrombosis. Int J Lab Hematol. 2011; 33(4): 333–342, doi: 10.1111/j.1751-553X.2011.01345.x, indexed in Pubmed: 21692994.
5. Riddle DL, Hillner BE, Wells PS, et al. Diagnosis of lower-extremity deep vein thrombosis in outpatients with musculoskeletal disorders: a national survey study of physical therapists. Phys Ther. 2004; 84(8): 717–728, indexed in Pubmed: 15283622.
6. Rabinovich A, Cohen JM, Cushman M, et al. Inflammation markers and their trajectories after deep vein thrombosis in relation to risk of post-thrombotic syndrome. J Thromb Haemost. 2015; 13(3): 398–408, doi: 10.1111/jth.12814, indexed in Pubmed: 25495610.
7. Aydın U. Is low serum albumin level a risk factor for deep venous thrombosis in temporary hemodialysis catheter inserted patients? Turkish Journal of Thoracic and Cardiovascular Surgery. 2013; 21(4): 955–958, doi: 10.5606/tgkdc.dergisi.2013.7721.
8. Rezende SM, Lijfering WM, Rosendaal FR, et al. Hematologic variables and venous thrombosis: red cell distribution width and blood monocyte count are associated with an increased risk. Haematologica. 2014; 99(1): 194–200, doi: 10.3324/haematol.2013.083840.
9. Byrnes JR, Wolberg AS, Walton BL, et al. Fibrinogen and red blood cells in venous thrombosis. Thromb Res. 2014; 133 Suppl 1(16): S38–S40, doi: 10.1016/j.thromres.2014.03.017, indexed in Pubmed: 24759140.
10. Wakefield TW, Strieter RW, Schaub R. Venous thrombosis prophylaxis by inflammatory inhibition without anticoagulation therapy. J Vasc Surg. 2000; 31(2): 309–324, doi: 10.1016/s0741-5214(00)90162-9, indexed in Pubmed: 10664500.
11. Gulcan M, Varol E, Etli M, et al. Mean platelet volume is increased in patients with deep vein thrombosis. Clin Appl Thromb Hemost. 2012; 18(4): 427–430, doi: 10.1177/1076029611427437, indexed in Pubmed: 22110160.
12. Lai HM, Xu R, Yang YN, et al. Association of mean platelet volume with angiographic thrombus burden and short-term mortality in patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention. Catheter Cardiovasc Interv. 2015; 85 Suppl 1: 724–733, doi: 10.1002/ccd.25860, indexed in Pubmed: 25630273.
13. Tanboga IH, Topcu S, Aksakal E, et al. Determinants of angiographic thrombus burden in patients with ST-segment elevation myocardial infarction. Clin Appl Thromb Hemost. 2014; 20(7): 716–722, doi: 10.1177/1076029613483169, indexed in Pubmed: 23539672.
14. Erkol A, Oduncu V, Turan B, et al. Neutrophil to lymphocyte ratio in acute ST-segment elevation myocardial infarction. Am J Med Sci. 2014; 348(1): 37–42, doi: 10.1097/MAJ.0000000000000188, indexed in Pubmed: 24172233.
15. Barker T, Rogers VE, Henriksen VT, et al. Is there a link between the neutrophil-to-lymphocyte ratio and venous thromboembolic events after knee arthroplasty? A pilot study. J Or-

thop Traumatol. 2016; 17(2): 163–168, doi: 10.1007/s10195-015-0378-3, indexed in Pubmed: 26387114.

16. Canan A, Halıcioğlu SS, Gürel S. Mean platelet volume and D-dimer in patients with suspected deep venous thrombosis. J Thromb Thrombolysis. 2012; 34(2): 283–287, doi: 10.1007/s11239-012-0746-2, indexed in Pubmed: 22588535.
17. Klovaite J, Nordestgaard BG, Tybjærg-Hansen A, et al. Elevated fibrinogen levels are associated with risk of pulmonary embolism, but not with deep venous thrombosis. Am J Respir Crit Care Med. 2013; 187(3): 286–293, doi: 10.1164/rccm.201207-1232OC, indexed in Pubmed: 23220916.
18. Joven J, Clivillé X, Camps J, et al. Plasma protein abnormalities in nephrotic syndrome: effect on plasma colloid osmotic pressure and viscosity. Clin Chem. 1997; 43(7): 1223–1231, indexed in Pubmed: 9216460.
19. Folsom AR, Lutsey PL, Heckbert SR, et al. Serum albumin and risk of venous thromboembolism. Thromb Haemost. 2010; 104(1): 100–104, doi: 10.1160/TH09-12-0856, indexed in Pubmed: 20390234.
20. Sapmaz I, Saba T, Haberal C, et al. Fibrinogen- Albumin Ratio: An Intriguing Relationship for Assessing Trombosis Risk and Suspicious Effect on Blood viscosity. International Cardiovascular Research Journal. 2011; 5(4): 153–154, doi: 10.5812/icrj.4418.
21. Karahan O, Yavuz C, Kankilic N, et al. Simple blood tests as predictive markers of disease severity and clinical condition in patients with venous insufficiency. Blood Coagul Fibrinolysis. 2016; 27(6): 684–690, doi: 10.1097/MBC.0000000000000478, indexed in Pubmed: 26650463.

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Serum soluble lectin-like oxidized low-density lipoprotein receptor-1 as a diagnostic marker for acute ST-elevation myocardial infarction

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Abstract

Introduction: *ST-elevation myocardial infarction (STEMI) is a major cause of mortality and morbidity worldwide, but fast and reliable diagnosis can reduce mortality. Therefore, this study aimed to assess the diagnostic value of serum soluble lectin-like oxidized low-density lipoprotein receptor-1 (sLOX-1) among patients with acute STEMI, and also its importance to monitor the response to percutaneous coronary intervention (PCI). A total of 30 healthy subjects and 150 acute STEMI patients treated by PCI were enrolled into our study. Besides the routine lab work, serum sLOX-1 level was measured using a commercial ELISA kit.*

Results: *Our results revealed the increased serum sLOX-1 level among patients with acute STEMI (112.79 ± 10.76) than controls (47.75 ± 12.87). After the treatment of acute STEMI patients with the primary PCI, the level of serum sLOX-1 was not sigificantly decreased either after 12 hrs (111.04 ± 11.06) or 48 hrs (110.31 ± 11.24) from PCI management. Our results also showed that serum sLOX-1 level was positively correlated with cholesterol, LDL, troponin I, CK-MB, CRP, TG, and VLDL. Results obtained from ROC curve analysis showed that serum sLOX-1 is an excellent biomarker for acute STEMI disease, its AUC is one with 100% sensitivity and specificity.*

Conclusions: *Finally, from these results, we can conclude that LOX-1 has a crucial role in the pathogenesis of acute STEMI; also, serum sLOX-1 could be a good diagnostic clinical biomarker for the detection of acute STEMI disease and to monitor the response to PCI.*

Key **words:** acute coronary syndrome (ACS), coronary heart disease, lectin-like oxidized low-density lipoprotein receptor-1 (LOX-1), percutaneous coronary intervention (PCI), myocardial infarction (MI), ST-elevation myocardial infarction (STEMI)

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Introduction

Acute coronary syndrome (ACS) is a type of coronary heart disease and refers to a spectrum of conditions that range from non-ST elevation myocardial infarction (NSTEMI), and unstable angina to ST-elevation myocardial infarction (STEMI) [1]. ACS is considered a major cause of mortality and morbidity and accounts for more than 2.5 million hospitalizations annually worldwide [2]. An acute ST-elevation myocardial infarction (STEMI) is a disease in which myocardial injury or necrosis is caused by transmural myocardial ischemia.

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The current 2018 clinical definition of myocardial infarction (MI) needs myocardial ischemic injury confirmation by abnormal cardiac biomarkers associated with ECG changes and chest pain [3]. The management of ACS patients is a global challenge to clinicians and healthcare systems [4]. Percutaneous coronary intervention (PCI) with a coronary stent is considered as a major standard-of-care procedure in the manipulation of angina or ACS worldwide [5].

Lectin-like oxidized low-density lipoprotein receptor-1 (LOX-1) belongs to class E scavenger transmembrane receptor that mainly binds oxidized low-density lipoprotein (ox-LDL) [6]. It is 50-kDa glycoproteins consisting of 4 domains: a short N-terminal cytoplasmic domain, a transmembrane domain, a neck domain, and a lectin-like extracellular C-terminal domain which binds with OxLDL [7]. The extracellular domain of LOX-1 proteolytically cleaved generating soluble LOX-1 (sLOX-1) which released into the bloodstream reflecting the expression of LOX-1 [8]. It was found that sLOX-1 was elevated in acute coronary syndromes and stable coronary disease in which sLOX-1 can distinguish the disease severity and monitor response to treatment [9].

Therefore, this is a case-control study aimed to assess the importance of the use of sLOX-1 as a diagnostic maker and also its importance to monitor the response to PCI with a coronary stent in acute STEMI patients.

Material and methods

Ethics statement

The current study was approved by the ethics committees of El-Demerdash Hospital, Faculty of Medicine, Ain Shams University. Informed consent were obtained from all patients. All procedures performed in this study were in accordance with the ethical standards of the ethics committees of the Faculty of Medicine, Ain Shams University, and also Helsinki Declaration.

Human subjects

The current study was conducted on 30 healthy controls and 150 patients with acute STEMI treated by PCI. All patients were successfully revascularized achieving normal coronary blood flow during the PCI procedure. All study subjects were investigated for age, gender, body mass index (BMI), and blood pressure. Laboratory tests were conducted at admission, including blood levels of random blood sugar (RBS), C-reactive protein (CRP), triglycerides (TG), high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), and very low-density lipoprotein cholesterol (VLDL) levels in all study subjects. Blood samples were collected before the PCI procedure (zero time), and repeated after 12, and 48 hours from PCI for all patients.

Measurement of sLOX-1

Serum sLOX-1 concentration was measured using Human sLOX-1 ELISA Kit (cat# E1424Hu) (BIOTECH, Inc., China) according to the manufacturer's instructions.

Statistical analysis

Statistical analysis was performed using SPSS software (version 20.0; SPSS Inc., Chicago, Illinois, USA), and Quantitative data were expressed as mean ± standard deviation (SD). Qualitative data were expressed as frequency and percentage. Comparison between estimated parameters was done by means of independent-samples T-test. Pearson's correlation coefficient was used to determine significant correlations of sLOX-1 and other clinical parameters. The Receiver Operating Characteristic curve (ROC curve) was used to calculate the area under the curve (AUC) of serum sLOX-1 in order to evaluate its sensitivity and specificity as a biomarker for the detection of acute ST-elevation myocardial infarction. The criterion for significance was $p<0.05$.

Results

Demographic and biochemical data of acute STEMI patients

The current study included 150 acute STEMI patients treated with PCI; 92 male and 58 female; with mean age 48.40 ± 10.82 years; the clinical and biological data of healthy subjects and acute STEMI patients are summarized in Table 1.

Data obtained from laboratory routine work of acute STEMI patients revealed a highly significantly ($P < 0.001$) increase in blood pressure (systolic and diastolic) and the serum levels of Troponin I, LDH, AST, CK-Total, CK-MB, CRP, RBD, cholesterol, TG, HDL, LDL, and VLDL when compared to controls; as shown in Table 1.

Serum level of sLOX-1 in acute STEMI patients

As depicted from Figure 1A, the level of serum sLOX-1 was found to be highly significantly ($P < 0.001$) increased in acute STEMI patients (112.79 ± 10.76) when compared to the control group (47.75 ± 12.87).

Also, the level of serum sLOX-1 was measured after 12hrs and 48hrs from PCI to assess its impor-

Table 1. Clinicopathological characteristics of acute STEMI patients and controls

Group Parameter	Control group (n = 30) Mean ± SD	Patients Group (n = 150) Mean ± SD	p-value
Gender Female Male	 12 (40.0%) 18 (60.0%)	 58 (38.7%) 92 (61.3%)	 0.913
Age (years)	46.80 ± 6.69	48.40 ± 10.82	0.192
BMI [wt/(ht) ^ 2]	22.50 ± 1.96	24.24 ± 3.07	0.254
Blood pressure [mm Hg] Systolic Diastolic	 116.50 ± 6.90 75.00 ± 6.88	 168.69 ± 7.95 95.28 ± 3.39	 <0.001** <0.001**
Troponin I [ng/ml]	0.02 ± 0.01	0.55 ± 0.76	< 0.001**
LDH [U/L]	91.70 ± 11.97	566.76 ± 121.07	< 0.001**
AST [U/L]	21.75 ± 7.00	41.80 ± 20.09	< 0.001**
CK-total [U/L]	69.25 ± 16.56	322.59 ± 209.65	< 0.001**
CK-MB [U/L]	13.40 ± 4.38	54.98 ± 26.57	< 0.001**
CRP [mg/dl]	3.21 ± 1.45	11.52 ± 10.27	< 0.001**
RBS [mg/dl]	87.85 ± 11.72	190.07 ± 94.05	< 0.001**
Cholesterol [mg/dl]	153.28 ± 19.10	200.93 ± 35.73	< 0.001**
TG [mg/dl]	87.70 ± 10.21	157.48 ± 51.63	< 0.001**
HDL [mg/dl]	50.92 ± 4.69	43.46 ± 5.98	< 0.001**
LDL [mg/dl]	84.82 ± 21.98	125.98 ± 34.68	< 0.001**
VLDL [mg/dl]	17.54 ± 2.04	31.49 ± 10.33	< 0.001**

* Significant at p-value < 0.05
** Highly significant at p-value < 0.001

Table 2. Area under the curve (AUC), cut-off value, sensitivity and specificity of serum sLOX-1, and other parameters in acute STEMI patients

	sLOX-1 [pg/ml]	Troponin [ng/ml]	LDH [U/L]	AST [U/L]	CK-Total [U/L]	CK-MB [U/L]	CPR [mg/dl]
AUC	1	1	1	0.81	1	1	0.91
Cut-off value	78.92	0.065	234	25.9	96	21.98	4.25
Asymptotic Sig.	0.000**	0.000**	0.000**	0.000**	0.000**	0.000**	0.000**
Sensitivity	100%	100%	100%	71.1%	100%	100%	81.6%
Specificity	100%	100%	100%	76.2%	100%	100%	71.4%

* Significant at p-value < 0.05
** Highly significant at p-value < 0.001

tance to monitor the response to PCI. Our results revealed that serum sLOX-1 is not significantly decreased (P > 0.05) either after 12 hrs (111.04 ± 11.06) or 48 hrs (110.31 ± 11.24) when compared with zero time (112.79 ± 10.76); as shown in Figure 1B.

Correlation of serum sLOX-1 level with clinical variables in acute STEMI patients

The correlation matrix of serum sLOX-1 with the different clinical parameters in this study was assessed. Our results revealed that the level of serum sLOX-1 had

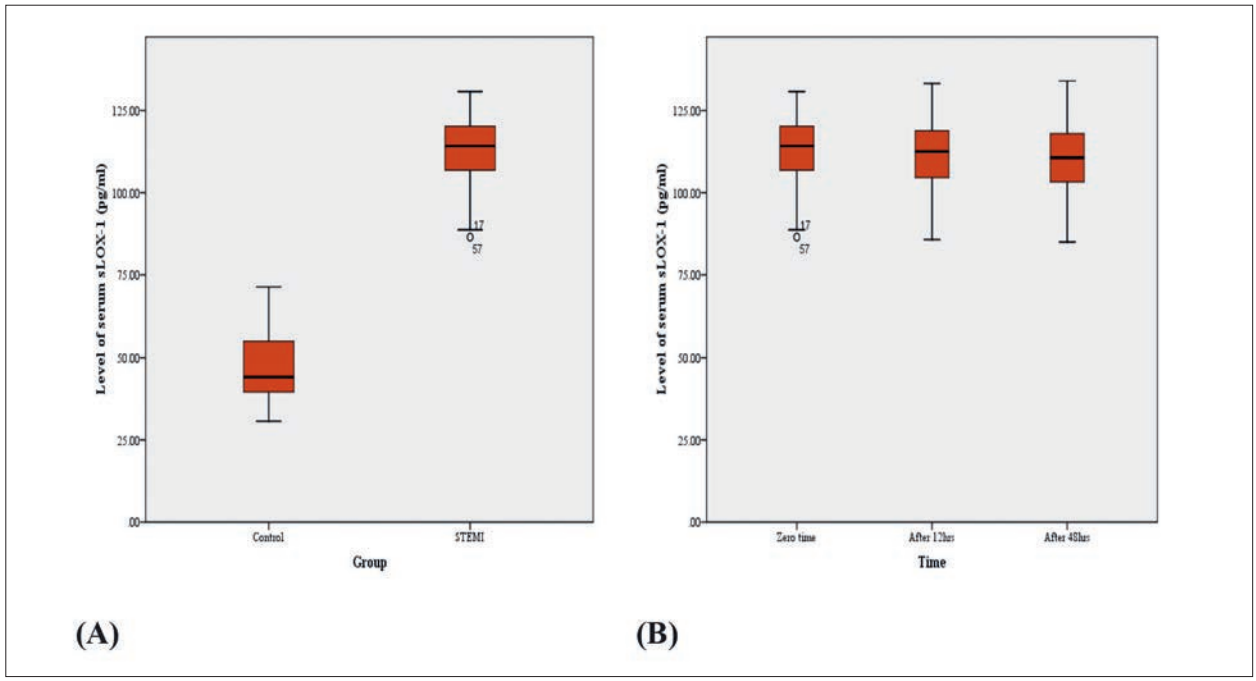

Figure 1. The level of serum sLOX-1 in: (A) acute STEMI patients and controls; (B) acute STEMI patients before and after 12 or 48 hours from PCI

highly significant positive correlations ($P < 0.001$) with cholesterol and LDL serum levels; while it had significant positive correlations ($P < 0.05$) with troponin I, CK-MB, CRP, TG, and VLDL; as shown in Figure 2 (A–G).

Receiver operating characteristic (ROC) curves analysis

To evaluate the sensitivity and specificity of the serum sLOX-1 level as a marker for the detection of acute STEMI disease, ROC curve analysis was done. Our results showed that AUC for sLOX-1 is 1 with 100% sensitivity and specificity, as shown in Table 2 and Figure 3.

Discussion

Worldwide, MI is the main cause of mortality and morbidity, but fast and reliable diagnosis can reduce mortality [10]. Therefore, this study aimed to assess the diagnostic value of serum sLOX-1 among patients with acute STEMI, and also its importance to monitoring the response to PCI.

Results of the current study revealed that the level of serum sLOX-1 was significantly increased in acute STEMI patients when compared with healthy subjects, which indicates that sLOX-1 may play a crucial role in the pathogenesis of acute STEMI disease. These results are consistent with Mehta et al. [11] who reported that LOX-1 is a critical player in the development of atherosclerosis and related disorders, and also with Caglar et al. [12] who found that sLOX-1 levels were associated with coronary slow flow phenomenon which linked with myocardial ischemia, myocardial infarction, life-threatening arrhythmias, sudden cardiac death and increased cardiovascular mortality similar to coronary artery disease (CAD). This is in addition to Takanabe-Mori et al. [13] who found that LOX-1 had an important role in vascular inflammation in current smokers. There is a multicenter pilot study reported that higher serum LOX-1 in patients with stable coronary artery disease was associated with major adverse cardiovascular events [6]. All these observations with our results ascertain that LOX-1 has a great role in the pathogenesis of acute STEMI disease.

Furthermore, serum level of sLOX-1 was found in other diseases such as type 2 diabetes mellitus [14, 15], coronary artery disease in patients with metabolic syndrome [16], polycystic ovary syndrome [17], and hypertension [18], which all associated with endothelial dysfunction.

Our results also showed that serum sLOX-1 level was positively correlated with cholesterol, LDL, troponin I, CK-MB, CRP, TG, and VLDL. As consistent with our results, Balin et al. [19] suggested that as the level of sLOX-1 was positively correlated with CK, CK-MB, and TnT, it could be a biomarker to predict the risk of periprocedural myocardial damage in stable patients undergoing PCI. Also, serum sLOX-1 levels were

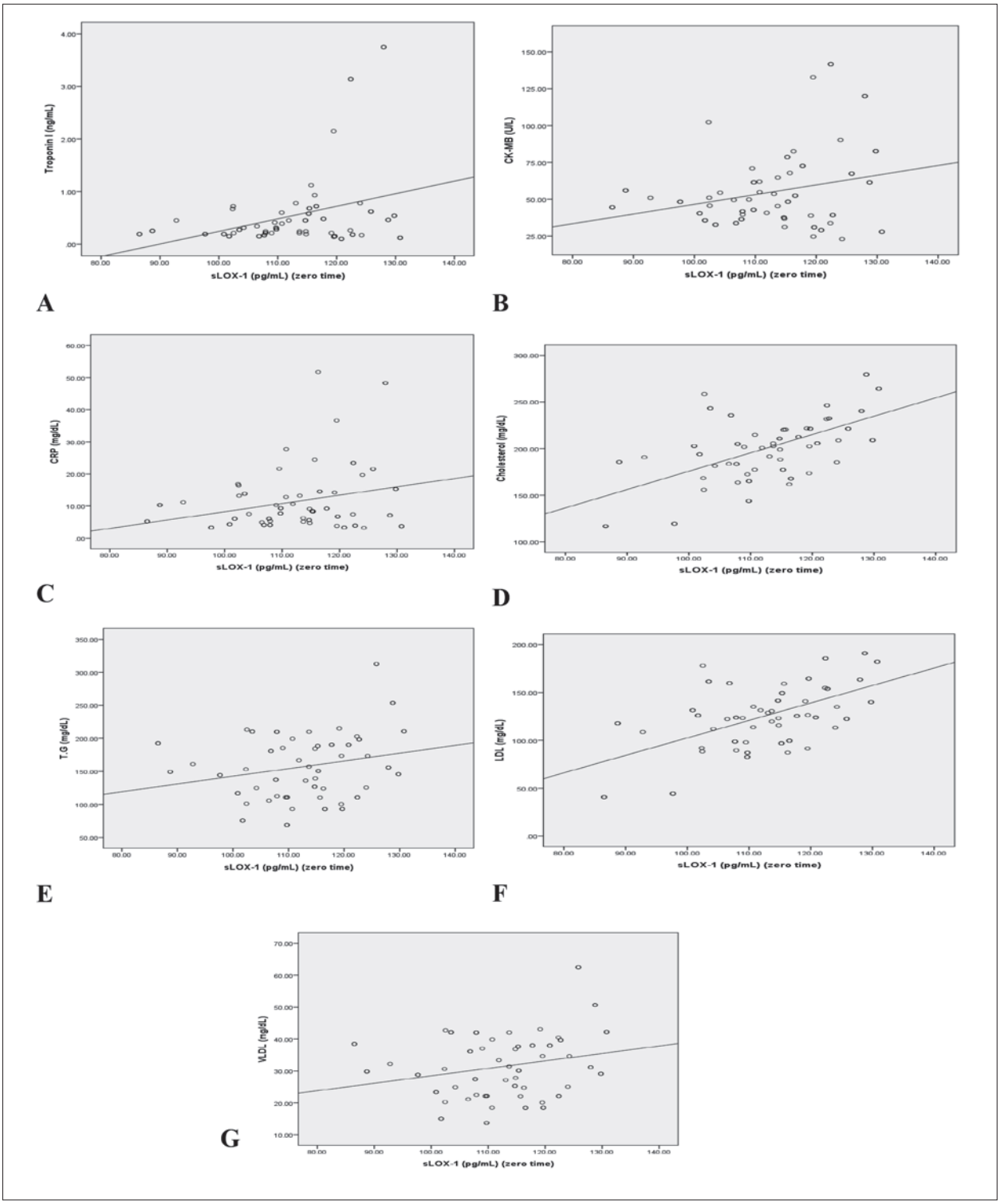

Figure 2. Correlations of serum sLOX-1 with different parameters among acute STEMI patients

measured before and after the procedure to assess whether it could predict in-stent restenosis (ISR) during the follow-up of patients with MI who underwent successful primary PCI [20]. According to our results, after the treatment of acute STEMI patients with the primary PCI, the level of serum sLOX-1 was not sigificantly decreased either after 12 hrs or 48 hrs from PCI management, which may reflect that these patients are at low risk to develop ISR.

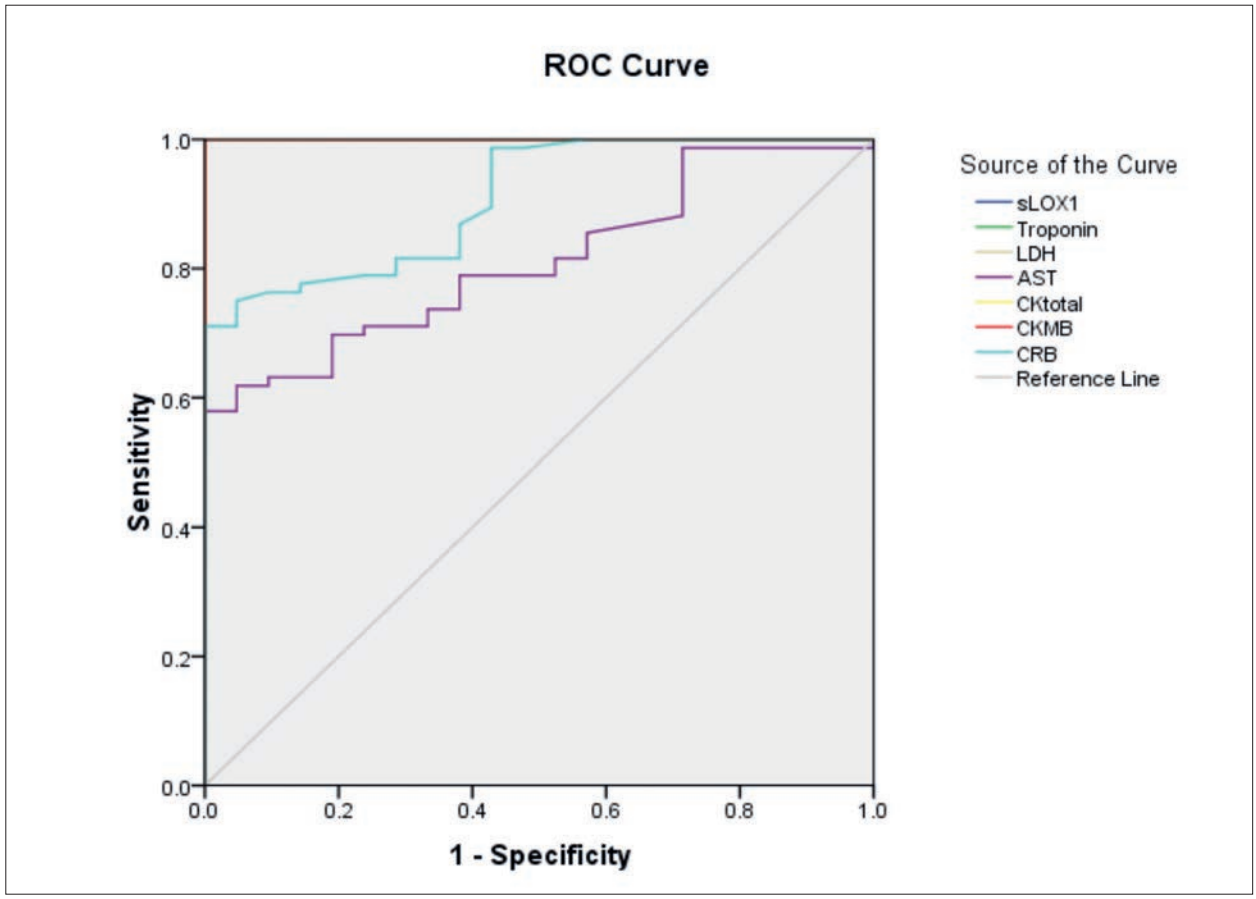

Figure 3. ROC curve of serum sLOX-1 and other parameters for detection of acute STEMI disease

LOX-1 is undetectable in healthy vessels but overexpressed in atherosclerotic lesions [21], and sLOX-1 is generated through proteolytic cleavage of the extracellular domain of LOX-1, released into the bloodstream reflecting the expression of LOX-1, therefore sLOX-1 can be used as a diagnostic biomarker of the acute coronary syndrome [22].

Results obtained from ROC curve analysis showed that serum sLOX-1 is an excellent biomarker for acute STEMI disease, its AUC is one with 100% sensitivity and specificity, such as global cardiac biomarkers like troponin I, LDH, and CK-MB.

It was found that the level of sLOX-1 was elevated at the earliest stages of acute STEMI (about one hour and a half from the symptom onset) and then declined to basal levels after 16 days from the onset of STEMI, while other cardiac biomarkers peaked later (troponin T and CK-MB after 6 hrs from the symptom onset) and declined rapidly [23]. Also, Kume et al. [24] reported that the circulating sLOX-1 is a more sensitive and specific biomarker for ACS than troponin and can detect ACS in subjects with normal troponin levels. Therefore, it was suggested that circulating sLOX-1 may be a useful biomarker for diagnosing STEMI, and the evaluation of sLOX-1 combined with troponin levels could improve the accuracy of ACS diagnosis [25].

Results obtained from this study also revealed that our STEMI patients had significantly increased values of systolic and diastolic blood pressure. Several studies reported that there is a crosstalk between LOX-1 and renin-angiotensin system (RAS) and therefore evolution of blood pressure [26–28], also blockade and deletion of LOX-1 was found to reduce angiotensin II type 1 receptor (AT1R) expression in the cardiovascular system [29]. The authors believed that LOX-1 may contribute to the evolution of hypertension in STEMI patients. It is well known that LOX-1 mainly binds ox-LDL which is more important in the genesis and progression of hypertension leading to endothelial dysfunction, an early and common event in the pathogenesis of hypertension [30]. One of the limitations of this study is the impact of elevated blood pressure values on the increase of sLOX-1 and further investigations are needed to explore this and clarify the link between hypertension and sLOX-1.

Conclusions

Finally, from the above results, we can conclude that LOX-1 has a crucial role in the pathogenesis of acute STEMI; also, serum sLOX-1 could be a good diagnostic clinical biomarker for the detection of acute STEMI disease and to monitor the response to PCI.

References:

1. Singh A, Museedi AS, Grossman SA. Acute Coronary Syndrome. 2020 Jul 17. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan–. PMID: 29083796.
2. Liu Y, Huang Da, Li B, et al. Association between 1-antitrypsin and acute coronary syndrome. Exp Ther Med. 2020; 20(5): 119, doi: 10.3892/etm.2020.9247, indexed in Pubmed: 33005245.
3. Akbar H, Foth C, Kahloon RA, Mountfort S. Acute ST Elevation Myocardial Infarction. 2020 Aug 8. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan–. PMID: 30335314.
4. Henderson RA. Acute coronary syndrome: optimising management through risk assessment. Clin Med (Lond). 2013; 13(6): 602–606, doi: 10.7861/clinmedicine.13-6-602, indexed in Pubmed: 24298110.
5. Saito Y, Kobayashi Y. Update on Antithrombotic Therapy after Percutaneous Coronary Intervention. Intern Med. 2020; 59(3): 311–321, doi: 10.2169/internalmedicine.3685-19, indexed in Pubmed: 31588089.
6. Zhao ZW, Xu YW, Li SM, et al. Higher serum lectin-like oxidized low-density lipoprotein receptor-1 in patients with stable coronary artery disease is associated with major adverse cardiovascular events: A multicentre pilot study. Biochem Med (Zagreb). 2019; 29(1): 010705, doi: 10.11613/BM.2019.010705, indexed in Pubmed: 30799974.
7. Pirillo A, Catapano AL. Soluble lectin-like oxidized low density lipoprotein receptor-1 as a biochemical marker for atherosclerosis-related diseases. Dis Markers. 2013; 35(5): 413–418, doi: 10.1155/2013/716325, indexed in Pubmed: 24198442.
8. Murase T, Kume N, Kataoka H, et al. Identification of soluble forms of lectin-like oxidized LDL receptor-1. Arterioscler Thromb Vasc Biol. 2000; 20(3): 715–720, doi: 10.1161/01.atv.20.3.715, indexed in Pubmed: 10712396.
9. Dey AK, Gaddipati R, Elnabawi YA, et al. Association Between Soluble Lectinlike Oxidized Low-Density Lipoprotein Receptor-1 and Coronary Artery Disease in Psoriasis. JAMA Dermatol. 2020; 156(2): 151–157, doi: 10.1001/jamadermatol.2019.3595, indexed in Pubmed: 31746956.
10. Aydin S, Ugur K, Aydin S, et al. Biomarkers in acute myocardial infarction: current perspectives. Vasc Health Risk Manag. 2019; 15: 1–10, doi: 10.2147/VHRM.S166157, indexed in Pubmed: 30697054.
11. Mehta JL, Chen J, Hermonat PL, et al. Lectin-like, oxidized low-density lipoprotein receptor-1 (LOX-1): a critical player in the development of atherosclerosis and related disorders. Cardiovasc Res. 2006; 69(1): 36–45, doi: 10.1016/j.cardiores.2005.09.006, indexed in Pubmed: 16324688.
12. Caglar IM, Ozde C, Biyik I, et al. Association between soluble lectin-like oxidized low-density lipoprotein receptor 1 levels and coronary slow flow phenomenon. Arch Med Sci. 2016; 12(1): 31–37, doi: 10.5114/aoms.2015.51412, indexed in Pubmed: 26925116.
13. Takanabe-Mori R, Ono K, Wada H, et al. Lectin-like oxidized low-density lipoprotein receptor-1 plays an important role in vascular inflammation in current smokers. J Atheroscler Thromb. 2013; 20(6): 585–590, doi: 10.5551/jat.16436, indexed in Pubmed: 23665840.
14. Tan KCB, Shiu SWM, Wong Y, et al. Soluble lectin-like oxidized low density lipoprotein receptor-1 in type 2 diabetes mellitus. J Lipid Res. 2008; 49(7): 1438–1444, doi: 10.1194/jlr.M700551-JLR200, indexed in Pubmed: 18408244.
15. Stankova TR, Delcheva GT, Maneva AI, et al. Serum Levels of Carbamylated LDL, Nitrotyrosine and Soluble Lectin-like Oxidized Low-density Lipoprotein Receptor-1 in Poorly Controlled Type 2 Diabetes Mellitus. Folia Med (Plovdiv). 2019; 61(3): 419–425, doi: 10.3897/folmed.61.e39343, indexed in Pubmed: 32337929.
16. Stankova T, Delcheva G, Maneva A, et al. Serum Levels of Carbamylated LDL and Soluble Lectin-Like Oxidized Low-Density Lipoprotein Receptor-1 Are Associated with Coronary Artery Disease in Patients with Metabolic Syndrome. Medicina (Kaunas). 2019; 55(8), doi: 10.3390/medicina55080493, indexed in Pubmed: 31443320.
17. Oncul M, Albayrak M, Sozer V, et al. Polycystic ovary syndrome and endothelial dysfunction: A potential role for soluble lectin-like oxidized low density lipoprotein receptor-1. Reprod Biol. 2020; 20(3): 396–401, doi: 10.1016/j.repbio.2020.04.006, indexed in Pubmed: 32409108.
18. Ayashi S, Assareh AR, Jalali MT, et al. Role of antioxidant property of carvedilol in mild to moderate hypertensive patients: A prospective open-label study. Indian J Pharmacol. 2016; 48(4): 372–376, doi: 10.4103/0253-7613.186206, indexed in Pubmed: 27756946.
19. Balin M, Celik A, Kobat MA, et al. Circulating soluble lectin-like oxidized low-density lipoprotein receptor-1 levels predict percutaneous coronary intervention-related periprocedural myocardial infarction in stable patients undergoing elective native single-vessel PCI. J Thromb Thrombolysis. 2012; 34(4): 483–490, doi: 10.1007/s11239-012-0770-2, indexed in Pubmed: 22797935.
20. Li Bo, Zhang Lh, Yang Xg, et al. Postprocedural serum sLOX-1 levels are associated with coronary in-stent restenosis in patients with stable coronary artery disease. Coron Artery Dis. 2011; 22(4): 259–263, doi: 10.1097/MCA.0b013e328344ede9, indexed in Pubmed: 21346562.
21. Kataoka H, Kume N, Miyamoto S, et al. Expression of lectinlike oxidized low-density lipoprotein receptor-1 in human atherosclerotic lesions. Circulation. 1999; 99(24): 3110–3117, doi: 10.1161/01.cir.99.24.3110, indexed in Pubmed: 10377073.
22. Yokota C, Sawamura T, Watanabe M, et al. High Levels of Soluble Lectin-Like Oxidized Low-Density Lipoprotein Receptor-1 in Acute Stroke: An Age- and Sex-Matched Cross-Sectional Study. J Atheroscler Thromb. 2016; 23(10): 1222–1226, doi: 10.5551/jat.32466, indexed in Pubmed: 27025681.
23. Kobayashi N, Hata N, Kume N, et al. Soluble lectin-like oxidized low-density lipoprotein receptor-1 as an early biomarker for ST elevation myocardial infarction: time-dependent comparison with other biomarkers: time-dependent comparison with other

biomarkers. Circ J. 2011; 75(6): 1433–1439, doi: 10.1253/circj.cj-10-0913, indexed in Pubmed: 21467660.

24. Kume N, Mitsuoka H, Hayashida K, et al. Soluble lectin-like oxidized LDL receptor-1 (sLOX-1) as a sensitive and specific biomarker for acute coronary syndrome--comparison with other biomarkers. J Cardiol. 2010; 56(2): 159–165, doi: 10.1016/j.jjcc.2010.05.002, indexed in Pubmed: 20605699.
25. Kobayashi N, Hata N, Kume N, et al. Soluble lectin-like oxidized LDL receptor-1 and high-sensitivity troponin T as diagnostic biomarkers for acute coronary syndrome. Improved values with combination usage in emergency rooms. Circ J. 2011; 75(12): 2862–2871, doi: 10.1253/circj.cj-11-0724, indexed in Pubmed: 21937834.
26. Wang X, Phillips MI, Mehta JL. LOX-1 and angiotensin receptors, and their interplay. Cardiovasc Drugs Ther. 2011; 25(5): 401–417, doi: 10.1007/s10557-011-6331-7, indexed in Pubmed: 21861069.
27. Wang X, Khaidakov M, Ding Z, et al. Lectin-like oxidized low-density lipoprotein receptor-1 (LOX-1) and cardiac fibroblast growth. Hypertension. 2012; 60(6): 1437–1442, doi: 10.1161/HYPERTENSIONAHA.112.200659, indexed in Pubmed: 23045471.
28. Liang YQ, Kakino A, Matsuzaka Y, et al. LOX-1 (Lectin-Like Oxidized Low-Density Lipoprotein Receptor-1) Deletion Has Protective Effects on Stroke in the Genetic Background of Stroke-Prone Spontaneously Hypertensive Rat. Stroke. 2020; 51(6): 1835–1843, doi: 10.1161/STROKEAHA.120.029421, indexed in Pubmed: 32397936.
29. Li X, Tang X, Liu Bo, et al. LOX-1 Deletion Attenuates Myocardial Fibrosis in the Aged Mice, Particularly Those With Hypertension. Front Cardiovasc Med. 2021; 8: 736215, doi: 10.3389/fcvm.2021.736215, indexed in Pubmed: 34712709.
30. Luo P, Yan M, Frohlich ED, et al. Novel concepts in the genesis of hypertension: role of LOX-1. Cardiovasc Drugs Ther. 2011; 25(5): 441–449, doi: 10.1007/s10557-011-6337-1, indexed in Pubmed: 21912849.

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REVIEW

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Is there something new in the diagnosis and treatment of TOS and Paget-Schroetter syndrome?

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Abstract

Thoracic outlet syndrome is a syndrome of pathologic neurologic and vascular symptoms involving the upper limb. Its most serious complication, Paget-Schroetter syndrome, is a major clinical problem, posing a significant diagnostic and therapeutic challenge to specialists not only in angiology and vascular surgery but also in neurology and physiotherapy. There is a need for in-depth examination and differentiation of patients with suspected compression syndrome. We present a review paper covering the diagnosis and treatment of thoracic outlet syndrome.

Key words: Paget-Schroetter syndrome, thoracic outlet syndrome, venous thrombosis, compression syndrome

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Introduction

Thoracic outlet syndrome (TOS) is a syndrome of pathologic neurologic and vascular symptoms involving the upper limb [1–3]. The most common cause is compression of the brachial plexus region and the upper limb's vascular bundle in this area, including the subclavian and axillary arteries and the subclavian vein [1, 4, 5]. Compression and damage most often occur at the neurovascular bundle between the cervical spine and the upper limb's axillary region [5, 6]. The causes of compression syndrome include anatomical conditions (congenital anomalies and past trauma), as well as postural abnormalities in the muscular structures and ligamentous apparatus of the upper thoracic orifice [5–8]. The literature emphasizes among the congenital anomalies causing compression of neurovascular structures such as defects as an additional cervical rib, residual first rib, first bicuspid rib, fibromuscular pathologies in the triangle of inclined muscles, displacement of inclined muscle attachments or their adhesions [4, 5, 9, 10]. Authors of publications covering this issue emphasize that, to a large extent, upper thoracic compression syndrome may develop in patients with abnormal posture during work, with the so-called physiological dropping of the shoulder girdle [7, 8]. However, it is also a phenomenon affecting athletes, especially those practicing sports requiring repeated use of specific movements with excessive upper limb strength (e.g. during gym exercises) [11]. There is also a large group of patients with

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excessive hypertrophy of the shoulder girdle muscles, such as bodybuilders, construction workers, or miners [11]. Trauma, especially to the clavicle and first rib, and less commonly, dislocations of the humeral head, also play a role in developing compression symptoms in the upper thoracic orifice [2, 4]. The importance of stress as a predisposing factor contributing factor in the weakening and decreased capacity of structures within the upper thoracic orifice has received increasing attention in the literature [4]. TOS syndrome is estimated to occur in approximately 0.3–8.0% of the population [10]. It is more repeatedly seen in women, and the average age of patients developing symptoms of the syndrome is between 30–40 years [1, 4]. Authors of publications related to this issue emphasize the variability of the symptoms of compression syndrome. It is emphasized that the manifestations of the upper thoracic compression syndrome depend primarily on the degree of compression applied to the brachial plexus and the choroid bundle [6]. They are usually classified in the literature into three primary groups of symptoms. In the first group, symptoms of the so-called venous syndrome are noted, which affect 3–5% of patients and result from compression exerted on the subclavian or axillary vein between the clavicle and the first rib [2, 5, 12]. This most severe complication of the venous component of compression has been described as the so-called Paget-Schroetter syndrome, resulting in thrombosis of the upper limb veins at the compression site, which can lead to life-threatening thromboembolic complications, including pulmonary embolism and even death [2, 3]. Paget-Schroetter syndrome usually affects young people and usually results from prolonged physical exertion involving the upper limbs. Among the predominant symptoms are dull pain and a feeling of heaviness of the limb, especially aggravated in the supine position due to prolonged fixed position of the upper limb, mainly during sleep [2, 3]. In the clinical presentation, purplish-red discoloration and increasing swelling of the limb are observed over time [1–3]. During the disease development, significantly dilated venous vessels of the upper extremity, chest wall, and neck are observed [3]. In the case of the so-called arterial syndrome, which affects 1–2% of patients with TOS, an acute or chronic disease course is noted [2]. The arterial syndrome symptoms often result from local irritation of the arterial wall against the base of the first rib, which leads to arterial fibrosis and sometimes to the development of an aneurysm [13–15]. In the acute state of the arterial syndrome, symptoms of acute limb ischemia are usually observed by thrombotic and embolic mechanisms within the artery and microemboli in the small vessels of distal parts of the upper limbs [16]. In the chronic phase, a cold sensation of the hand skin is observed, often Raynaud's sign and symptoms analogous to those observed in chronic ischemia, such as intermittent claudication, increasing trophic changes in fingers, and with increasing ischemia, even subungual ulceration and necrosis [2, 3]. The most numerous group of symptoms resulting from upper thoracic compression syndrome are those of neurogenic syndrome, which are reported in approximately 95% of patients with TOS and result from compression or injury to the brachial plexus [6]. As noted in the literature, patients with symptoms of neurogenic syndrome typically report complaints of cervical spine or shoulder pain, upper extremity paresthesias, numbness, and tingling in the entire arm or forearm and hand [1, 6]. Over time, motor and muscle strength disorders in the forearm and hand may also occur. In the case of compression syndrome of the upper thoracic aperture and its most serious complication, Paget-Schroetter syndrome, the diagnosis of the disease is based on the clinical history, the so-called provocative tests, and extensive imaging diagnostics including both non-invasive and invasive diagnostic procedures used in vascular surgery and angiology [2, 3, 17].

Diagnosis of TOS and Paget-Schroetter syndrome

Diagnosis of TOS and its complication Paget-Schroetter syndrome is based on medical history, provocative tests, diagnostic ultrasound, noninvasive and invasive radiological procedures [12, 18]. The literature emphasizes the significance of provocative tests such as Adson's test, Falconer and Weddel's test, Wright's hyperabduction test, AER (abduction-external-rotation) test, based mainly on the intensification of existing compression of structures of the upper limb neurovascular bundle [12, 18, 19]. As noted in the literature, provocative tests have limited specificity for these syndromes and are characterized by a high rate of false positives. One of the most frequently performed provocative tests is the Adson's test, which evaluates a segment of the subclavian artery in the triangle of the oblique muscle [12]. This test, described by American neurosurgeon Alfred Washington Adson, relies on the disappearance of the radial artery pulse when the subject turns his or her head toward the diseased side after taking a deep breath. One of the widely used clinical provocative tests is the hyperabduction test, which allows assessment of the subclavian artery at the pectoralis minor muscle attachment [4, 18]. This test is often used in conjunction with flow assessment of the subclavian vein and artery by ultrasound and arteriography. As emphasized in the literature and clinical studies, this test is currently not recommended due to a high rate of false-positive

results (about 50%) [19]. Clinical studies emphasize the significance of imaging in the diagnosis of TOS and its complications [19]. Special attention is given to the use of radiological examinations, including traditional X-rays of the chest and cervical spine and shoulder joints, which allow the diagnosis of possible anatomical and functional changes of the skeleton based on which the compression syndrome develops. Of particular importance in patients with TOS is ultrasound diagnostics, especially the dual ultrasound imaging method [2, 18, 19]. The literature emphasizes the high sensitivity and specificity of ultrasonography in diagnosing flow abnormalities in the upper extremities' venous and arterial vessels. In addition to anatomical changes and arterial complications, it allows functional assessment of the vascular system [18]. Nevertheless, the anatomy of the upper thoracic aperture region may pose some limitations to ultrasound evaluation, especially in the venous system, especially when thrombotic complications of upper thoracic aperture syndrome are suspected. It is recommended to extend the diagnosis with radiological studies using phlebography, arteriography, or phlebography and computed tomography arteriography in case of diagnostic doubt [1–3, 18]. Since venous thrombosis of the upper limb is the most severe complication of TOS, there are critical clinical reasons in the literature for using phlebography as the primary method of diagnosis [16, 20]. Phlebography is recommended in all cases of acute thrombosis of the subclavian vein, with attention paid to the fact that the examination should be performed using the Seldinger method [20]. It is crucial that phlebography, apart from its diagnostic value in diagnosing thrombotic complications of TOS, allows local thrombolysis and possible endovascular plastic surgery [21]. The authors of the studies are unanimous in stating that phlebography is one of the methods to determine the cause of the compression syndrome [2]. In the literature, the diagnosis of TOS is considered an indication for surgical treatment, which consists of resection of the first rib and scalenectomy [18]. Nevertheless, it is strongly stated that of great value in treating patients with this condition is the implementation as soon as possible of physical therapy treatment aimed at relieving the vascular and nerve bundle of the upper thoracic aperture region. [17, 21–23].

The treatment of TOS and Paget-Schroetter syndrome

Authors of clinical studies discussing the treatment of patients with TOS syndrome emphasize the importance of physical therapy, including rehabilitation, consisting of physical therapy and kinesitherapy [19, 24, 25]. The main goal of physical therapy in treating this condition is to reduce pain and increase muscle tone in the shoulder girdle and cervical spine. Physical therapy usually depends on the type of compression syndrome, the type of pain, and the patient's tolerance to the treatments. As emphasized in the literature, physical therapy is used to prepare the patient for kinesitherapy treatment, which may be successfully applied simultaneously [7, 24, 25]. Kinesitherapy in patients with TOS syndrome should be strictly personalized, subject to appropriate individual selection. Before initiating kinesitherapy treatment, the patient's capacity should be considered; after the physiotherapeutic examination, the type of therapeutic techniques and exercises, their starting position, and degree of intensity are selected [24]. The authors emphasize that kinesitherapy is one of the essential elements of the combined treatment of patients with compression syndrome [21]. Attention is drawn to the significant acceleration of repair processes, protects against the development of abnormal compensatory schemes, prevents secondary changes in the musculoskeletal system [25]. Particularly noteworthy is that in the applied assessment of the mobility of the joints of the upper thoracic orifice, segments are differentiated into hypomobile and hypermobile ones. Segments characterized by low mobility (hypomobile) should be mobilized in order to maintain maximum motor harmony. In segments with excessive mobility (hypermobility), treatments are aimed at stabilizing them. The stability of segments of the upper thoracic aperture, especially the cervical spine and shoulder girdle, depends on the functional and stable position of the scapula. The imbalance of muscle tone in the scapular region (weakening of the inferior part of the serrates anterior muscle and inferior part of the trapezius muscle, and excessive tension of the pectoralis minor and rhomboid muscles) leads to protraction of the scapula and distension of its lower angle from the thorax. A common postural problem in TOS is the presence of excessive forward head extension leading to overuse of the sternocleidomastoid muscles [7, 25]. When the superficial Sternocleidomastoid muscles are overactive, there may be a tendency to underactive the deep cervical flexors, leading to cervical dysfunction. Various soft tissue therapy techniques are used to reduce excessive muscle tension. However, what is crucial for physiotherapeutic management is the patient's education on ergonomics, especially during heavy work duties. The literature emphasizes that in patients with neurological symptoms in the compression syndrome, especially despite the intensification of conservative management, or especially in patients with vascular complications with particular emphasis on potential thromboembolic complications, surgical intervention should be considered [6, 18]. For potential arterial

complications, a vascular reconstruction procedure is usually performed [8]. As emphasized in the literature, occlusion of the arterial lumen due to compression by the cervical rib is usually eliminated by removing the first rib [10]. Surgical eligibility for surgical treatment in upper thoracic orifice compression syndrome is usually based on a broad diagnostic spectrum including clinical trials, noninvasive studies such as chest radiographs, cervical spine radiographs, computed tomography, and magnetic resonance imaging, especially with contrast and evaluation of the results of invasive imaging such as phlebography and arteriography [21]. As underlined extensively in the literature, the surgical treatment of choice mainly involves resection of the first rib, often combined with surgery to remove bony or fibromuscular pathologies [5, 10, 12, 19]. Surgery is usually assumed to be necessary when vascular complications, both venous and arterial, are confirmed on imaging examinations [5, 18]. In the case of the venous complication of TOS, such as Paget-Schroetter syndrome, it is believed that the effects of surgical treatment of venous compression allow stenting to be omitted, and decompression of the subclavian vein prevents recurrent occlusion or stenosis of the vessel in most cases [26, 27]. As pointed out in the literature, the preferred and appropriate method of revascularization in the subclavian vein is the use of thrombolytic therapy, noting that thrombectomy is rarely performed, potentially resulting in recurrent thromboembolism [21, 27].

Summary

Thoracic outlet syndrome, including its most serious complication, Paget-Schroetter syndrome, is a major clinical problem, posing a significant diagnostic and therapeutic challenge to specialists not only in angiology and vascular surgery but also in neurology and physiotherapy. It is particularly noted that patients complaining of TOS symptoms and diagnosed complications are mainly young, physically, and professionally active people. Thus, the symptoms of compression syndrome may cause a significant reduction in the quality of life and lead to life-threatening complications in extreme cases. As emphasized in the literature, there is a need for in-depth examination and differentiation of patients with suspected compression syndrome. The multitude of currently existing diagnostic methods greatly contributes to the improvement of the diagnosis and the incorporation of appropriate therapeutic management. The variety of symptoms, their varying nature and severity accompanying thoracic outlet syndrome, and potentially life-threatening complications such as Paget-Schroetter syndrome, among others, usually require a multidisciplinary evaluation of patients, their potential risk factors, and their possible response to the therapeutic management used.

Conflict of interest

None.

References:

1. Adamski S. Zespoły naczyniowo-nerwowe. In: Rykowski H. ed. Choroby naczyń. PZWL, Warszawa 1990: 442–454.
2. Sieroń A, Cierpka L, Rybak Z, Stanek A. Podręcznik angiologii. Alfa-medica Press 2009.
3. Craeger MA, Dzau V, Loscalzo J. Choroby naczyń. Elsevier 2006: Elsevier.
4. Mackinnon SE, Novak CB. Thoracic outlet syndrome. Curr Probl Surg. 2002; 39(11): 1070–1145, doi: 10.1067/msg.2002.127926, indexed in Pubmed: 12407366.
5. Mackinnon SE, Novak CB. Thoracic outlet syndrome. Curr Probl Surg. 2002; 39(11): 1070–1145, doi: 10.1067/msg.2002.127926, indexed in Pubmed: 12407366.
6. Davidovic L, Kostic D, Jakovljevic N, et al. Vascular thoracic outlet syndrome. World J Surg. 2003; 27(5): 545–550, doi: 10.1007/s00268-003-6808-z.
7. Novak C. Thoracic outlet syndrome. Clinics in Plastic Surgery. 2003; 30(2): 175–188, doi: 10.1016/s0094-1298(02)00095-0.
8. Schneider D, Curry T, Eichler C, et al. Percutaneous Mechanical Thrombectomy for the Management of Venous Thoracic Outlet Syndrome. Journal of Endovascular Therapy. 2003; 10(2): 336–340, doi: 10.1583/1545-1550(2003)010<0336:pmtftm>2.0.co;2.
9. Edwards DP, Mulkern E, Raja AN, et al. Trans-axillary first rib excision for thoracic outlet syndrome. J R Coll Surg Edinb. 1999; 44(6): 362–365, indexed in Pubmed: 10612957.
10. Hempel GK, Shutze WP, Anderson JF, et al. 770 consecutive supraclavicular first rib resections for thoracic outlet syndrome. Ann Vasc Surg. 1996; 10(5): 456–463, doi: 10.1007/BF02000592, indexed in Pubmed: 8905065.
11. Koffler KM, Kelly JD. Neurovascular trauma in athletes. Orthop Clin North Am. 2002; 33(3): 523–34, vi, doi: 10.1016/s0030-5898(01)00004-9, indexed in Pubmed: 12483948.
12. Pupka A, Szyber P. Zespół uciskowy górnego otworu klatki piersiowej — diagnostyka i leczenie. e-Anatomy. 2021; 8: 16–21.
13. Davidović L, Marković D, Pejkić S, et al. Subclavian Artery Aneurysms. Asian Journal of Surgery. 2003; 26(1): 7–11, doi: 10.1016/s1015-9584(09)60206-2.
14. Kostewicz W. Tętniaki tętnicy podobojczykowej. Medycyna 2000. 1992; 3: 10–11.
15. Szydłowski Z., Szyber P., Pupka A. i wsp. Tętniaki tętnicy podobojczykowej w przebiegu zespołu uciskowego górnego otworu klatki piersiowej. Pamiętnik XXIV Zjazdu Sekcji Chir. Kl. Piersiowej, Serca i Naczyń TchP. Poznań 1992: 311.
16. Pupka A., Szydłowski Z., Janczak D. i wsp. Zakrzepica żyły podobojczykowej i pachowej w przebiegu zespołu uciskowego górnego otworu klatki piersiowej. Flebolimfologia. Wydanie specjalne. II Kongres Pol. Tow. Flebol. Wrocław 1997: 16–18.
17. Angle N, Gelabert HA, Farooq MM, et al. Safety and efficacy of early surgical decompression of the thoracic outlet for Pag-

et-Schroetter syndrome. Ann Vasc Surg. 2001; 15(1): 37–42, doi: 10.1007/s100160010017, indexed in Pubmed: 11221942.
18. Dunant JH. Diagnosis of thoracic outlet syndrome and indications for surgery. Vasa. 1987; 16(4): 345–348, indexed in Pubmed: 3424952.
19. Pupka A. Ocena wyników badań diagnostycznych i leczenia operacyjnego w zespole uciskowym górnego otworu klatki piersiowej. Acta Angiologica. 1995; 1: 51–59.
20. Feugier P, Aleksic I, Salari R, et al. Long-term results of venous revascularization for Paget-Schroetter syndrome in athletes. Ann Vasc Surg. 2001; 15(2): 212–218, doi: 10.1007/s100160010043, indexed in Pubmed: 11265086.
21. Schmacht DC, Back MR, Novotney ML, et al. Primary axillary-subclavian venous thrombosis: is aggressive surgical intervention justified? Vasc Surg. 2001; 35(5): 353–359, doi: 10.1177/153857440103500505, indexed in Pubmed: 11565039.
22. Lokanathan R, Salvian AJ, Chen JC, et al. Outcome after thrombolysis and selective thoracic outlet decompression for primary axillary vein thrombosis. J Vasc Surg. 2001; 33(4): 783–788, doi: 10.1067/mva.2001.112708, indexed in Pubmed: 11296332.
23. Novak CB, Collins ED, Mackinnon SE. Outcome following conservative management of thoracic outlet syndrome. J Hand Surg Am. 1995; 20(4): 542–548, doi: 10.1016/S0363-5023(05)80264-3, indexed in Pubmed: 7594276.
24. Aligne C, Barral X. Rehabilitation of patients with thoracic outlet syndrome. Ann Vasc Surg. 1992; 6(4): 381–389, doi: 10.1007/BF02008798, indexed in Pubmed: 1390029.
25. Novak CB. Conservative management of thoracic outlet syndrome. Chest Surg Clin N Am. 1999; 9: 747–760.
26. Reineberg PB, Chang B, Darling III RC. Long-term results in patients treated with thrombolysis, thoracic inlet decompres- sion, and subclavian vein stenting for Paget-Schroetter syndrome. J Vasc Surg . 2001; 33: 100–105, doi: 10.1201/9780429434020-47.
27. Urschel H, Patel A. Paget-Schroetter syndrome therapy: failure of intravenous stents. The Annals of Thoracic Surgery. 2003; 75(6): 1693–1696, doi: 10.1016/s0003-4975(03)00116-4.