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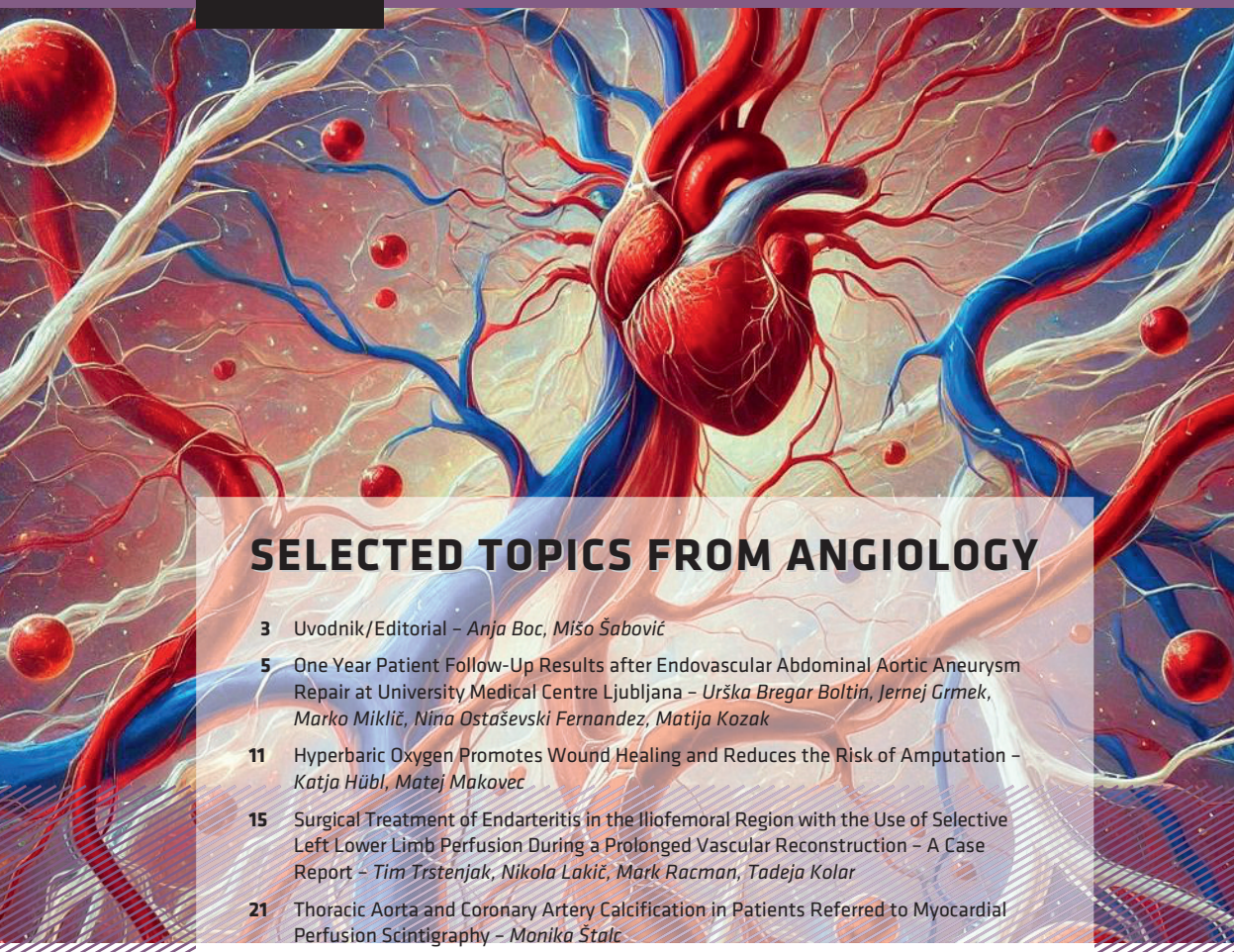
LETNIK 63 SUPPLEMENT 2 SEPTEMBER 2024



SELECTED TOPICS FROM ANGIOLOGY

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LETNIK 63 SUPPLEMENT 2 SEPTEMBER 2024

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Uvodnik

Pričujoči zbornik vsebuje prispevke z mednarodnega angiološkega kongresa v Ljubljani v organizaciji Združenja za žilne bolezni pri Slovenskem zdravniškem društvu. Prispevki so namenjeni kot študijsko gradivo za študente Medicinske fakultete Univerze v Ljubljani, in sicer v okviru predmeta Izbrane teme iz interne medicine.

Gradivo obravnava tematiko žilnih bolezni oz. vaskularne medicine. Te bolezni doslej niso bile v takem žarišču pozornosti kot koronarna arterijska bolezen. Njihovo poznavanje je izjemnega pomena, saj je pogostnost teh bolezni velika in še narašča, bolnike pa izpostavljajo velikemu tveganju za poslabšanje kakovosti življenja, zmanjšanje pokretnosti ter za srčno-žilne dogodke in smrt.

Žilne bolezni zajemajo široko skupino heterogenih bolezni. Poleg zelo pogostih bolezni, med katere sodijo periferna arterijska bolezen, aortna anevrizma, globoka venska tromboza in pljučna embolija, kronična venska bolezen in površinski tromboflebitis, so v skupini žilnih bolezni tudi nekatere redkejše in tudi zelo redke bolezni, ki pa so klinično prav tako zelo pomembne in jih je treba poznati.

Gradivo je napisano strokovno, a razumljivo tudi študentom in specializantom interne medicine. Predstavlja korak naprej v poznavanju in razumevanju žilnih bolezni, s katerimi so se študenti srečali že pri predmetu Interna medicina, zdaj pa lahko svoje dosedanje znanje nadgradijo. Ker so prispevki napisani v obliki člankov, bodo študenti ob njihovem prebiranju lahko razvijali tudi svoje znanje branja in pisanja strokovnih prispevkov. Nenehno pridobivanje znanja je za zdravnike ključno; dodiplomski študij predstavlja le prve, začetne korake na dolgi in zanimivi poti usvajanja znanja.

Doc. dr. Anja Boc, dr. med. in Prof. dr. Mišo Šabović, dr. med.
urednika

Editorial

This publication contains the articles presented at the international angiology congress in Ljubljana, organised by the Slovenian Society for Vascular Diseases of the Slovenian Medical Society. The contributions are intended as a study material for students of the Faculty of Medicine at the University of Ljubljana, specifically within the course Selected Topics in Internal Medicine.

The articles deal with the topic of vascular diseases within the issue of vascular medicine. So far, these diseases have not been as much of a focus of interest as coronary artery disease. However, their knowledge is extremely important as the incidence of these diseases is high and continiously increasing. They expose patients to a high risk of deterioration in quality of life, reduced mobility, cardiovascular events and death.

Vascular diseases include a large group of heterogeneous diseases. In addition to the very common diseases, as peripheral arterial disease, aortic aneurysm, deep vein thrombosis and pulmonary embolism, chronic venous disease and superficial thrombophlebitis, the vascular diseases also include some rarer and even very rare diseases that are equally important clinically and need to be known.

The material is written by specialists, but understandable for students and residents in internal medicine. It represents an advance in the knowledge and understanding of vascular diseases that students have already learned about in the Internal Medicine at Faculty, and here they can expand their knowledge. As the text is in the form of articles, students can also improve their skills in reading and writing articles. Continuous knowledge acquisition is crucial for physicians; the undergraduate study is only the first, initial step on the long road of learning and acquiring knowledge.

assist. prof. Anja Boc, MD, PhD and prof. Mišo Šabovič, MD, PhD
Editors

Urška Bregar Boltin[1], Jernej Grmek[2], Marko Miklič[3], Nina Ostaševski Fernandez[4], Matija Kozak[5]

One Year Patient Follow-Up Results after Endovascular Abdominal Aortic Aneurysm Repair at University Medical Centre Ljubljana

ABSTRACT

KEY WORDS: EVAR, endoleaks

BACKGROUNDS. Endovascular abdominal aortic aneurysm repair (EVAR) is commonly used to treat abdominal aortic aneurysms (AAA). In our department, the outcomes following EVAR after 30 days, one year and later have been monitored systematically in all patients since 2023. METHODS. All the patients after EVAR, which were hospitalized at our department from January 2023 until May 2024, have been included in our analysis. Our aim is to follow the outcomes in patients after EVAR during hospitalization, after 30 days, one year and later. RESULTS. This analysis included 107 patients after EVAR (elective and urgent) since the first of January 2023, of these 87 were men and 20 were women (mean age 74.4 ± 5.2). The mean AAA diameter was 58 ± 7 mm. We analysed the duration of hospitalization in elective and urgent patients (5.6 ± 2.9 days and 16.2 ± 8.2 days, respectively). 50% of patients after EVAR had a haematoma on the puncture site. 69 patients already had CT angiography after EVAR by the end of April 2024; there were 23 endoleaks detected (type 2 in 21 patients, type 1 in one patient and type 3 in one patient). DISCUSSION. Since January 2023 and up until now, 107 patients have been treated with EVAR at our centre. The presence of endoleaks type 1, 2 and 3 and other complications are comparable with the data from other registries.

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BACKGROUNDS

Endovascular abdominal aortic aneurysm repair (EVAR) has become a key treatment option for patients with an abdominal aortic aneurysm (AAA) and at our centre it is offered to patients eligible for EVAR according to the guidelines of the European Society for Vascular Surgery (ESVS) *(1)*. It is the preferred option since both short and mid-term outcomes are as good as or better than open surgical repair, but mid- and long-term complications such as endoleaks, graft infection, graft migration, graft obstruction or post-EVAR rupture can lead to endovascular reintervention or conversion to open surgical repair *(1, 2)*.

The University Medical Centre (UMC) Ljubljana is a high-volume centre, and the majority of procedures nationwide are performed here. The outcomes in patients that have been treated with EVAR will be compared with data from other studies and registries, which will allow us to evaluate the quality and possible deficiencies of this treatment at our centre. Data on early and late complications, post-operative computer tomography angiography (CTA) or ultrasound and follow-up after 30 days, one year and later are collected.

METHODS

Our data was collected on an observational, non-randomised, prospective »all comer« basis. All patients, who underwent EVAR and were hospitalized at our department, were included. Information on AAA diameter, duration of hospitalization, early complications during the procedures and during hospitalization (haematoma, other early complications), outcomes after 30 days, one year and later (endoleaks, aneurysm sac growth, infections, ruptures, other adverse events, death) were collected and analysed. Our follow-up included a CTA and a clinical examination after EVAR at recommended intervals. All patients after EVAR were included, be it elective or urgent, but there were no patients with a ruptured AAA.

RESULTS

From January 2023 until May 2024, a total of 107 patients underwent EVAR and were admitted before the procedure and hospitalized at our department, of that 87 were men (82%) and 20 were women (18%). The average patient age was 74.4 ± 5.2 years. 96 operations were elective and 11 patients required urgent EVAR due to a symptomatic AAA (90% versus 10%). There were no patients with ruptured AAAs after EVAR since they were admitted to other departments. The AAA diameter was 58 ± 7 mm; 56 ± 6 mm in elective patients, and 70 ± 14 mm in urgent patients. AAA diameter advanced with patient age (figure 1). The hospitalization duration was different for elective and urgent patients; 5.6 ± 2.9 days (median 4 days) for elective patients, and 16.2 ± 8.2 days (median 16 days) for urgent patients. 50% of patients had a haematoma on the puncture site, but only one patient required surgical revision of the pseudoaneurysm. In the first 30 days after EVAR, two patients returned because of complications on puncture sites – the first patient was re-admitted due to bleeding from the wound after EVAR and required additional procedures; the second patient needed additional procedures and antibiotic treatment due to an infection of the puncture site.

Patients with a detected type 1 endoleak (1 patient) and type 3 endoleak (1 patient) at procedure were treated immediately during the procedures.

One patient was re-admitted after one week due to a type B aortic dissection, which was managed conservatively. One patient was admitted after a couple of months due to graft aortitis and was treated with long-term antibiotics. One patient died six months after the procedure, her death was not aneurysm-related.

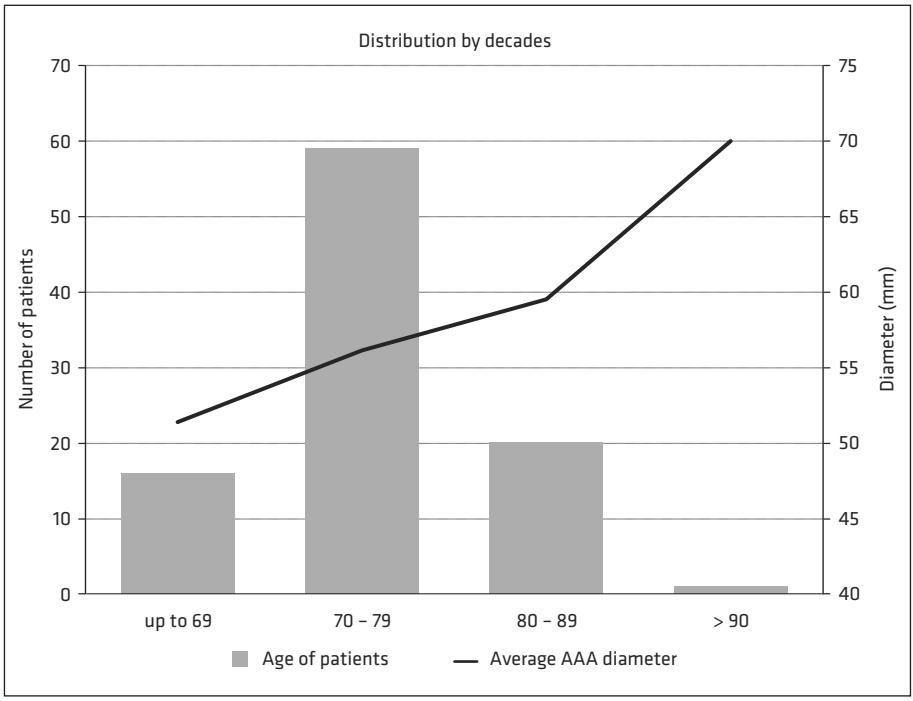

Figure 1. Comparison of abdominal aortic aneurysm (AAA) diameter and patient age.

So far, 69 patients have had the first CTA after EVAR at intervals, recommended by an interventional radiologist or a specialist of vascular medicine (one to six months after EVAR). A type 2 endoleak was detected in 21 patients (31%) with a stable aneurysm sac or detected aneurysm growth (three patients), one of them was already referred for the embolization of lumbal arteries, others will all be closely monitored. Two patients with a detected type 1 and type 3 endoleak on follow-up CTA had additional procedures. Patient characteristic, hospitalization duration and outcomes are presented in table 1.

DISCUSSION

The one-year follow-up of patients after EVAR has shown promising outcomes regarding early complications, the presence of endoleaks and aneurysm-related deaths in comparison with data from other registries *(2, 3)*.

There were no patients included with ruptured AAAs, 10% patients with AAA were admitted due to symptoms (stomach or back pain), which could not be attributed to other causes. The management and hospitalization of these patients were longer than for elective patients, as they needed more diagnostics and had to wait for the procedure in the hospital. Elective patients were admitted one day before the planned procedure. AAA diameter in urgent patients was larger compared to elective patients. In literature, there is not much data comparing outcomes after EVAR in elective and urgent patients without a ruptured AAA. This distinction is taken in consideration mainly due to analysis purposes.

The most frequent complication during hospitalization is a haematoma on the puncture site, which can be managed conservatively in most cases. Only one patient needed a surgical revision of the pseudoaneurysm. Two patients were re-admitted

in the first 30 days after EVAR due to either bleeding or wound infection (1.8%). In general, local wound complications include groin hematoma, infection, or lymphocele, the incidence is 1 to 10%. Arterial thrombosis, dissection, or pseudoaneurysm formation can occur in up to 3% of EVAR procedures *(4)*. Half of our patients had a haematoma on the puncture site, but we included all haematoma with a diameter of over 5 cm and which do not necessarily require further management.

One patient was re-admitted after one week due to a type B aortic dissection, which

Table 1. Patient characteristics, duration of hospitalization and outcomes. EVAR – endovascular abdominal aortic aneurysm repair, SD – standard deviation, CTA – computer tomography angiography.

Characteristic	
Age	74.4 ± 5.2
Sex	
male	87 (81%)
female	20 (18%)
All EVAR	107
electivež	96 (90%)
urgent	11 (10%)
Diameter of aneurysm	58 ± 7 mm
elective	56 ± 6 mm
urgent	70 ± 14 mm
Duration of hospitalization	
mean value and SD	6.7 ± 4.2 days
median	4 days
min	2 days
max	36 days
Duration of hospitalization – elective	
mean value and SD	5.6 ± 2.9 days
median	4 days
Duration of hospitalization – urgent	
mean value and SD	16.2 ± 8.2 days
median	16 days
Presence of hematoma	
no hematoma	54 (50%)
hematoma	53 (50%)
With control CTA scan	69
no enodoleak	46 (67%)
endoleak type 1	1
endoleak type 2	21 (31%)
endoleak type 3	1

was a complication of EVAR – a rare but serious adverse event. There have only been few reports of similar events in literature *(5)*. Most cases of type B dissections are uncomplicated and can be managed by medical therapy, including antihypertensive drugs, which was the case with our patient as well.

One patient was admitted after a couple of months due to graft aortitis, which has so far been managed conservatively with antibiotics. Due to the patient's age and psychophysical condition, new invasive therapies or reinterventions are not recommended. EVAR infections show high mortality rates for every kind of treatment employed, as patients unsuitable for major surgery experience the same chance of survival as patients submitted to an endograft explant *(6)*.

In our cohort study, endoleaks were present either at procedure or on the first follow-up CTA. Reinterventions were necessary for type 1 and type 3 endoleaks, patients with type 2 endoleaks are currently under surveillance. Type 2 endoleaks are most common and the early incidence is usually reported to be around 25%, but most resolve spontaneously during the first six months. Up to 10% of type 2 endoleaks persist and they may cause aneurysm growth, in which case, treatment should be considered *(7)*. In our cohort, type 2 endoleaks are present in 31% of patients. In one patient, the embolization of lumbal arteries was already performed, other patients with a type 2 endoleak and aneurysm sac growth will be closely monitored.

Limitations

Registries, by nature, are observational and are not designed in the same manner as a randomized control trial would be. Maintaining adherence to follow up in patient registries is more challenging than in a trial. Data is collected in real life and although the compliance with follow up has been excellent (almost 100%) so far, we expect a drop in the following years.

CONCLUSIONS

The outcomes of the one-year follow-up on patients after EVAR at the UMC Ljubljana have been positive so far. There has been no rupture or aneurysm-related deaths and patients with a type 2 endoleak will be monitored further. Longer term follow up is necessary for the assessment and comparison of the outcomes in our patients against existing data from other registries and trials.

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Katja Hübl[1], Matej Makovec[2]

Hyperbaric Oxygen Promotes Wound Healing and Reduces the Risk of Amputation

ABSTRACT

KEY WORDS: hyperbaric oxygenation, chronic wound, gangrene, chronic limb-threatening ischemia

BACKGROUNDS. The aim of this pilot study was to determine the benefits of hyperbaric oxygen (HBO) therapy for chronic wounds in patients with chronic limb-threatening ischemia (CLTI). METHODS. The study was performed as a retrospective cohort study, with five patients with CLTI included. Patients were treated with HBO after endovascular treatment (EVT). Treatment sessions involved daily exposure to high oxygen at higher-than--atmospheric pressures in a hyperbaric chamber. RESULTS. Out of five patients with CLTI, three had diabetes, while two did not. Following EVT, three patients underwent toe-level amputations, and two required a debridement of necrotic tissue. HBO therapy administered post-EVT enhanced wound healing, eliminating the need for further amputations in all five patients. DISCUSSION. The treatment of chronic wounds in patients with CLTI requires a multidisciplinary approach. HBO therapy can be used as an adjunctive therapy to the standard therapy modality, as it can increase the healing rate of wounds and reduce the number of amputations.

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BACKGROUNDS

Hyperbaric oxygen (HBO) therapy promotes the healing of ischemic wounds by utilizing high levels of oxygen to achieve antimicrobial effects and stimulating long-term neovascularization *(1–3)*. This treatment can be particularly beneficial for patients with chronic limb-threatening ischemia (CLTI) and nonhealing wounds. The most common cause of peripheral arterial disease leading to CLTI is atherosclerosis, which is frequently associated with arterial hypertension, hypercholesterolemia, smoking, and diabetes mellitus. In these patients, nonhealing wounds typically develop in areas of foot trauma caused by improperly fitting shoes or injuries *(2)*. Treating nonhealing wounds in CLTI patients requires a multidisciplinary approach, with the primary goal being limb preservation. However, many patients still require amputation *(3)*. Revascularization therapy (RT) can often limit the need for major amputations, instead resulting in minor amputations, such as at the toe level, which generally preserves ambulatory functions. Although revascularization is necessary, it can sometimes cause the spread of infection due to remaining gangrene or necrotic tissue. Consequently, early debridement of necrotic tissue or minor amputation of gangrenous areas is usually recommended soon after the revascularization procedure *(3)*.

HBO therapy involves the intermittent inhalation of 90–100% oxygen at a pressure higher than 1atm absolute. HBO therapy favourably increases the amount of oxygen dissolved in arterial blood and leads to hyperoxia even in poorly perfused tissues *(4–6)*.

A minimal skin perfusion pressure (SPP) of over 40 mmHg is generally required for a planned minor amputation, such as at the toe level, after RT. However, higher perioperative SPP values in patients with SPP above 40 mmHg are associated with better success rates for the procedure *(3)*.

The duration and number of HBO therapy sessions patients typically receive depend on specific protocols tailored to each individual. Each person and condition are unique, so the protocol is determined by a hyperbaric medicine specialist. Hyperbaric treatment sessions can range from one to two hours *(7)*. Most treatments are administered once a day, five days a week, and can continue for several weeks. In severe cases, sessions may occur twice daily. Non-healing wounds typically require an average of 25–40 therapy sessions *(7)*.

METHODS

The study was conducted as a retrospective cohort study. It included five patients with CLTI accompanied by ulcers or gangrene who received HBO therapy following successful endovascular treatment (EVT) at the University Medical Centre Maribor between December 2022 and November 2023. HBO therapy was administered at 1.5 atm with 90% oxygen for 90 minutes per session daily, except on weekends, for 20–40 sessions.

Wound healing was assessed at the end of HBO therapy and again six months after treatment. Outcomes were determined based on the results of wound healing. Complete wound closure without any leakage was considered a successful healing outcome. Both healing and minor amputations were regarded as favourable outcomes. Conversely, no improvement or major amputations were considered as unfavourable outcomes.

RESULTS

The study involved five patients with CLTI (three males, two females) with an average age of 64.2 ± 7.3 years (table 1), which were all previously treated at the University Medical Centre Maribor. There was no clinical improvement in any leg treated with technically successful EVT. The average number of HBO sessions was 42.0 ± 23.9. HBO chamber treatments began a few days

after EVT for all but one patient, with an average start time of 8.7 ± 5.9 days post-EVT. Toe-level amputations were performed in three patients after EVT, and necrotic tissue debridement was required in two limbs.

All patients responded positively to the treatment. The introduction of hyperbaric oxygenation halted the progression of gangrene, and after three weeks of daily treatments, the wounds became clean and began to show signs of healing. Upon treatment completion, the wounds were successfully healed (figure 1). Pain relief was typically achieved after an average of six sessions, and over 90% of patients experienced an improvement in their ability to walk without discomfort. In addition to standard wound healing assessments for the legs, we conducted quality of life evaluations through patient interviews. We observed improved vitality and well-being in all patients.

Table 1. Characteristics of patients. AH – arterial hypertension, HLP – hyperlipidemia, DM – diabetes mellitus, WC – Wagner Classification.

Patient	Age	AH	HLP	DM	Smoker	Obesity	Previous	Minor amputation	Major amputation	Pre-treatment WC	Post-treatment WC
1	65	yes	yes	no	yes	no	yes	yes	no	3	2
2	70	yes	yes	yes	no	yes	yes	yes	no	3	2
3	53	yes	yes	yes	no	no	yes	yes	no	2	1
4	62	yes	yes	yes	yes	no	yes	no	no	2	2
5	71	yes	yes	no	yes	no	yes	no	no	3	1

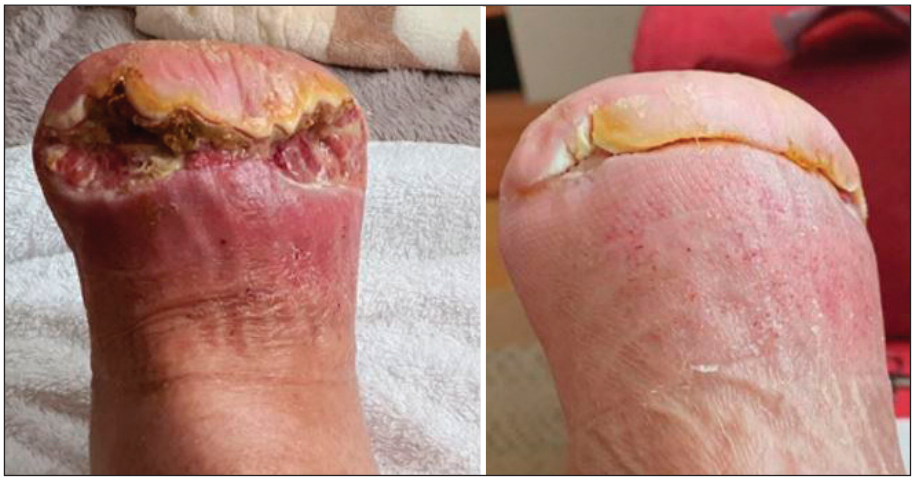

Figure 1. Clinical case from practice before (left) and after (right) hyperbaric oxygen (HBO) therapy, where successful healing was achieved after 40 sessions.

DISCUSSION

In patients with CLTI, persistent hypoxia prolongs wound healing. HBO therapy exposes the patient to an environment with elevated atmospheric pressure and increased oxygen concentration, leading to tissue hyperoxia. This can be beneficial due to antimicrobial effects and the increased activity of white blood cells *(1–7)*. Additionally, HBO therapy may promote long-term neovascularization *(1–3)*. It is essential to distinguish between oxidative stress and oxygen toxicity. While excessive reactive oxygen species (ROS) are associated with harmful effects, studies have shown that the body's antioxidant defences protect against the limited ROS generated during HBO therapy sessions *(7)*.

Limitations

This study has some limitations. First, it was conducted as a retrospective cohort study with a small sample size and, second, there was no control group for comparison.

CONCLUSION

Our research suggests that HBO therapy could be beneficial for patients with CLTI and nonhealing wounds following successful EVT, regardless of whether they have diabetes or not. Hyperoxia might also aid wound healing in patients for whom EVT was unsuccessful. Further studies that include a larger number of patients are needed.

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Tim Trstenjak[1], Nikola Lakič[2], Mark Racman[3], Tadeja Kolar[4]

Surgical Treatment of Endarteritis in the Iliofemoral Region with the Use of Selective Left Lower Limb Perfusion During a Prolonged Vascular Reconstruction – A Case Report

ABSTRACT

KEY WORDS: septic endarteritis, selective distal perfusion, *Staphylococcus aureus*, homograft

Surgical treatment of septic endarteritis of the iliofemoral region can result in prolonged ischemia of the lower extremities. Distal perfusion of the limb can improve early postoperative outcomes. We present a case of a 35-year-old woman who was diagnosed with septic endarteritis of the right iliofemoral region as a consequence of residual wire fragments from a prior endovascular procedure. During the intervention, the entire right iliofemoral arterial segment was replaced with a homograft due to the destruction of native arterial walls. Because of the extent of the replacement and predicted duration of the procedure, we used selective distal perfusion of her right leg to minimize the possibility of ischemia and reperfusion injury to the tissues, which is usually followed by compartment syndrome. The patient recovered fully. This case highlights the importance of a multidisciplinary approach when it comes to the treatment of rare and complex cases.

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INTRODUCTION

Septic endarteritis following endovascular procedures is a rare complication, reported in less than 1% of patients. Presentation within one to two weeks after the procedure is most common. Sites of infection usually include the groin region with inflamed skin, endarteritis, and/or pseudoaneurysm formation. Intravenous antibiotic treatment is considered the first line of treatment, but most patients require some sort of surgical intervention *(1)*. In case of extensive arterial wall destruction, it is necessary to surgically replace the entire vessel segment. A reperfusion injury after such a procedure is a very common complication. Using selective perfusion of the affected limb could minimize the reperfusion injury to the limb and kidneys following the procedure.

Written informed consent was obtained from the patient for publication of this case report and accompanying images.

CASE REPORT

A 35-year-old female with a history of endovascular procedures presented with a fever, headache, vomiting, pain in her right leg, and Osler's nodes (onset of symptoms two days prior to hospitalization). Inflammatory markers were elevated. An empirical intravenous antibiotic treatment was started (flucloxacillin, ceftriaxone). Haemocultures and the fluid from arthrocentesis of the right knee were later positive for *Staphylococcus aureus*, so antibiotic treatment was readjusted (flucloxacillin only). An echocardiography displayed no evidence of endocarditis. An X-ray and a CT scan showed foreign material (residual wire) present in the right iliac and femoral arteries with thrombosis in the right common femoral artery from prior endovascular procedures (from 2006 and 2012). A positron emission tomography combined with a CT (PET-CT) scan showed significantly elevated metabolic activity along the iliac arteries, common femoral artery (CFA), and superficial femoral artery (SFA) indicating possible inflammation in this region.

After two weeks of conservative medical treatment, the patient underwent an endovascular procedure to extract the residual material. The attempt was unsuccessful due to wire adhesion to the arterial wall. Five days later, the patient was operated on again, this time with an open surgical technique to remove foreign material and replace the extensive vessel segment, severely affected by endarteritis. Following proximal and distal exposure of the vessels, common iliac artery was clamped proximally and SFA distally. We perfused the distal part of the right leg via arterial cannulas (size 8 Fr) inserted in the distal SFA and femoral vein with a venous cannula (size 10 Fr) (figure 1). We used a roller pump and a children's oxygenator (Dideco Kids D101). The priming fluid was Ringer's lactate with a 50 mg dose of heparin. The limb was supported with a flow of 50–130 mL/min (average: 86.00 ± 0.35 mL/min). Arterial line pressure was 59–70 mmHg (average: 60.60 ± 6.58 mmHg). Hematocrit values during selective perfusion from the oxygenator were between 23.6–26.8% (average: 25.12 ± 1.44%) and activated clotting time (ACT) was 361–564 s (average: 446.33 ± 105.29 s). Then the rest of the vessels were exposed, the wire and the affected arteries were removed, and the segment was replaced with two homografts. Selective perfusion of the leg was discontinued after 73 minutes by removing the clamps. Before closing, the wound was thoroughly rinsed.

After the surgery, the patient was prescribed lifelong acetylsalicylic acid and antibiotics for four weeks. Creatinine and myoglobin were only slightly elevated immediately after the procedure (probably due to ischemia of the thigh and buttock) and returned to normal values the same day. The patient gained full function of her lower limb during hospitalization.

The patient was discharged from hospital after seven weeks. On the six-month follow-up appointment, the patient denied any problems concerning the functionality of her right leg or any signs of inflammation.

DISCUSSION

To our knowledge, this is the first case of peripheral vascular reconstructive surgery to treat septic endarteritis, where selective perfusion of a limb during the procedure was used to minimize ischemia and reperfusion injury due to predicted longer duration of intraoperative limb ischemia.

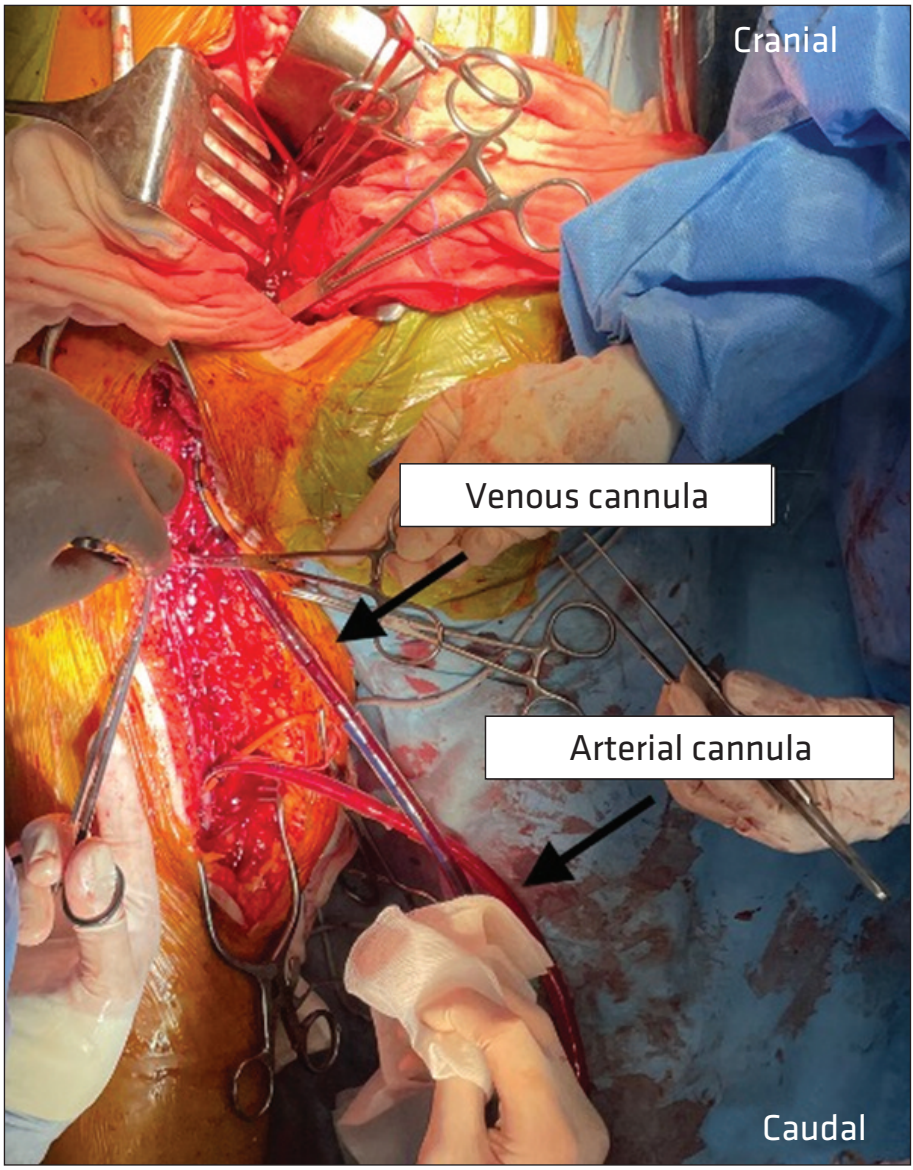

Figure 1. Cannulation of the superficial femoral artery and femoral vein, and selective perfusion.

Ischemic injury is responsible for cellular death and also for cellular edema, which can further compromise tissue perfusion *(2)*. The reperfusion of ischemic tissues leads to the release of bioproducts of muscle ischemia and cell necrosis into circulation (potassium, phosphate, organic acids, myoglobin, creatine kinase, and thromboplastin), and can cause systemic complications such as cardiac depression, acute lung injury, renal failure and poorer limb-related functional outcomes *(3)*. A study by Perkins and colleagues on the impact of ischemia duration on lower limb salvage in combat casualties showed that the threshold to restitution of blood flow should be much less than the ubiquitous six hours – the probability of limb salvage was still only around 60% when ischemia was < 3 hours *(4)*. Current therapies aimed at mitigating ischemia-reperfusion injury are mostly just supportive, by providing adequate hydration, electrolyte correction, vasopressor support, and acid-base management only after reperfusion has occurred.

A controlled reperfusion of the lower extremity was shown to improve outcome after acute severe lower-limb ischemia by using a crystalloid reperfusion solution with glucose, tromethamine glutamate, aspartate, allopurinol, and sodium citrate *(5)*. During elective major vascular operations, ischemic postconditioning proved to be capable of conferring protection against different organ injuries caused by longer circulatory occlusions *(6)*. Several studies suggest that selective renal and visceral perfusion during thoracoabdominal aortic aneurysm repair improves outcomes *(7)*.

In our case, selective distal perfusion in a peripheral vascular surgery offers a solution through which malperfusion of a limb can be completely avoided during an operation, thereby, avoiding the possibility of reperfusion injury. It is particularly suitable for major reconstructive vascular surgery, where the procedure itself is the cause of temporary acute ischemia.

CONCLUSIONS

The use of distal perfusion of the limb during a reconstructive vascular procedure highlights the importance of interdisciplinary involvement in the improvement of patient outcomes, especially in those with anticipated prolonged limb ischemia due to a surgical procedure.

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Monika Štalc[1]

Thoracic Aorta and Coronary Artery Calcification in Patients Referred to Myocardial Perfusion Scintigraphy

ABSTRACT

KEY WORDS: myocardial perfusion scintigraphy, coronary calcification, thoracic aorta calcification, CT

BACKGROUNDS. Myocardial perfusion imaging (MPI) is a well-established non-invasive imaging technique for the diagnosis of coronary artery disease (CAD). MPI may detect obstructive CAD but fail to discover subclinical atherosclerosis. With advances in technology, low-dose CT for attenuation correction has become an important part of nuclear cardiology. CT in MPI allows for the visualization of thoracic aorta calcification (TAC) and coronary artery calcification (CAC). The aim of the study was to evaluate the prevalence of TAC and CAC in patients referred to MPI. METHODS. Clinical characteristics, MPI results, and prevalence of CAC and TAC were collected from 90 consecutive patients with an intermediate likelihood of CAD and without previously known atherosclerosis who were admitted to MPI. RESULTS. Out of 90 patients, 32 (35.6%) had ischemia, and 58 (64.4%) patients had normal MPI. Calcification was present in 63.3% of all patients on low-dose CT (75.0% with ischemia versus 57.0% with normal MPI, $p = 0.09$). Most patients with CAC had concomitant TAC. In more than a quarter of patients, only TAC was present. More patients with ischemic MPI had CAC compared to patients with normal MPI (53.1% versus 25.8%, $p = 0.01$). Patients with normal MPI and TAC or CAC were older (71.1 ± 7.6 years versus 56.5 ± 9.2 years, $p < 0.001$) and had more arterial hypertension (78.9% versus 52.0%, $p = 0.03$) than patients without calcification. Patients with normal MPI and suffering only from TAC had more arterial hypertension than patients with CAC (94.4% versus 60.0%, $p = 0.01$). CONCLUSIONS. The combination of myocardial perfusion, CAC, and TAC from a single MPI scan may have a complementary role in the management of patients with an intermediate risk of CAD. In addition to improving risk estimation, reporting visually estimated calcification may influence patient management decisions.

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INTRODUCTION

Myocardial perfusion imaging (MPI) is a well-established non-invasive imaging technique for the diagnosis and prognosis of coronary artery disease (CAD) in patients with an intermediate pretest probability for CAD *(1)*. A functional assessment of CAD through the evaluation of stress-induced ischemia is provided by MPI. Detecting obstructive CAD may be possible with MPI, but it may fail to discover subclinical atherosclerosis.

Coronary artery calcification (CAC) and thoracic aorta calcification (TAC) are frequent incidental findings on non-gated thoracic CT. With advances in technology, low-dose CT has become an important part of nuclear cardiology. Gamma cameras have a built-in CT scanner, which is routinely used for attenuation correction. The visualization of TAC and CAC is possible with CT in MPI. When paired with nuclear medicine imaging, these two modalities can provide complementary diagnostic information. Until recently, calcination was not routinely evaluated or reported in MPI *(2)*.

The quantitative Agatston score is a well-established prognostic marker for CAD. A dedicated non-contrast ECG-gated cardiac CT is used to formally evaluate CAC. However, CAC can be identified on non-gated thoracic CT with excellent diagnostic accuracy compared to gated CT. For non-gated thoracic CT in routine clinical practice, a simple visual quantification is recommended. The low-dose CT visual calcium score correlated well with the Agatston score. Visually estimated CAC on chest CT in patients without known CAD is associated with an increased rate of major adverse cardiovascular events. An increased rate of myocardial infarction and a need for revascularization interventions were found to be associated with CAC on routine chest CT. The visually estimated coronary calcium score has also been shown to improve MPI risk stratification in clinical practice *(2, 3)*.

A wealth of data has also emerged regarding TAC and risk stratification, principally from additional analyses of primary prevention cohorts that focused on CAC. Systemic atherosclerosis is reflected by TAC, and its severity may be associated with the severity of CAD. All-cause mortality has been related to TAC, independently of conventional risk factors and the presence of CAC. A few studies reported no significant correlation between TAC and cardiac events. Despite the limited prognostic role of TAC beyond CAC, the reporting of TAC on all non-contrast chest CT and calcium scoring scans even without CAC is recommended *(4–6)*.

Since a CT for attenuation correction is embedded within the MPI workflow with no additional cost or radiation, it is beneficial to extract anatomical information from the exam. The aim of our study was to evaluate the prevalence of TAC and CAC in patients referred to MPI.

PATIENTS AND METHODS

This was a retrospective study with a population taken from a single tertiary medical centre. Data was analysed from 90 consecutive patients with an intermediate likelihood of CAD and without previously known atherosclerosis who were referred for MPI. The clinical characteristics of the patients were prospectively collected at the time of the MPI study. All patients were assigned to a two-day stress/rest protocol. They underwent either bicycle exercise stress (ERG 911 S plus, Schiller™) or vasodilator stress (regadenoson 400 µg or dipyridamole 0.56 mg/kg). An hour after the intravenous injection of Technetium-99m tetrofosmin 450 MBq (Myoview™, GE Healthcare), we imaged the patients on a Symbia Intevo® gamma camera with a two-slice CT. The CT parameters for the attenuation correction included a tube current of 30 mAs, a voltage of 130 kVp, a pitch of 1.5 and a B08s kernel for reconstruction. We performed stress protocols, image acquisition, and recon-

struction according to the guidelines of the European Association of Nuclear Medicine (EANM). Two experienced nuclear cardiologists interpreted the stress MPI. The presence of CAC and TAC was detected visually on dedicated commercial software using a soft-tissue window, and expressed binary (present or absent). The reader was blinded to the MPI results.

Statistical methods

The Kolmogorov-Smirnov test was used to assess normal distribution in all cases. Continuous variables are presented as mean ± standard deviation and were compared using Student's t-test. Categorical variables are reported as frequencies with percentages and were compared using the x^2 test. A p-value of ≤ 0.05 was considered statistically significant.

RESULTS

The clinical characteristics and calcification data of the patient population stratified by MPI result are shown in table 1. Out of 90 patients, 32 (35.6%) had ischemia and 58 (64.4%) had normal MPI. More patients with ischemia had diabetes; there were no differences in other cardiovascular risk factors between the groups. Patients with ischemic MPI had more CAC compared to patients with normal MPI. Most patients with CAC had concomitant TAC. In more than a quarter of patients, only TAC was present. Calcification was present in 57.0% of patients with normal MPI. A representative case with no evidence of ischemia on MPI but CAC and TAC on CT is shown in figure 1. Patients with normal MPI and calcification were older (71.1 ± 7.6 versus 56.5 ± 9.2, p < 0.001) and had more arterial hypertension (26 (78.9%) versus 13 (52.0%), p = 0.03) than patients without calcification. Patients with normal MPI and suffering only from TAC (N = 18) had more arterial hypertension than patients with CAC (N = 15) (17 (94.4%) vs. 9 (60.0%), p = 0.01).

Table 1. Clinical characteristics and calcification data in patient population. N – number, MPI – myocardial perfusion imaging, SD – standard deviation, CAC – coronary artery calcification, TAC – thoracic aorta calcification.

	All (N = 90)	Ischemia on MPI (N = 32)	Normal MPI (N = 58)	P-value
Age (mean ± SD) (years)	65.7 ± 10.6	67.3 ± 9.5	64.8 ± 11.1	0.28
Female gender	51 (56.6%)	15 (46.8%)	36 (62.0%)	0.16
Arterial hypertension	64 (71.1%)	25 (78.1%)	39 (67.2%)	0.88
Diabetes mellitus	23 (25.5%)	12 (37.5%)	11 (18.9%)	0.05
Hyperlipidemia	42 (46.7%)	18 (56.2%)	24 (41.4%)	0.17
Smoking	13 (14.4%)	5 (15.6%)	8 (13.8%)	0.81
All calcification	57 (63.3%)	24 (75.0%)	33 (56.9%)	0.09
CAC	32 (35.5%)	17 (53.1%)	15 (25.8%)	0.01
TAC	53 (58.9%)	23 (71.8%)	30 (51.7%)	0.06
Only CAC	4 (4.5%)	1 (3.1%)	3 (5.1%)	0.65
CAC and TAC	28 (31.1%)	16 (50.0%)	12 (20.7%)	0.004
Only TAC	25 (27.8%)	7 (21.9%)	18 (31.0%)	0.35

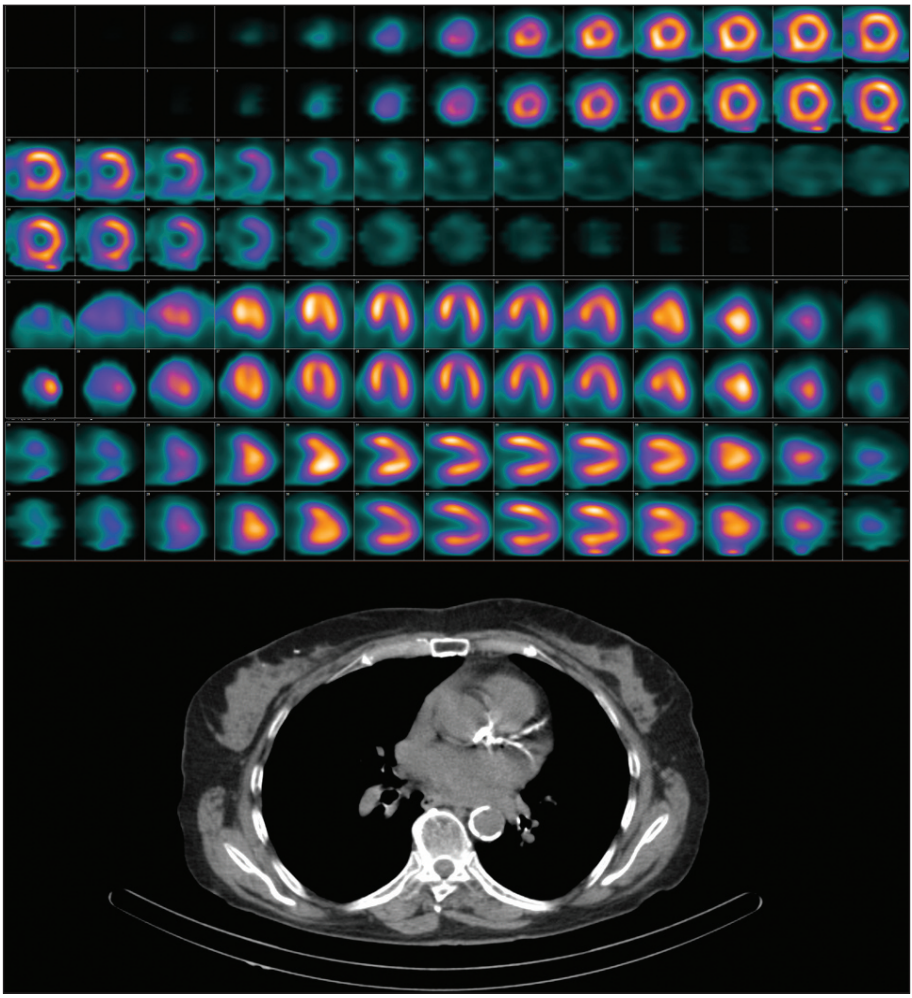

Figure 1. Coronary and thoracic aorta calcification were noted in a 73-year-old female patient with no evidence of ischemia on the stress myocardial perfusion scintigraphy.

DISCUSSION

The present study demonstrated that almost two-thirds of the patients without previously known atherosclerosis referred for MPI had TAC or CAC. Most patients with CAC had concomitant TAC; in more than a quarter of patients, only TAC was present. Our study also showed a high prevalence of subclinical atherosclerosis in patients with normal MPI.

Patients with ischemic MPI had more CAC compared to patients with normal MPI. However, 26.0% of patients with normal MPI had CAC. Coronary atherosclerosis is indicated by CAC, however, it does not necessarily imply obstructive CAD. In contrast, ischemia is the consequence of a flow-limiting lesion or a microvascular dysfunction. The integration of CAC in MPI results may provide an opportunity for intensive risk factor modification, including the treatment of hyperlipidemia *(2)*.

In a recent study, 69% of patients with a normal MPI had an Agatston score > 0 *(2)*.

The percentage of our patients with normal MPI and CAC was significantly lower. The main reason for the difference is that the visually estimated CAC on a CT for attenuation correction may underestimate the extent of CAC due to cardiac motion artifacts, slice thickness, and low image resolution.

Almost one third (31.0%) of our patients with normal MPI had only TAC. Published data on TAC on a low-dose CT in MPI is scarce. In a previous study, TAC on echocardiography was associated with abnormal myocardial perfusion *(5)*. In contemporary practice, the value of any imaging test is framed within a hierarchical context, beginning with technical considerations, diagnostic accuracy and culminating with changes in therapy and improved outcomes. This high standard has not yet been met by TAC. Although TAC may identify a patient at higher risk for noncoronary events, the extent of reclassification and implications for management remain unclear. One of the reasons for the inconclusive results from the studies regarding TAC and risk stratification are different fields of view used on a CT. The most important distinction is whether the aortic arch and proximal descending aorta have been included, since 60% of all TAC are found in this area *(5)*. In our patients, all parts of the thoracic aorta were visualized.

Only 43.0% of patients with normal MPI have no calcification. They were younger and had less arterial hypertension than patients with calcification. A strong association between the presence of CAC and advancing age in patients with normal MPI was already shown in a previous study. They also found no association between CAC and arterial hypertension *(7)*.

Limitations

There are several limitations to our study. The study was conducted as a retrospective single tertiary centre study, and we do not have a correlation between our results and invasive or CT coronary angiography. The studied patient population was too small to draw definite conclusions. Due to the lack of standardization, we chose a binary approach for CAC and TAC reporting. For patient risk stratification, calcification can be categorized as mild, moderate, or severe. With low-dose CT, only TAC is detected; in the thoracic aorta, the noncalcified atheroma may be especially prominent, and calcification may not completely encompass cardiovascular risk related to thoracic aorta atherosclerosis.

CONCLUSIONS

The combination of myocardial perfusion, CAC, as well as TAC from a single MPI scan may have a complementary role in the management of patients with an intermediate risk of CAD. In addition to improving risk estimation, reporting visually estimated calcification may influence patient management decisions. Further prospective, large-scale studies are needed to investigate the presence of subclinical atherosclerosis (CAC and TAC) in patients referred to MPI for better risk stratification.

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Gregor Tratar[1]

Cancer-associated Venous Thromboembolism and Thrombocytopenia

ABSTRACT

KEY WORDS: cancer-associated thromboembolism, thrombocytopenia, venous thromboembolism, anticoagulation therapy

Venous thromboembolism often occurs in patients with cancer. The risk of venous thromboembolism is increased because of the prothrombotic state (platelet activation, increased tissue factor expression) as well as cancer treatment (surgery, central venous lines, chemotherapy). On the other hand, thrombocytopenia also frequently develops in cancer patients due to cancer itself (e.g., in haematological malignancies) or due to anti-cancer therapy. The management of cancer-associated thromboembolism in patients with thrombocytopenia is therefore challenging due to increased risk of recurrent venous thromboembolism on one hand and increased risk of bleeding on the other. Generally, the use of full-dose anticoagulation is considered safe in patients with a platelet count above 50×10^9/L. However, in patients with more pronounced thrombocytopenia, a careful assessment of venous thromboembolism recurrence risk and risk of bleeding must be made. In this paper, we review the current recommendations regarding thrombocytopenia and cancer-associated thromboembolism management in these patients.

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CANCER AND VENOUS THROMBOEMBOLISM

Venous thromboembolism (VTE), encompassing deep vein thrombosis (DVT) and pulmonary embolism (PE), is a common complication in cancer patients. It is estimated that approximately 15% of cancer patients will develop VTE during the course of their disease and that active cancer is responsible for up to 20% of otherwise unexplained VTE *(1, 2)*. According to recent data, the risk of VTE in cancer patients is 15-times higher than in patients without cancer *(3)*. Patients with cancer who develop VTE have a worse prognosis than those without VTE. The mechanisms of cancer-associated thromboembolism (CAT) include all the components of the Virchow triad (vessel wall damage, stasis, hypercoagulability). Many of them are cancer specific: thrombocytosis with platelet activation, leucocytosis and neutrophil extracellular traps, the expression of tissue factor and elevated levels of plasminogen activator inhibitor-1 (PAI-1). Other factors also influence the risk of CAT, i.e. cancer surgery, the insertion of central venous catheters, and chemotherapy. Because CAT recurrence rate is high and associated with poor prognosis, CAT management is challenging *(4, 5)*.

The Low-Molecular-Weight Heparin versus a Coumarin for the Prevention of Recurrent Venous Thromboembolism in Patients with Cancer (CLOT) trial in 2003 clearly showed that treatment with low-molecular-weight heparins (LMWH) in the first six months after CAT was more effective than warfarin and this approach has long represented the mainstay of anticoagulation in CAT *(6)*. However, in recent years, several trials proved the effectiveness of direct oral anticoagulants (DOACs) for the treatment of CAT, and DOACs (rivaroxaban, apixaban, edoxaban) are now recommended as the first line anticoagulant treatment option in CAT as well *(7, 8)*. An increased risk of bleeding in gastrointestinal tumours and possible interactions with cancer treatment must be taken into account.

CANCER AND THROMBOCYTOPENIA

Thrombocytopenia often occurs in cancer patients. It can be a result of the underlying disease (e.g., in haematological malignancies), but most often it is a consequence of oncological treatment. Severe thrombocytopenia occurs in about 30% of patients with solid tumours and in about 50% of patients with haematological malignancies *(8)*. Without anticoagulant treatment, the risk of bleeding increases at a platelet count $< 25 \times 10^9$/L and the risk of spontaneous major bleeding increases at a platelet count $< 10 \times 10^9$/L. Chemotherapy-induced thrombocytopenia (CIT) is usually managed with platelet transfusions although the duration of platelet count improvement is short-lived and transfusions are not practical for the long-term maintenance of platelet count throughout chemotherapy. Therefore, platelet transfusions are usually only used in severe thrombocytopenia (platelet count $< 10 \times 10^9$/L) and/or in case of bleeding complications *(8)*. Thrombopoietin receptor agonists (TPO-RAs) are a promising therapeutic option in patients with solid tumours but are currently only approved for the treatment of specific types of thrombocytopenia (e.g. immune thrombocytopenia) and have not been tested in CIT. Due to a lack of phase 3 clinical trials, the current guidelines of the Scientific and Standardization Committee (SSC) of the International Society on Thrombosis and Haemostasis (ISTH), suggest the use of TPO-RAs only in the setting of clinical trials or the use of romiplostim when considering TPO-RA use outside of clinical trial settings *(8)*.

THE MANAGEMENT OF CANCER-ASSOCIATED THROMBOEMBOLISM IN PATIENTS WITH THROMBOCYTOPENIA

CAT is associated with an increased risk of recurrence but the use of full-dose anticoagulation in thrombocytopenic patients is considered risky due to an increased risk of bleeding. Generally, the use of full-dose anticoagulation is considered safe in patients with a platelet count > 50×10^9/L *(9)*. The management of anticoagulation in patients with more pronounced thrombocytopenia is uncertain. Usually, LMWHs are used due to the lack of data on the use of DOACs in this setting. For patients with severe thrombocytopenia and acute CAT (up to one month), the guidelines suggest either a full-dose of LMWH and platelets transfusions to maintain a platelet count of 40–50×10^9/L in patients with a high risk of thrombosis progression or a 50% reduction of the LMWH dose in patients with low risk of thrombosis progression. For subacute CAT (more than one month), the guidelines suggest a 50% reduction of the LMWH dose or the use of a prophylactic LMWH dose. In patients with a platelet count < 25×10^9/L, temporary discontinuation of anticoagulation is suggested *(9)*. Some recommendations use a somewhat higher cut-off value for the discontinuation of anticoagulation at 30×10^9/L *(10)*.

CONCLUSION

CAT management is especially challenging in cancer patients with thrombocytopenia. The cause and the degree of thrombocytopenia, risk of bleeding, risk of recurrent VTE and other patient characteristics must be taken into account when selecting optimal anticoagulant treatment for such patients.

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Barbara Eržen[1]

Native Aortic Valve Thrombosis: What's Behind?

ABSTRACT

KEY WORDS: native aortic valve, thrombosis, cancer, transesophageal echocardiography

Native aortic valve thrombosis is an exceptionally rare and serious condition characterized by the formation of a thrombus on the native aortic valve. It presents a significant clinical challenge and can lead to severe complications, including heart failure or cardiogenic shock due to a heart attack or aortic valve dysfunction, neurological issues such as stroke, and peripheral embolisms affecting the arteries of the arms, legs, kidneys, and other organs. Given the numerous potential causes of peripheral embolism, native aortic valve thrombosis is an extremely rare source. Due to its low incidence, there is limited data on its aetiology, treatment, complications, and clinical outcomes, with most information derived from individual case reports. It is imperative to identify the underlying cause, which frequently poses a significant clinical challenge. We present the case of a 55-year-old patient with a pronounced prothrombogenic condition, which manifested as a venous thromboembolism and thrombosis of the native aortic valve. This condition led to a repeated embolism into the central nervous system and peripheral arteries of the arms and legs. The underlying cause of the prothrombogenic state was a newly diagnosed lung carcinoma.

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CASE REPORT

A previously healthy 55-year-old woman, a non-smoker, presented to the angiology outpatient clinic with a three-week history of left swelling. Her medical history was notable only for asthma. Clinical examination revealed no abnormalities other than left leg calf swelling. An ultrasound of the left leg veins indicated acute popliteal and posterior tibial deep vein thrombosis and treatment with therapeutic doses of dalteparin was initiated.

Baseline laboratory tests, including complete blood count, troponin level, screening rheumatological examinations, liver and kidney function, were normal, except for an elevated D-dimer level of 21,114 µg/L. There was no clinical evidence of infections. A chest X-ray showed thickening in the left hilum but no other pathological changes. One week later, the patient reported tingling and weakness in her right arm and leg. A head CT revealed two acute ischemic lesions. Anticoagulant therapy was immediately discontinued, and a filter was inserted into the inferior vena cava. Despite this, hemiparesis recurred the next day, and a follow-up head CT revealed another ischemic lesion measuring 2 × 1 cm.

Suspecting paradoxical embolism, a transthoracic echocardiography (TTE) was performed, which showed a thickening of the right and non-coronary aortic valve leaflets, mild aortic valve insufficiency, no shunt, and otherwise normal findings. A transesophageal echocardiography (TEE) confirmed a mass on the right and non-coronary aortic valve leaflets (figure 1). To further characterize the mass, a cardiac CT angiography was performed, revealing hypodense changes measuring 11 × 11 × 6 mm on the non-coronary leaflet, 7 × 7 × 6 mm on the right coronary leaflet, as well as a smaller hypodense change on the left coronary leaflet. These lesions did not enhance convincingly after contrast administration and were most likely thrombi. According to the cardiosurgical council, surgical treatment of the aortic valve thrombosis was not indicated. The patient was treated conservatively, initially with subtherapeutic doses of dalteparin due to a recent ischemic stroke, and after ruling out the haemorrhagic trans-

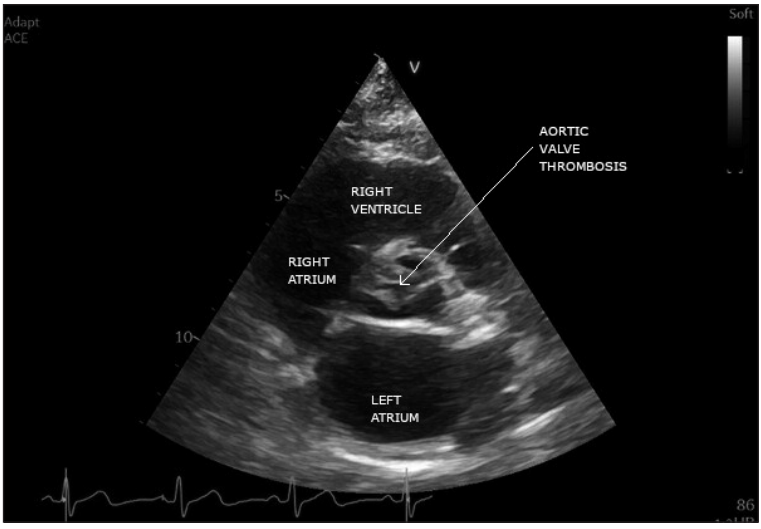

Figure 1. Transthoracic echocardiography (parasternal window, short axis) showing mass (thrombosis) on the right and non-coronary aortic valve leaflets.

formation of ischemic lesions by a head CT, therapeutic doses were resumed.

A contrast-enhanced chest CT showed a 6.5 cm consolidation in the lingula suspicious for pulmonary malignancy, signs of lymphangitic carcinomatosis, bilateral pleural effusion, and a small pulmonary thromboembolism. The preliminary radiological stage was assessed as T3 N2 M1a. An abdominal CT showed no signs of malignancy in the abdomen. A head MRI revealed multiple small acute ischemic lesions consistent with microembolisms. A pleural puncture confirmed a malignant exudate, cytomorphological indicating non-small cell carcinoma, most likely adenocarcinoma of the lung. Molecular genetic testing revealed the presence of a proto-oncogene tyrosine-protein kinase-1 (ROS-1) gene fusion.

The thoracic-oncology council recommended systemic immunotherapy with entrectinib. However, before systemic targeted therapy could be initiated, the patient's condition rapidly deteriorated despite therapeutic doses of dalteparin with recurrent emboli affecting both the central nervous system and peripheral arteries of the arms and legs. She developed tetraparesis, and acute ischemia of the fingers and toes, and experienced severe pain. Unfortunately, only palliative treatment was possible for the patient, a palliative mobile unit was activated, and the patient died two months after the first symptoms appeared.

DISCUSSION

Unlike thrombosis on an artificial, mechanical aortic valve, thrombosis on a native aortic valve is extremely rare, resulting in very limited data in the literature. However, the number of published cases of thrombosis on native valves has increased with each decade, primarily due to improved imaging techniques. By 2020, 74 cases had been described. That is why this condition poses significant diagnostic and therapeutic challenges *(1)*.

The most common clinical presentations of aortic valve thrombosis are myocardial infarction, acute limb ischemia, cerebrovascular incidents, and heart failure *(1)*. In our clinical case, the first manifestations were tingling and weakness in patient's right arm and leg due to an embolism into the central nervous system, followed by several embolisms into the peripheral arteries of the arms and legs, resulting in acute limb ischemia.

The diagnostic work-up typically relies on an echocardiography, particularly TEE, due to its superior temporal and spatial resolution compared with TTE *(2)*. A TTE with 59% and a coronary angiography with 29% sensitivity are not sufficiently sensitive examinations for detecting aortic valve thrombosis. Therefore, it is essential to perform either TEE or aortic root angiography, which achieves 100% sensitivity. Other imaging modalities, such as cardiac CT, can also be useful but may yield false negatives, especially in cases involving mobile thrombi *(1)*. In our clinical case, in addition to TEE, we also performed a CT angiography of the heart to obtain additional information regarding the aetiology of the mass on the valve.

Given the rarity of native aortic valve thrombosis, it is essential to investigate underlying causes thoroughly. In most described cases, native aortic valve thrombosis occurs in hypercoagulable conditions, with antiphospholipid syndrome being the most common, in systemic connective tissue disease, alternatively formed on a diseased valve (calcifications), followed by aortic root/valve structural abnormalities such as a bicuspid aortic valve, degenerative aortic valve, left ventricular assist device, hypoplastic left heart syndrome or as a consequence of trauma (surgery catheterization) *(1, 3)*. Therefore, in the absence of structural abnormalities of the aortic valve and endothelial lesions, it is reasonable to check autoantibodies

(anti-cardiolipin, lupus anticoagulants, anti-b2GPI antibodies), tumour markers, and coagulopathy markers (prothrombin gene mutation, C-S protein deficiency, antithrombin III, resistance to activated protein C). We must also always consider the possibility of an underlying malignancy and conduct a thorough screening for cancer *(4)*.

In our case, we observed simultaneous deep vein thrombosis and thrombosis on the native aortic valve. Suspecting an occult malignancy, we performed a CT scan of the abdomen and chest, which revealed a tumour in the lingula. This tumour was diagnosed as non-small cell carcinoma, most likely adenocarcinoma of the lung. We have found another case report in the literature describing thrombotic masses on the native aortic and mitral valves in a patient with lung cancer *(5)*.

Differentiating native aortic valve thrombosis from tumours, particularly papillary fibroelastoma, which is the most common valvular tumour, can be challenging. Both native valve thrombus and papillary fibroelastoma can cause systemic embolic events *(6)*. The definitive diagnosis is made histologically.

The risk of in-hospital clinical deterioration in patients with native aortic valve thrombosis is 38%, and the overall in-hospital mortality is 20% *(1)*. Therefore, native aortic valve thrombosis predicts an unfavourable prognosis. Some authors advocate for the prompt surgical resection of this valvular disease, regardless of its size and shape, not only to confirm the pathology but also due to the potential for life-threatening complications from a left-sided mass and for representing a poor prognosis *(5)*.

Due to the lack of evidence, decision-making regarding the treatment approach is often based on individualized care, the recommendations of a heart team, or expert opinion. Anticoagulation treatment decisions are complex, especially when central nerve system embolisms prevent treatment with therapeutic doses of anticoagulant drugs. The optimal treatment approach is unclear; there are no guidelines to definitively recommend thrombectomy accompanied with anticoagulation versus anticoagulation alone.

Our patient was treated conservatively with anticoagulation and supportive therapy. Based on the systematic review, patients who were not treated with thrombectomy and those who experienced clinical deterioration or recurrence during hospitalization had worse outcomes with statistically significant increased in-hospital mortality *(1)*. In our case, a neurological complication (hemiparesis) recurred during hospitalization and, according to the cardio surgery council, she was treated conservatively without surgery, which was somehow understandable given the newly discovered metastatic malignant disease *(2)*. However, thrombectomy is worth considering in patients who are otherwise reasonable candidates for surgery.

In our patient, following conservative treatment, the condition rapidly deteriorated due to recurrent central and peripheral embolisms, resulting in critical limb ischemia. Consequently, only palliative therapy could be administered, and the patient passed away two months after the onset of the initial symptoms. This case underscores the severity and extremely poor prognosis associated with aortic valve thrombosis. In any case, serious consideration of operative treatment would be necessary in the absence of disseminated malignancy. The literature review indicates that surgical intervention has a better outcome in these cases *(1)*.

CONCLUSIONS

A thrombosis on the native aortic valve is an extremely rare, urgent, and dangerous condition with a poor prognosis and high mortality. It is essential to investigate underlying causes thoroughly. Rapid action

and treatment are necessary, though challenging, as decisions often must be made on a case-by-case basis. Due to the rarity of the disease and the consequent lack of data, there are no established guidelines. There is a need to report cases that can enhance knowledge about this condition. Our report represents a rare case of spontaneous native aortic valve thrombosis in a patient with newly discovered pulmonary carcinoma, who was treated conservatively.

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Andrej Juretič[1]

Vaccines Directed Against Proprotein Convertase Subtilisin/Kexin Type 9

ABSTRACT

KEY WORDS: Vaccines, PCSK9, primary prevention, animal models, LDL

Despite progress in primary and secondary prevention, atherosclerotic cardiovascular disease remains one of the leading causes of mortality. Long-term exposure to elevated levels of low-density lipoprotein (LDL) cholesterol is a significant risk factor for its development. Various treatment strategies for hypercholesterolemia exist; however, their success is limited. Treatment with tested and registered humanized monoclonal antibodies against proprotein convertase subtilisin/kexin type 9 (PCSK9) is not widely available due to high costs. One potentially effective treatment currently under preclinical and clinical investigation is the development of vaccines against PCSK9. This could ensure a long-term reduction of total and LDL cholesterol in an effective and affordable way. Preclinical research on animal models and a smaller clinical study indicate that these vaccines induce a significant, long-lasting antibody response that effectively lowers LDL and total cholesterol levels without significant side effects. Larger clinical phase II and III studies are still needed to further elucidate the safety and efficacy of PCSK9 vaccines. In this article, the current knowledge in the field is briefly summarized.

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INTRODUCTION

Atherosclerotic cardiovascular disease is a degenerative inflammatory process characterized by the accumulation of lipids and inflammatory cells within arterial walls *(1)*. Lipid-rich deposits, known as plaques, gradually narrow the arteries, causing ischemia or, in the case of plaque rupture, thrombosis. The interplay between elevated levels of cholesterol in low-density lipoproteins (LDL) and other cellular processes (endothelial cell dysfunction, formation of foam cells, activation of various immune cells) in the arteries leads to the gradual progression of atherosclerosis throughout life *(1)*. The proprotein convertase subtilisin/kexin type 9 (PCSK9) molecule influences cholesterol homeostasis by binding to the epidermal growth factor-like domain A (EGF-A) on the LDL receptor in hepatocytes, initiating the degradation of the LDL receptor and thereby reducing the serum clearance of LDL cholesterol *(1)*. Several genotypes related to PCSK9 and its ability to influence cholesterol homeostasis affect the phenotype: mutations that enhance PCSK9 function cause a rare form of familial hypercholesterolemia, while loss of function (LOF) mutations that reduce PCSK9 function result in lower levels of LDL cholesterol and protect against atherosclerotic cardiovascular disease *(2)*. People who carry homozygous or two heterozygous LOF mutations have undetectable PCSK9 levels and exhibit very low LDL cholesterol levels and are protected from developing atherosclerosis and its atherothrombotic complications *(3)*. Current therapeutic strategies for treating atherosclerosis involve lowering LDL cholesterol levels using statins, which is an effective approach. However, many individuals, particularly patients with familial hypercholesterolemia, do not respond to or tolerate such therapy. PCSK9 emerges as a natural target for preventing hypercholesterolemia, as it has been shown that people with heterozygous LOF mutations live without serious side effects *(4)*. Large clinical studies have demonstrated that patients receiving PCSK9 inhibitors in the form of fully human neutralizing antibodies significantly reduced their LDL cholesterol levels *(4, 5)*. Despite the effectiveness of monoclonal antibodies, there are several drawbacks to this type of treatment. First, antibodies have a relatively short half-life *in vivo*, and second, the therapy, which requires frequent dosing once or twice a month, is expensive *(4)*. A PCSK9 vaccine could represent a cheaper but still safe alternative for effectively lowering LDL cholesterol and preventing atherosclerotic complications.

VACCINES AND IMMUNE RESPONSE

In recent years, we have witnessed rapid progress in the development of vaccines extending beyond the prevention of infectious diseases. The functioning of the immune system can be divided into innate and acquired immune responses. Upon encountering a foreign antigen, antigen-presenting cells (APC) take it up from the environment, degrade it into shorter peptide molecules via endosomal pathways, and present these within the framework of the major histocompatibility complex (MHC) I or II to cluster of differentiation (CD) 8-positive and CD4+ lymphocytes *(6)*. This is the innate immune response. When foreign immunogenic molecules are recognized and encountered by B lymphocytes, a signalling pathway is triggered, causing the production of foreign-specific B lymphocytes, their maturation, and differentiation into plasma cells that secrete foreign-specific neutralizing antibodies. This is the so-called acquired immune response: neutralizing antibodies deactivate the antigen and mark it for elimination before it can cause damage to the organism, while remaining antibodies act as a part of the immune response »memory« *(6)*. For the

development of vaccines against external antigens, it is desirable that the vaccines induce a specific and targeted immune response based on the development of specific neutralizing antibodies and/or cytotoxic T lymphocytes, while this response is maintained for potential future infections *(6)*. To prevent an autoimmune response to the organism's own (endogenous) proteins, immune cells are subjected to negative selection during maturation. This does not mean that the formation of antibodies against endogenous proteins and/or their fragments cannot be triggered; this can be ensured provided there is stimulation of B lymphocyte activation by helper T lymphocytes *(6)*. If we simultaneously prevent the formation of CD8+ cytotoxic lymphocytes, which would cross-reactively attack cells producing the target endogenous protein, we can ensure the safety of the vaccine against endogenous targets without causing systemic inflammation in otherwise healthy tissues of the organism.

Vaccines inducing antibody response against proprotein convertase subtilisin/kexin type 9

Vaccines against PCSK9 stimulate the production of neutralizing antibodies that prevent the binding between the PCSK9 molecule and the LDL receptor. Several preclinical studies indicate that this could be an effective and safe way to lower LDL cholesterol. Galabova and colleagues used short peptides composed of 8–13 amino acids from the N-terminal part of human PCSK9, conjugated to a carrier protein that does not elicit self T cell responses *(7)*. Upon adding an aluminium adjuvant, they demonstrated the induction of antibodies against PCSK9, and a reduction of LDL and total cholesterol in laboratory rats. They also showed a reduction in total and LDL cholesterol in mice, which persisted even after six months compared to controls. No cytotoxic T cell response was observed *(7)*. The same group used the AFFITOPE technology to create peptides similar to PCSK9, thereby producing specific antibodies against PCSK9 *(8)*. Using this technology, they developed two vaccines: AT04A and AT06A, which were used in a phase I clinical trial to investigate safety, tolerability, immunogenicity, and the impact on LDL and total cholesterol concentration in healthy subjects. The single-blind, randomized, controlled trial included 72 subjects with an average LDL cholesterol value of 3.0 mmol/L. Subjects were randomly divided into three equal groups that received the AT04A, AT06A, or placebo vaccine for four weeks *(9)*. This was followed by a second phase in which subjects underwent regular check-ups without receiving therapy. In the final phase, they received a booster dose of the vaccine or placebo. The study concluded with 49 subjects, with both vaccines being safe and immunogenic, but only the AT04A vaccine showed a statistically significant reduction in LDL and total cholesterol levels. Further research with the AT04A vaccine is planned *(9)*.

CONCLUSION

Vaccines targeting PCSK9 appear to be potentially successful, safe, and cheaper alternatives to the established therapy with fully humanized monoclonal antibodies against PCSK9. In some studies, they successfully reduced total and LDL cholesterol levels and decreased the growth of atherosclerotic plaques. Peptide vaccines AT04A and AT06A were the only ones tested in humans in a phase I study, examining safety, effectiveness, and observing changes in total and LDL cholesterol levels. Only the AT04A vaccine proved to be safe and effective, but in a small number of subjects. As possible alternatives to peptide vaccines, nanoliposomal vaccines and virus-like particle vaccines are being tested. These have indicated the potential for safely and effectively lowering LDL and total cholesterol

by inhibiting PCSK9 molecules in animal models. Vaccination continues to be an interesting and potentially effective addition to established, evidence-based therapy, primarily limited by the discontinuation of prescribed oral therapy and the high cost of biological drugs *(4)*. Research conducted so far indicates moderate treatment effectiveness in animal models, but vaccine improvements and the successful completion of all phases of clinical trials will be necessary before use in humans.

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Venous Thromboembolism in Pregnancy

ABSTRACT

KEY WORDS: venous thromboembolism, pregnancy

Hormonal-induced changes in haemostasis, fibrinolysis, blood flow, and the vessel wall are the reasons why venous thromboembolisms are more common in pregnancy than in non-pregnant women of the same age. The clinical presentation of venous thromboembolisms is more unreliable than in non-pregnant women; an objective diagnosis should be performed in suspected cases, and some peculiarities related to pregnancy should be considered. Venous thromboembolism treatment in pregnancy is based on heparins, preferably low-molecular-weight, while oral drugs (vitamin K antagonists and direct oral inhibitors of coagulation) are contraindicated. Venous thromboembolism treatment should last at least throughout the whole pregnancy and six weeks postpartum.

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VENOUS THROMBOEMBOLISM IN PREGNANCY

In pregnancy, a changed hormonal status results in increased venous capacity, and changes in coagulation and fibrinolytic processes result in a procoagulant state. Therefore, a venous thromboembolism (VTE) is more common in pregnant women. The additional reasons for increased risk for VTE in pregnant women are slower blood flow through the affected veins and possible endothelial trauma during delivery. All three factors of Virchow's triad (hypercoagulability, hemodynamic changes, endothelial injury) are involved, but changes in the coagulation system are probably the most important.

Hemostasis Changes in Pregnancy and Postpartum

In normal pregnancy, marked procoagulant activity is observed. It is evolutionarily reasonable, because it protects the mother against bleeding, which has historically been the leading cause of maternal mortality and still is in developing countries *(1)*. Increased levels of coagulation factors V, VII, VIII, IX, X, XI, and XII, von Willebrand's factor and fibrinogen are detected. Changes in antithrombin and protein C concentrations are minor. The protein C-dependent pathway is less effective due to thrombomodulin and protein C receptor changes. This can be described as acquired activated protein C resistance, which could also be congenital in patients with factor V Leiden mutation. Protein S concentration is lowered in pregnancy. All described changes result in procoagulant activity. Fibrinolysis, the opposite physiological process of coagulation, is less active in pregnancy due to increased concentrations of plasminogen activator inhibitors 1 (PAI 1) and 2 (PAI 2). An elevated D-dimer concentration is detected because of accelerated clot generation and fibrinolysis. However, most of the described changes are normalized by the end of the sixth week postpartum, when the maternal procoagulant hemostatic system gradually returns to a state close to that of non-pregnancy. This process is finished after the twelfth week postpartum *(1)*.

Epidemiology

The incidence of VTE in pregnancy is around 199 per 100,000 pregnancies. It is around four times more common than in non-pregnant women of the same age *(2)*. VTE is slightly more common in the last than in the first two trimesters. About half of VTE events are detected postpartum – the majority in the first six weeks postpartum *(2)*. This period lasts until the end of the tenth week postpartum, but after the sixth week, the incidence is remarkably lower *(2)*. Pulmonary embolism (PE) remains a leading cause of maternal death in the developed world, causing 0.8–1.49 deaths per 100,000 pregnancies *(2)*. Death from PE represents about one-tenth of all maternal deaths. The post-thrombotic syndrome is also important – these are chronic changes after acute deep vein thrombosis (DVT), which can worsen during the following years and may represent serious problems due to functional and aesthetic disability.

In addition to changes in coagulation and fibrinolysis, there are some other risk factors related only to pregnancy: over 35 years of age, caesarean section (urgent cases represent a higher risk), multiparity, infection, bleeding, preeclampsia, eclampsia, assisted reproduction, placenta praevia, obesity, and prolonged bed rest *(3)*. The precise risk is sometimes difficult to assess because of the combination of different risk factors.

Clinical Picture

Symptoms and signs of VTE are the same as in non-pregnant women. However, leg swelling, often bilateral, is a frequent complaint or finding in normal pregnant women. Dyspnea is also quite common in healthy

pregnant women, and therefore PE is sometimes suspected. This explains why VTE is confirmed in only 10% of suspected pregnant women *(1)*. Diagnostic procedures already established in non-pregnant populations have some differences related to pregnancy.

Diagnosis of Deep-Vein Thrombosis

The diagnostic procedure is the same as in non-pregnant women. It starts with a clinical assessment, followed by D-dimer testing and ultrasound (US) investigation. Rarely some other examinations are used.

Clinical Assessment

While clinical decision rules have been demonstrated to be very useful in assigning pretest probability outside pregnancy, studies deriving and validating these models did not include pregnant patients. Nevertheless, the diagnostic procedure begins with a clinical prediction rule, which should be confirmed by objective testing.

D-dimer

In VTE, the D-dimer is usually elevated. However, the usefulness of D-dimer testing in pregnancy is potentially limited by normal physiological increases in D-dimer levels, although it is still used in diagnostic procedures.

Ultrasound Investigation

A pregnancy US is the most important investigation. Two strategies are used; the serial US – proximal veins twice in one week, when the first investigation is negative, or the whole leg US in one – the first session. We propose to investigate the whole leg at first visit; if negative and DVT is still suspected, the US should be repeated in one week. A US could be nondiagnostic in the investigation of iliac veins when iliac vein thrombosis is suspected. Then, indirect measures, such as the absence of flow or visible thrombus on B-mode imaging of the vessels, can be useful *(4)*. The accuracy of these indirect US assessments of iliac veins is uncertain. If there is strong clinical suspicion of iliac vein thrombosis and the US is negative, MRI without contrast or classic phlebography is proposed *(5)*.

Treatment of Deep-Vein Thrombosis

VTE treatment in pregnancy is generally the same as in non-pregnant women with some modifications. Nevertheless, some pregnancy-related characteristics must be considered.

Anticoagulant Treatment

Vitamin K antagonists are probably acceptable until the sixth week of pregnancy but are later contraindicated due to teratogenicity and increased risk for fetal bleeding. They can be used postpartum in breastfeeding mothers. Direct anticoagulant drugs (DOACs: rivaroxaban, dabigatran, apixaban, and edoxaban) are contraindicated in pregnancy and during breastfeeding. Unfractionated heparin (UFH) and low-molecular-weight heparins (LMWH) are allowed in pregnancy. The anticoagulation effects of LMWHs are more predictable, therefore, these are the drugs of choice during pregnancy. Because of its shorter half-life and the ability to fully reverse its anticoagulant activity, if necessary, UFH could be used, especially at the time of delivery or in some other procedures with a high risk of bleeding *(3, 5)*. During treatment with LMWH, clinical bleeding could be expected in around 2% of treated patients: 0.4% before delivery, 1% after delivery, and 0.6% from post-operative wounds. Allergic reactions are described in 1.8% of patients, and heparin-induced thrombocytopenia can occur very rarely (0.025%) *(3, 4)*. Reduced bone density, which is to some degree physiological in pregnancy, is detected in

less than 0.04% of treated patients. LMWH should be given subcutaneously once or twice daily and adjusted to body weight. We suggest using the twice-daily regimen in the last month of pregnancy and the once-daily regimen outside of this period and postpartum. The exceptions are patients with a body weight of over 100 kg, in whom a twice-daily regimen is prescribed by the drug producers as in non-pregnant population. The treatment should last the whole pregnancy and six weeks postpartum but at least three months if VTE is detected late during pregnancy. That is important in patients who develop VTE late. In patients with late VTE, occurring in the last weeks of pregnancy, the treatment should be prolonged until the end of the third month after VTE was detected *(4, 6)*. Monitoring anti-Xa levels in women on LMWH is rarely needed. The current recommended anti-Xa range in pregnancy with LMWH twice-daily is 0.5–1.0 IU/ml (blood drawn 4 hours after the dose). In patients treated with LMWH once-daily, the target range at 4–6 hours after the dose is less clear, but 1.0–2.0 IU/mL is considered reasonable. UFH should be monitored, and the dose adjusted according to activated partial thromboplastin time (aPTT) as in the non-pregnant population *(6)*. In the management of pregnant women with acute VTE close to the term of delivery, the risk of stopping anticoagulation must be balanced with the risk of recurrent VTE. There are no general precise recommendations on how to handle anticoagulation treatment. We suggest a twice-daily regimen in the last month of pregnancy. The last half dose is administered the day before the delivery, and we suggest starting anticoagulation treatment 12 hours postpartum. If VTE is diagnosed near the term (over 37 weeks), then consideration should be given to the placement of an inferior vena cava (IVC) retrievable filter. This is followed by anticoagulation reversal with a planned induction performed after the anticoagulation reversal. Anticoagulation reversal without IVC filter protection is strongly discouraged in the two weeks after the diagnosis of the VTE, given the mortality of untreated VTE in this period in non-pregnant patients. In these cases, UFH is suggested close to term *(3)*. Lacking proper studies, the time window for the first dose of anticoagulation postpartum is 6–24 hours. Usually, the prophylactic dose is suggested. Twelve hours later, we proceed with the prelabour regimen, which lasts at least six weeks postpartum. In case of cesarean delivery, the risk of bleeding is increased. However, the risk of thrombosis is higher than in vaginal delivery. Therefore, the administration of the first dose of LMWH is also 6–12 hours postpartum. When neuraxial anesthesia is administered, the time of placement of the catheter should be at least 24 hours after the half-therapeutic dose of LMWH. When the prophylactic dose is used, the first dose after catheter removal should be administered at least 2 hours later, and at least 12 hours later when the half therapeutic dose is used *(3, 6)*. The filter could be considered also when therapeutic anticoagulation is contraindicated because of a high risk of bleeding, or in patients who have objectively confirmed recurrent VTE despite proper therapeutic anticoagulation *(7)*.

Pulmonary Embolism

The clinical assessment of PE in pregnancy is less reliable than in non-pregnant women. The Geneva pregnancy adapted risk assessment score (age > 40 years, surgery or limb fracture, previous VTE, unilateral limb pain, hemo-ptysis, pain on lower limb palpation and unilateral edema, heart rate > 110 per minute) or the YEARS algorithm (clinical signs of DVT, hemoptysis, and PE as the most likely diagnosis) both with D-dimer testing could be used to diminish the need for a CT pulmonary angiography (CTPA). However, CTPA is still needed in

about 10% of suspected pregnant women. Sometimes, the ventilation perfusion scintigraphy could be used as well. Radiation is a concern, but the radiation is very low, and not harmful for the fetus. Postpartum MRI angiography is probably the safest option. However, breastfeeding should be omitted for 12 hours after MR investigation *(3, 5, 6)*.

Recanalization Procedures in Patients with Pulmonary Embolism

Pregnant women with a high-risk PE have an approximately 37% risk of PE case fatality *(5)*. Therefore, in pregnant women with high-risk PE, which is associated with hypotension circulatory collapse at presentation, thrombolysis or some other recanalization procedures, for example the aspiration of the pulmonary artery thrombus with some dedicated devices with or without extracorporeal membrane oxygenation, should be considered. Surgical removal of the thrombus is also possible *(5)*.

CONCLUSION

Cases of VTE – namely DVT and PE are common during the whole pregnancy and postpartum due to pregnancy-related changes. They are serious adverse events and should be properly treated in an experienced specialized centre.

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Martina Turk Veselič[1]

Peri-operative Myocardial Infarction/Injury after Peripheral Artery Disease Revascularization

ABSTRACT

KEY WORDS: peri-operative myocardial infarction/injury, myocardial injury after non-cardiac surgery, peripheral artery disease, critical limb ischemia, revascularization, troponin, major adverse cardiovascular events

The use of a serial high-sensitivity troponin assays enables the diagnosis of a peri-operative myocardial infarction/injury (PMI), which proved to be a valuable peri-operative prognostic marker. An absolute increase of post-operative high-sensitivity cardiac troponin T or I in more than the upper limit of normal above the pre-operative concentration was associated with an important increase in 30-day and long-term mortality and cardiovascular events. In patients after revascularization, the incidence of PMI is approximately 20% which is higher than after non-cardiac surgery in general. Only a minority of patients with PMI after revascularization have clinical symptoms or ECG changes suggestive of myocardial ischemia. Therefore, active surveillance is mandatory to promptly address their residual atherosclerotic risk.

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INTRODUCTION

The presence of peripheral artery disease (PAD) confers a three- to six-fold higher risk for major adverse cardiovascular events (MACE) compared to the general population. The prognosis of patients with critical limb ischemia is especially poor, with a 25–% mortality expected in one year. This may be linked to the presence of concomitant coronary artery disease (presumably in 50–60% patients) *(1)*. Recently, troponin values before and after a PAD revascularization procedure showed to enable peri-procedural risk stratification that is based on the detection of so-called peri-operative myocardial infarction/injury (PMI).

DEFINITION AND RECOMMENDATIONS

PMI is described as a post-operative high-sensitivity cardiac troponin T or I (hs-cTn T/I) release that indicates acute cardiomyocyte damage, not necessarily being accompanied by concordant symptoms, ischemic ECG changes, or imaging findings. It is defined as an absolute increase in the hs-cTn T/I concentration of more than the upper limit of normal on days one or two after a procedure. The hs-cTn T concentration complements clinical evaluation and ECG in risk prediction and is therefore recommended in patients who undergo high-risk or intermediate-risk procedures, the latter including peripheral arterial angioplasty.

Based on emerging data, serial troponin assessment is advised in the European Society of Cardiology (ESC) guidelines as an IB recommendation *(2)*. Symptomatic and asymptomatic PMI have the same impact on 30-day mortality.

INCIDENCE AND PROGNOSTIC VALUE

Large prospective studies have confirmed the association of PMI with an increased risk of 30-day and one-year mortality and non-fatal MACE after non-cardiac surgeries. Approximately 16% of high-risk patients develop PMI. Among those, 30-day mortality was 8.9% and one-year mortality was 22.5% (compared to 1.5% and 9.3% in patients without PMI). PMI is a heterogeneous syndrome that can result from various cardiac and non-cardiac causes. Invasive coronary angiography was advised only in 10% of patients being managed for PMI *(3)*.

In the Puelacher report, only 7% of all PMI cases were type 1 myocardial infarction (MI), of those 41% developed clinically overt MACE and 27% died in one year. The most common presentation of PMI was type 2 MI, in this group, 25% of patients developed overt MACE and 17% died in one year, compared to 7% and 9%, respectively in non-PMI patients. Other etiologies of PMI were extra-cardiac, tachy-arrhythmia, and acute heart failure *(4)*. The baseline hs-cTn T/I value, when increased, already proved to be a strong independent predictor of combined cardiovascular endpoints.

PERI-OPERATIVE MYOCARDIAL INFARCTION/INJURY AFTER VASCULAR SURGERY AND ENDOVASCULAR LIMB REVASCULARIZATION

There is a discrepancy between different studies regarding the definition of PMI. Many are using the term MINS – myocardial injury after non-cardiac surgery – that excludes cardiac non-coronary aetiology, the assessment of troponin (I or T, being high sensitivity) and troponin threshold or absolute/relative increase values. In a study that evaluated troponin (that was not high sensitivity) in patients after lower extremity revascularization, there was a 23.7% incidence of MINS after open surgical revascularization, 19.5% after endovascular revascularization, and 36% after a hybrid procedure. Transcriptome profiling analysis was performed and found gene upregulation for trombospondin 1 that was associ-

ated with long-term cardiovascular events. This is only one of possible mechanisms explaining increased risk in patients with PAD exhibiting PMI *(5)*.

A study of vascular surgical patients (after thoracic aorta, aorto-iliac or peripheral artery reconstruction, extracranial cerebrovascular surgery, and endovascular aortic repair), which defined MINS as an elevated troponin T value within 30 days after the operation, found that without screening, MINS would not be recognized in 74.1% patients. The incidence of MINS was 19.1%. 30-day all-cause mortality was 12.5% (versus 1.5% in patients without MINS) and was similar in MINS patients with and without ischemic feature *(6)*.

In a study that investigated chronic limb ischemia patients after endovascular limb revascularization, the incidence of PMI was 25.5%. The value of hs-cTn T was determined on admission, three to six hours after revascularization, and the next morning. PMI was defined as a hs-cTn T value above 14 ng/L with a relative increase ≥ 30% from the baseline. One year mortality in patients with critical limb ischemia that manifested with PMI was 14.2%, and one year occurrence of MACE was 20.5%. Interestingly, 62.1% of patients had a baseline hsTnT value above the threshold level. Only 14.8% patients with PMI after endovascular revascularization had clinical symptoms or ECG changes suggestive of myocardial ischemia *(1)*.

THE MANAGEMENT OF PERI-OPERATIVE MYOCARDIAL INFARCTION/INJURY IN VASCULAR PATIENTS

A transthoracic echocardiography should be performed on the day of PMI detection. An invasive coronary angiography is indicated in case of type 1 MI or in certain clinical settings of type 2 MI or missed type 1 MI. The last two could also be scheduled for outpatient stress imaging or coronary CT angiography. In case of severe anaemia, other triggers of type 2 MI (such as hypoxemia, tachycardia, and hypertension), other cardiac causes (e.g. acute heart failure, aortic valve stenosis) or non-cardiac causes (e.g. sepsis, pulmonary embolism, stroke) should be treated *(2)*.

Patients with PAD with confirmed PMI require even stronger clinical attention in terms of optimal medical therapy. Acetylsalicylic acid (ASA) and statins are already part of their regular the-rapy. Additional measures are required when target LDL cholesterol is below 1.4 mmol/L and at least 50% LDL cholesterol reduction from baseline are not met (adding ezetimibe and consequently a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor) *(7)*. PAD patients without relevant contraindications are candidates for the addition of a low dose rivaroxaban (2.5 mg twice a day) to ASA according to the VOYAGER PAD study *(8)*.

Based on the MANAGE study, the addition of dabigatran 110 mg twice a day may be considered about one week after non-cardiac surgery in patients with a low risk of bleeding as the study showed a 28% relative reduction of major vascular complications. Patients who developed MINS after orthopaedic, general, or vascular surgery were randomized to receive dabigatran 110 mg twice a day or a placebo (with initiation six days after operation) and were followed approximately nine months. 60% of patients already had ASA or an adenosine diphosphate receptor P2Y12 inhibitor as part of their therapy. The composite primary outcome of vascular mortality, MI, non-haemorrhagic stroke, peripheral arterial thrombosis, amputation and symptomatic venous thromboembolism was 11% in the dabigatran group and 15% in the placebo group. There was no difference in major bleeding *(9)*.

CONCLUSIONS

PAD patients have significant atherosclerotic burden involving coronary arteries that predisposes them to a worse cardiovascular prognosis. Determining PMI among PAD patients is beneficial and should be used as a diagnostic and prognostic tool leading to personalized short- and long-term post-procedural treatment.

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Dimitrij Kuhelj[1]

Efficacy and Durability of Multilayer Flow Modulators in Aortic Aneurysms

ABSTRACT

KEY WORDS: multilayer flow modulators, aortic aneurysm, endovascular management

BACKGROUNDS. In favourable anatomical conditions, endovascular abdominal aneurysm repair (EVAR) or thoracic endovascular aortic repair (TEVAR) are the established treatments of aortic aneurysms. The treatment of other areas is more complex and demands more complex endovascular procedures or open surgery. Multilayer flow modulators (MFM) were developed to treat aortic aneurysms in areas where standard EVAR or TEVAR are not feasible. MFM implantation is simple and arterial coverage by the device should not compromise arterial flow. The aim of our study was to determine long-term efficacy and durability of MFM in the treatment of aortic aneurysms. METHODS. Our study included 16 male and one female patient, treated in a 91-month period (starting in March 2011); the follow-up period extended to March 2023. The patient mean age was 68 years and none of the patients were suitable for EVAR, TEVAR, or open surgical management. The data collection was concluded in May 2023; the median follow-up was 25 months (range 7–76 months). RESULTS. MFMs were successfully implanted in all patients, with no 30-day mortality observed. By the end of the follow-up period, five patients were alive. Three patients died due to an aortic rupture at 9th, 40th, and 51st month post-implantation, respectively. Most additional procedures were performed due to Type 1a endoleak, with one occurring within the first month, and four occurring later. During the follow-up, we observed occlusions of two superior mesenteric arteries, one renal artery, one subclavian artery, and one celiac trunk. Only the renal artery occlusion was symptomatic. No cases of paraplegia were detected. The mean aneurysmal flow volume was reduced in most patients (64.5%); however, this did not correspond to a reduction in mean volume or mean diameter, which increased in 59% and 88.2% of patients, respectively. CONCLUSIONS. MFMs are simple and safe to implant in patients with aortic aneurysm, however, the long-term results did not confirm the efficacy and durability of the procedure in the majority of patients. Further studies will be needed to highlight reasons for our results.

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BACKGROUNDS

Endovascular exclusion of aortic aneurysms, including procedures like endovascular abdominal aneurysm repair (EVAR) or endovascular thoracic aortic repair (TEVAR), became available more than 30 years ago and have proved effective and durable in short- and long-term follow-ups *(1, 2)*. However, anatomical limitations still present a major drawback in the treatment of aortic regions where the branching of aortic vessels prevents stent graft implantation. Open surgical treatment, available for almost 70 years, represents a more invasive approach in often fragile and elderly patients, requiring aortic clamping and a complex aortic approach, especially in areas where simple endovascular treatment is not feasible *(3)*. The aortic arch, thoracoabdominal and perirenal aorta are still areas where complex open or endovascular solutions are required in order to avoid vital organ ischaemia, including the spinal cord.

Alternatively, multilayer flow modulators (MFMs) (Cardiatis, Isnes, Belgium) were proposed for the treatment of aortic aneurysms more than a decade ago, introducing flow-laminating technology, which successfully treated intracerebral aneurysms *(4)*. MFMs are woven 3-layered stents, aimed to laminate flow through an aneurysm, producing gradual aneurysmal thrombosis without compromising flow in the aortic branches. The MFMs is self-expandable and easy to position, since there is no need to avoid branching arteries, and no significant reduction in blood pressure is required during deployment.

In Slovenia, aortic MFMs became available in 2011, however, due to unclear results of the aortic MFMs and alternative endovascular options, like fenestrated and branched endovascular aortic repair options (FEVAR, BEVAR), they have not been implanted since 2019. The aim of our study was to evaluate the efficacy and durability of MFMs implanted in our patients with aortic aneurysms in order to determine long--term results, which are currently lacking in literature, as is the case with many devices with questionable or poor efficacy.

METHODS

Between March 2011 and October 2019, 16 male and one female patient (median age 68 years; range 48–81) were treated with MFM implantation for an aortic aneurysm. All the procedures were elective, the decision for MFM implantation was made by a multidisciplinary board because no open or endovascular alternative treatment was feasible. A computed tomography angiography (CTA) was used for both diagnostic and control imaging, with all procedures performed by two experienced interventional radiologists completely percutaneous with surgical back-up in case of a failed percutaneous haemostasis. Six patients were treated for an aneurysm of the thoracic aorta, in four of which, the aortic arch was affected, in other four, the abdominal aorta was dilated. Three patients were treated for an aneurysm of the thoracoabdominal aorta. The follow-up extended until May 2023; over-all and aorta-related survival were determined, along with complications and changes in diameter, flow-volume and aneurysmal volume. Causes of death were obtained from the National Registry.

All procedures were performed under general anaesthesia. Patients received antibiotic prophylaxis and 5000 IU of heparin during the procedure. Clopidogrel was prescribed for three months, and acetylsalicylic acid was prescribed for lifelong use. Haemostasis was achieved by percutaneous suture systems by Abbott Laboratories IL, USA (ProStar/ProGlide), 22 and 24 Fr introducers were used.

The statistical analysis was performed by GraphPad Prism 10 (GraphPad Software Inc, San Diego, CA, USA). Diameters were measured on CTA images by two experienced radiologists, who also performed sizing

that was confirmed by the manufacturer. Flow-volume and aortic volume were measured by the manufacturer, using Osirix (Pixmeo, Geneve, Switzerland).

RESULTS

The median follow-up period of patients exceeded two years (median 25 months; range 7–76). The 30-day post-procedural mortality rate was 0%. One patient (5.9%) died due to an aortic rupture during the first year of follow-up. As of May 2023, five patients (29.4%) have still been alive. There were three aortic ruptures during the follow-up period, occurring at 9th, 40th and 51st month after MFM implantation.

Periprocedural complications during the first 30 days following MFM implantation occurred in three cases, none of which required conversion to open surgery. A stent graft was implanted proximally to seal a Type 1a endoleak in one patient. Another patient experienced a retrograde dissection, which was managed conservatively as no extension was detected on CTA controls. A dissection of the celiac trunk was observed in one patient without clinical symptoms. No cases of paraplegia, vital organ ischemia, or aortic rupture were observed during the first month of the follow-ups.

Aortic branch occlusions following MFM implantations were observed in another five patients. This included a renal artery occlusion leading to renal failure, two occlusions of superior mesenteric artery, an occlusion of the celiac trunk, and an occlusion of the subclavian artery, all of which were asymptomatic. Additionally, an ischemic stroke occurred months after MFM implantation in the aortic arch of a female patient caused by thrombosis of a carotid artery in a previously stenosed brachiocephalic trunk and carotid artery; the event occurred during stent implantation. This patient did not comply with the prescribed medical treatment, which likely contributed to the thrombosis.

Additional procedures were performed in seven patients (41.2%) overall. One procedure occurred within the first 30 days, and six were carried out between one and 74 months after MFM implantation. During this period, the most common reason was a Type 1a endoleak in four patients, where three MFMs and one stent graft were added due to poor sealing. The remaining two patients had two additional MFMs implanted, one due to MFM migration and another due to MFM displacement.

The median aneurysmal volume during the follow-up period increased from 309 to 355 ml, and the median aneurysmal diameter increased from 58 to 76 mm. However, the aneurysmal volume decreased in five patients, remained stable in another two, and increased in 10 patients (59%). The aneurysmal diameter increased in almost 90% of patients (15 patients, 88.2%), decreased in one patient, and remained stable in another patient.

During the follow-up period, a flow in the aneurysm was present in 14 patients, in two of these, there were no presence of thrombi. A complete aneurysmal thrombosis was present in only three patients (17.6%). Aneurysmal flow volume was reduced in 11 patients (64.7%) and increased in all the remaining ones.

DISCUSSION

The endovascular management of aortic aneurysms in designated anatomic areas proved its long-time durability and effectiveness throughout the decades *(2)*. Other anatomical regions remain challenging for EVAR/TEVAR and for open surgical management due to high morbidity and mortality rates *(5)*.

Flow-lamination technology proved effective in the management of intracranial aneurysms, and aortic MFMs were proposed as a simple alternative with acceptable morbidity and mortality rates on a short and mid-term basis *(4, 6)*. However,

long-term results still remain questionable, and the aim of our study was to determine the efficacy and durability of such treatment in our patients.

The first patient was treated in 2011. In the following 91 months, we treated 17 consecutive patients with aortic aneurysms, unsuitable for other endovascular or open surgical repair. MFM implantation proved technically simple, and all the procedures were performed completely percutaneous. The relatively high number of reinterventions in the first patients was reduced after changes in the device's design. Clinically symptomatic occlusions of covered aortic branches were rare, and no paraplegia was present during the follow-up period.

In almost two thirds of the patients, the aneurysmal flow was reduced, however, this did not translate into a stabilization of the aneurysmal diameter or volume in the majority of the patients. A possible explanation is proposed in the study by Antkiewicz and colleagues, which reports that MFM does not reduce pressure in the aneurysmal sac, in contrast to branched endovascular repair (BEVAR), which significantly reduces aneurysmal pressure *(7)*.

Limitations

The main limitations of our study are the small sample size and the variety of aneurysm anatomical locations treated over nearly eight years. None the less, our study represents an insight into the long-term efficacy and durability of treating aortic aneurysms with MFM, which the literature currently lacks. Despite that, additional studies and larger follow-up series should determine why in some patients MFM positively influences aneurysmal course – in 40.1% of our patients, the aneurysmal volume decreased or remained stable, and the aneurysmal diameter was reduced in one and remained stable in another patient.

CONCLUSIONS

The reduction of aneurysmal flow volume in the majority of our patients did not equate to mean diameter and mean aneurysmal volume reduction. Consequently, despite the simplicity of the MFM implantation procedure, it did not demonstrate long-term benefits in the majority of patients. However, in a minority of patients, MFM implantation benefits were detected, and further data will provide clearer insight into the reasons behind these results.

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Marko Miklič[1]

New Strategies in the Treatment of Pulmonary Embolism

ABSTRACT

KEY WORDS: pulmonary embolism, catheter-based therapy, thrombolysis

Pulmonary embolism (PE) represents a major cause of cardiovascular morbidity and mortality. Over the last few years, there has been an increase in the incidence of PE, while simultaneously the mortality rates associated with PE have been declining. The improved survival rates in PE are likely to result from the better availability of more precise diagnostic methods, better adherence to guidelines and the use of new enhanced therapeutic options. Since hemodynamic compromise is the principal cause of poor outcome in patients with acute PE, early identification of patients at risk and appropriate risk stratification of patients with PE are essential for further management and can direct the use of more invasive treatment strategies. Anticoagulation therapy is the cornerstone of treatment for acute PE, while for hemodynamically unstable patients, systemic thrombolysis is the recommended treatment of choice. However, systemic thrombolysis comes with a cost of increased risk for major bleeding, including possibly fatal intracranial bleeding. Interventional catheter-based therapies with mechanical thrombectomy or catheter-directed thrombolysis with very low doses of thrombolytic offer the possibility for this bleeding risk to be minimized, while sufficient recanalization of pulmonary arteries allows for hemodynamic stabilization and improves the patient's symptoms. The decision when to use interventional procedures over pharmacological treatment is still a matter of debate, especially in the intermediate-high-risk group of PE patients. Ongoing studies comparing one interventional method against another, and catheter-based therapies against anticoagulation are ongoing. While the results of these studies are eagerly awaited, implementations of local hospital protocols for optimal PE treatment with consultations between multidisciplinary specialists in the so-called PE response team are suggested.

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INTRODUCTION

Venous thromboembolism, encompassing deep vein thrombosis and pulmonary embolism (PE), represents the third most frequent cause of cardiovascular disease, with PE being one of the leading causes of death in hospitalized patients. The incidence of PE varies between regions and is reported to range from 39–115 per 100,000 persons, with a higher incidence amongst the elderly. Due to the increasing use of diagnostic high-resolution contrast-enhanced CT of the chest in everyday clinical practice, especially in cancer patients and the aging population, the incidence of PE has been increasing in the last 20 years. However, time trend analysis suggests that case fatality rates of acute PE may be decreasing in the last years *(1)*. This can be explained by more incidental diagnosis of PE and reports of minor subsegmental PE, which may not have the same serious consequences, but also by better patient and physician disease awareness, adherence to guidelines, and possibly also due to the use of new more effective treatment strategies.

Since the pulmonary circulation in healthy individual is a low-pressure and low-resistance circuit, the right ventricle (RV) is especially susceptible to failure in response to sudden increases in vascular resistance, as is seen with acute PE. A failing RV leads to impaired left ventricle filling and increased pericardial pressure from the enlarging right heart. Since the interventricular septum is affected, left ventricular stroke output is also decreased, leading to neurohormonal activation to stimulate the contractility and inotropy of the myocardium. Low cardiac output and pulmonary vasculature obstruction cause ventilation/perfusion mismatch, which contributes to hypoxemia. The reduction in systemic blood pressure together with the rise in RV end-diastolic pressure impairs the right coronary perfusion causing a further imbalance between oxygen demand and myocardial oxygen delivery, which leads to myocardial ischemia, further worsening of RV performance and ultimately death *(1)*.

PATIENT STRATIFICATION AND TREATMENT OPTIONS

Early identification of PE patients that are at risk of hemodynamic compromise and death is of paramount importance, and the stratification of patients based on their clinical state, comorbidities, laboratory markers of myocardial ischemia and presence of right heart dysfunction guides further therapeutic decisions. Incorporating validated clinical scores, such as the Pulmonary Embolism Severity Index (PESI) and the simplified PESI, allows for the assessment of a patient's overall mortality risk and early outcome.

Patients with hemodynamic instability are stratified into a high-risk group, while hemodynamically stable patients are further stratified into a low- or intermediate-risk group based on the above-mentioned criteria.

The intermediate-risk group of patients is further divided into intermediate-low and intermediate-high-risk, with the latter having both positive serum troponin and signs of RV dysfunction on imaging, while the intermediate-low-risk group has none or only one of these criteria, but presenting an elevated PESI score.

Patients with PE, whose condition is hemodynamically stable and who have no RV strain, normal cardiac biomarkers and a low PESI score, are considered to have low-risk PE.

Current treatment guidelines recommend the prompt initiation of anticoagulation therapy in all patients with PE and also recommend systemic thrombolysis (ST) in high-risk PE patients *(1)*. ST is associated with a high risk of major bleeding, including possibly fatal intracranial haemorrhage, therefore, it is estimated that up

to half of high-risk patients do not get ST due to a perceived increased risk of bleeding *(2)*. In patients with intermediate-high-risk PE, thrombolytic therapy with full dose recombinant tissue-type plasminogen activator (rtPA) is associated with a significant reduction in the risk of hemodynamic decompensation or collapse, but it is paralleled by an increased risk of severe extracranial and intracranial bleeding. Smaller studies and meta-analyses have shown a favourable safety profile of ST with a reduced dose rtPA in these patients, which still proved good efficacy, while an ongoing study is set to confirm these findings *(4)*.

With the advancement of interventional therapies, new therapeutic options became available for high- and intermediate-high-risk PE patients who are not candidates for ST. A reperfusion of the pulmonary arteries can be achieved by inserting a catheter into the proximal pulmonary artery and aspirating the thrombus – mechanical thrombectomy (MT). Large bore aspiration catheters are used to remove the thrombus, which can be done quickly and without any patient sedation. Due to the large diameter of the catheter, careful manipulation and continuous patient monitoring during the procedure is suggested *(2)*.

Alternatively, a catheter can be left in place for a few hours, and very low-dose rtPA perfused through the catheter to achieve local thrombolysis with minimal systemic effect. The vast majority of data for the latter procedure in PE patients comes from using an ultrasound-facilitated catheter-directed thrombolysis (CDT). Both MT and CDT are effective in reducing the RV diameter and pulmonary artery pressures after reperfusion, but there is little data on hard clinical outcomes in PE patients, such as death or hemodynamic collapse from randomized controlled trials. The FLAME study, which was a prospective nonrandomized interventional study in high-risk PE patients with hemodynamic instability, has shown that patients who got MT had only a 1.9% in-hospital mortality and a 15.1% probability of clinical deterioration *(5)*. These numbers are much lower than expected in such a high-risk group, but those were selected patients in a nonrandomized study.

While the need for immediate reperfusion therapy in the high-risk group of PE patients is undeniable, this treatment strategy is less clear in the intermediate-risk group. As stated before, ST is effective, but its use was counterbalanced by increased risk of bleeding. It is still not known whether using interventional catheter-based therapies (CBT), MT or CDT, offers a better safety and efficacy profile than ST or even anticoagulation alone. There are ongoing studies that will hopefully answer this question. Meanwhile, implementations of local hospital protocols for optimal PE treatment with consultations between multidisciplinary specialists in the so-called PE response team are suggested *(1)*. Considering the patient's clinical state and the risk for hemodynamic collapse and bleeding, a decision is to be made regarding the best treatment option. An analysis of registry data has identified certain patient characteristics that are correlated with worse outcomes in intermediate-high-risk PE patients. These are elevated serum lactate levels, tachypnoea, sinus tachycardia, systolic blood pressure below 110 mmHg or shock index (pulse/systolic blood pressure) above 1, elevated markers of RV function and ischemia (elevated troponin, elevated B-type natriuretic peptide, reduced RV function), central and large thrombus burden (saddle PE), concomitant proximal deep vein thrombosis or a right heart thrombus *(6)*. Currently, CBT should be considered for patients with high-risk PE in whom thrombolysis is contraindicated or has failed. Failure after ST has been reported in up to 8% of patients and is defined as no hemodynamic improvement after two to four hours. CBT is also

a treatment option for initially stable patients in whom anticoagulant treatment fails, i.e., those who experience hemodynamic deterioration despite adequately dosed anticoagulation, and should be considered when no improvement is achieved after 24–48 hours of initial anticoagulation *(2)*.

In patients with intermediate-risk PE and after CBT, a full dose of parenteral anticoagulation, preferably with low-molecular-weight heparin, is recommended. For stable patients, a switch to a direct oral anticoagulant (DOAC), such as apixaban, edoxaban, rivaroxaban, or dabigatran is also possible. In intermediate-risk PE patients, a change to a DOAC after 72 hours of parenteral anticoagulant is safe, while in low-risk PE patients, an upfront DOAC therapy with apixaban or rivaroxaban is possible *(7)*.

CONCLUSION

PE treatment is evolving with new CBTs offering an effective and fast reperfusion of pulmonary vasculature in patients with high- or intermediate-high-risk PE. While these procedures are already performed in everyday clinical practice, their benefit is still to be proven. Results from ongoing randomized trials will hopefully give us a better insight into whom we should treat more aggressively and whether these procedures provide any benefit to PE patients in the long term.

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Superficial Venous Thrombosis in Atypical Locations

ABSTRACT

KEY WORDS: superficial venous thrombosis, atypical location, Mondor disease, Trousseau's syndrome

Superficial venous thrombosis (SVT) is an inflammation of the venous wall with subsequent secondary thrombus formation. In the majority of cases, it affects the superficial venous system of the lower extremities. SVT which appears in functionally and structurally normal veins without varicose changes is a heterogeneous group of diseases in which different etiopathogenetic mechanisms are present with varying expressions of inflammatory and thrombotic processes. Trousseau's syndrome is a rare variant of venous thrombosis that is characterised by recurrent, migratory thrombosis in superficial veins and in uncommon sites, such as the upper extremities, trunk, and chest wall. Superficial migratory thrombophlebitis is associated with systemic diseases like hypertension, Buerger syndrome/thrombophlebitis obliterans, hypercoagulable conditions like protein C and S deficiencies, lupus anticoagulant, factor XII deficiency, systemic inflammatory diseases, Behcet disease and cancer. Mondor disease describes a syndrome of sclerosing superficial thrombophlebitis of the veins of the anterior thoracic wall. The most commonly involved vessel is the superior epigastric vein, producing a palpable cord in the inferior outer quadrant of the breast. It has often been linked to local trauma, including repetition injury or direct injury associated with surgery. In addition to the diagnosis of superficial venous thrombosis using ultrasound, more extensive diagnostic procedures in order to look for a systemic procoagulant state are often needed, since underlying diseases are important for the treatment of SVT in an atypical location.

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INTRODUCTION

Superficial venous thrombosis (SVT) is an inflammation of the venous wall with subsequent secondary thrombus formation. In the past, it was perceived as a benign and self-limited disease. However, recent observations showed that SVT, particularly in the lower limbs, can cause different complications, attributed mostly to deep venous thrombosis (DVT) and pulmonary embolism (PE). Therefore, SVT was recently accepted as a part of venous thromboembolic syndrome. In most cases, it affects the superficial venous system of the lower extremities. It mainly occurs in varicose veins as a consequence of damage to the vessel wall because of turbulent blood flow, stasis and chronically increased venous pressure, which provokes an increase in the systemic inflammatory response and promotes the process of coagulation.

SVT that appears in functionally and structurally normal veins without varicose changes is a heterogeneous group of diseases in which the inflammatory and thrombotic processes are differently expressed. It can appear as an isolated clinical manifestation or as a part of different clinical conditions.

Trousseau's syndrome and Mondor disease are two specific forms of SVT in atypical locations, which have specific etiopathogenetic, clinical, and prognostic characteristics.

TROUSSEAU'S SYNDROME

Trousseau's syndrome, also known as superficial migratory thrombophlebitis, is a rare variant of venous thrombosis, characterised by recurrent, migratory thrombosis in superficial veins in uncommon sites, such as the upper extremities, trunk, and chest wall. It is usually associated with systemic diseases like Buerger disease, hypercoagulable conditions like protein C and S deficiencies, lupus anticoagulant, factor XII deficiency, systemic inflammatory diseases, Behcet disease and cancer, most commonly gastrointestinal (including pancreatic and gastric), lung and urogenital cancers *(1)*. It most commonly occurs between the ages of 25 and 50 years, three times more frequently in males than females.

Cancer-associated SVT is distinctive and its pathogenesis is not well understood. Research has reported the spectrum of overlapping mechanisms, including mucins that have been produced by some adenocarcinomas that trigger thrombotic cascades, as well as highly procoagulant tissue factor positive microparticles that are produced by cancer cells and cysteine proteinase expressed by malignant cells, which directly induces the conversion of factor X to factor Xa. There are reports that tumor tissue hypoxia increases the expression of tissue factor and plasminogen activator inhibitor type 1 (PAI-1) that facilitate coagulation *(2)*.

Patients with superficial thrombophlebitis present with pain, erythema, and induration along the course of a superficial vein. Due to a thrombus within the affected vein, a nodular cord is often palpable. A fever might be present. Signs and symptoms of DVT and PE should be evaluated in high-risk patients, such as patients older than 60 years, those of male sex with the presence of bilateral SVTs, and absence of varicose veins.

The diagnosis of superficial migratory thrombophlebitis is based on clinical presentation and is confirmed by ultrasound investigation. An ultrasound investigation is especially indicated in patients with pain along the course of the superficial vein but who have no physical exam findings suggestive of thrombophlebitis, obese patients, patients with SVT of the great saphenous vein or small saphenous vein, as they have a higher risk for DVT, and patients with significant extremity swelling.

The diagnosis of migratory thrombophlebitis is essential, as it correlates with cancer and other systemic disorders, and it

can be the initial presentation of underlying occult malignancy. These patients should undergo evaluation for underlying malignancy and other systemic disorders at the time of superficial migratory thrombophlebitis diagnosis.

The treatment goal is to relieve local symptoms and prevent the propagation of the thrombus. Supportive care includes an elevation of the affected extremity, nonsteroidal anti-inflammatory drugs, warm or cold compress, compression stockings, and increased ambulation.

In patients with superficial thrombo-p-hlebitis involving a vein segment of size segment smaller than 5 cm and a thrombus site remote from the saphenofemoral junction and saphenopopli-teal junction and no medical risk factors for venous thromboembolism, supportive care is indicated. These patients are followed up in seven to ten days or sooner if symptoms progress, and if there is no clinical improvement in symptoms, an ultrasound duplex is performed to rule out DVT.

Anticoagulation in therapeutic dosage is indicated in patients with the propagation of clots and also in high-risk patients with thrombus longer than 5 cm and within 5 cm from the saphenofemoral junction or saphenopopliteal junction and in patients with concomitant DVT and PE. In patients with SVTs longer than 5 cm and more than 5 cm distant from the saphenofemoral or saphenopopliteal junction, subcutaneous fondaparinux 2.5 mg daily or low-molecular-weight heparin in prophylactic dosage for 45 days is suggested *(3)*.

In patients with DVT and PE, longer--duration anticoagulation is the recommended course. In patients with Buerger disease, the clinician should strongly recommend smoking cessation. If present, underlying systemic or cancer disease should be properly treated.

The prognosis for migratory thrombophlebitis depends on the cause. For malignancies, the prognosis is poor. For benign disorders, the prognosis is good, but residual post-phlebitic syndrome is an issue and should be prevented by using compressive stockings.

MONDOR DISEASE

Mondor disease classically describes a syndrome of sclerosing superficial thrombophlebitis of the veins of the anterior thoracic wall veins. The most commonly involved vessel is the superior epigastric vein, producing a palpable cord in the inferior outer quadrant of the breast or superficial penile veins *(4)*. There are less than 400 reported cases of Mondor disease in medical literature *(5)*. Women are three times more likely to be affected than men. While cases are present in all ages, most are observed among patients between 30 and 60 years of age.

It is a rare clinical entity with a poorly understood etiology. Inciting factors such as direct trauma from tight clothing, surgery, or underlying system diseases such as breast cancer or hypercoagulable states have been described as causes for the resulting sclerosing thrombophlebitis of the affected superficial veins. A recent literature review by Amano et al. revealed that 45% of cases are idiopathic, 20% iatrogenic, 22% traumatic, and 5% related to breast cancer *(6)*.

The disease presents with a sudden onset of mild discomfort with a palpable cord in the affected area. Penile lesions may involve a history of excessive sexual activity, trauma, or abstinence. Anterior chest lesions may include a history of recent mammoplasty, oncologic surgery with either sentinel lymph node biopsy, axillary dissection or core needle biopsy, or another injury such as weightlifting.

The diagnosis of Mondor disease is based on clinical investigation. With so few cases represented in medical literature, there is no consensus on its evaluation or management. In patients with a classic history and no other systemic complaints

and otherwise regular physical exam, it is reasonable to proceed without a laboratory, radiographic, or other invasive testing for diagnosis. In those patients with signs or symptoms suggestive of under-lying pathology, further evaluation with either a mammography of the breast or ultrasound of the breast or penis is needed *(7)*. In cases where the clinical picture is not definitive, ultrasound is considered the first line in the imaging evaluation of Mondor disease. Mammography may be inconclusive, or it may reveal a linear density in the breast in patients with super-ficial thrombophlebitis. MRI and other advanced imaging techniques are generally not indicated in the evaluation of Mondor disease.

Supportive care and expectant management are sufficient in most cases of Mondor disease. Warm compresses, nonsteroidal anti-inflammatory medications, and abstinence from irritating clothing or activities are first-line therapies. Most lesions will resolve with the cessation of discomfort and dissolution of the palpable cord. Treatment with low-molecular-weight heparin or acetylsalicylic acid has been reported in some case series; however, this is not recommended in patients without an underlying hypercoagulable state inciting superficial thrombophlebitis and associated Mondor cord.

Migratory thrombophlebitis can be resistant to anticoagulation treatment in cancer patients, resulting in the progression of thrombus and recurrent PE. There are reports in patients with malignancy and migratory thrombophlebitis that surgical removal of cancer results in cancer cure as well as improves phlebitis symptoms and reduces thrombotic events.

Mondor disease is usually a self-limited condition that resolves in six to eight weeks. In cases where the situation is secondary to a hypercoagulable state, the prognosis is directly linked to the inciting condition.

CONCLUSIONS

SVT which appears in functionally and structurally normal veins at atypical locations is a heterogeneous group of diseases with heterogeneous and poorly understood etiopathogenetic mechanisms. Severe systemic diseases, including various types of cancers should be considered as underlying clinical conditions that might trigger coagulation. In addition to diagnosing SVT by using ultrasound, more extensive diagnostic procedures in order to look for a systemic procoagulant state are often needed since underlying diseases are important for the treatment of SVT in atypical locations.

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Rok Luciano Perme[1]

Caring for Chronic Limb-Threatening Ischemia Patients Undergoing Vascular Interventions

ABSTRACT

KEY WORDS: chronic limb-threatening ischemia, peripheral arterial disease, antithrombotic regimen

Chronic limb-threatening ischemia (CLTI) is a clinical diagnosis with objectively confirmed atherosclerotic peripheral arterial disease, leading to varying degrees of ischemia and presenting as ischemic rest pain and/or tissue loss, such as ulceration or gangrene. Hemodynamic parameters usually associated with CLTI are an ankle-brachial index < 0.4, absolute ankle perfusion pressure < 50 mmHg, toe pressure < 30 mmHg, or transcutaneous oximetry < 30 mmHg. The following article will cover the topics of CLTI prognosis and risk factor treatment as well as the approach to revascularisation procedures with periprocedural or postprocedural treatment especially regarding antithrombotic regimens to improve vessel patency.

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EPIDEMIOLOGY OF PERIPHERAL ARTERIAL DISEASE

Chronic limb-threatening ischemia (CLTI) is a manifestation of peripheral arterial disease (PAD), which is a consequence of the pathological process of atherosclerosis. PAD is defined by ankle-brachial index values ≤ 0.9. Based on these measurements, the worldwide prevalence of PAD is estimated at around 3–10%, in other words, in 2010, there were approximately 200 million persons globally having PAD with a ratio of asymptomatic versus symptomatic patients being 4 : 1 *(1)*. Epidemiological data on CLTI prevalence is unreliable and limited but possibly about 21% of patients with intermittent claudication progress to CLTI in 5-year period *(2)*. CLTI as the most serious clinical form of PAD increases patient risk of lower extremity tissue loss or amputation as well as causes a very high risk of cardiovascular adverse events. One-year mortality in CLTI patients is estimated at around 25%, mostly due to cardiovascular events, comorbidities or advanced age *(3)*. Therefore, there are two aims of treatment.

MEDICAL TREATMENT OF PATIENTS WITH CHRONIC LIMB-THREATENING ISCHEMIA

The first aim of the treatment is to reduce the risk of atherothrombotic events such as myocardial infarction or cerebrovascular insult. This is done by controlling risk factors following established guidelines *(4)*. Every CLTI patient should be treated with antiplatelet medications, usually low dose acetylsalicylic acid (ASA) with the possible addition of low dose (2.5 mg twice a day) rivaroxaban (RIVA) unless there are indications for anticoagulant treatment. Dyslipidemia should be addressed with potent statins with or without ezetimibe or proprotein convertase subtilisin/kexin type 9 (PCSK-9) inhibitors to reach low-density lipoprotein (LDL) cholesterol goal levels. Arterial hypertension and diabetes mellitus must also be treated according to the guidelines. It is of utmost importance that the patient adopts lifestyle changes with smoking cessation, a healthy diet and regular exercise if feasible *(4)*.

IMAGING METHODS

The second aim of treatment in CLTI patients is the improvement of perfusion to enable the healing process and possibly avoid amputation. A good morphological preprocedural diagnostic should be made to enable decision making. This is usually done with a duplex ultrasound, which also provides hemodynamic information, CT angiography or digital subtraction angiography (DSA) during the therapeutic procedure. An MRI is rarely utilised. After obtaining the imaging information, a decision is made on the revascularisation approach. Since patients with CLTI are often of advanced age, have multiple comorbidities, could have had several previous procedures and have multi-level disease, a shared decision is taken on the best approach. The decision making process usually involves an angiologist, an interventional radiologist and a vascular surgeon. Revascularisation can be done endovascularly, surgically or as a hybrid procedure *(1)*. A precise description of these methods is beyond the scope of this article.

LABORATORY MEASUREMENTS

Before the procedure, the patient should be adequately prepared to minimise the risk of complications. Laboratory work-up must include hemogram, myoglobin, electrolytes and creatinine as well as hemostatic parameters. Thresholds may vary between different centres, but generally, hemoglobin levels should be > 90 g/L in case of bleeding, and platelet count should be > 100×10^9/L for primary hemostasis. Electrolyte imbalances must be corrected and a reflection on parenteral hydration should be done to

prevent acute contrast-induced kidney injury in patients with advanced kidney disease.

With respect to hemostasis parameters in patients on vitamin K antagonists, the international normalised ratio (INR) value should be < 1.5, although there are reports that endovascular procedures can be done safely with higher values. Since more and more patients are taking direct oral anticoagulants (DOAC), strict instructions must be given on when to interrupt treatment. Percutaneous endovascular procedures carry an intermediate bleeding risk, and the last dose of DOAC should be taken at least 24 hours before the planned procedure. In case of kidney disease, this time window can increase to 48 hours. Vascular surgery operations carry a high bleeding risk, usually at least 48 hours should pass from the last dose of DOAC. It is also important to keep in mind the possible need for bridging anticoagulant treatment with low-molecular-weight or unfractionated heparin to avoid thrombotic complications *(5)*.

PAIN TREATMENT

One important component of treatment in CLTI patients is analgesia. It is well known that ischemic pain can be very strong and debilitating. Particularly for endovascular procedures, which are predominately performed under local anesthesia, patient cooperation must be good. A supine position during procedure can worsen perfusion, increase the level of pain and cause agitation, making the procedure difficult to perform successfully and without complications. Because of the above-mentioned reasons, sufficient analgetic treatment before and during the procedure is necessary, if needed, sedation can also be utilised. The choice of analgesic medication is at the discretion of the treating physician but usually a combination of several drugs including opioids is necessary *(1)*.

ANTITHROMBOTIC TREATMENT AFTER THE PROCEDURE – OUR EXPERIENCES

Improving patency-rates following revascularisation procedures is the ultimate goal in treating CLTI patients. Dissection, elastic recoil, and arterial thrombosis are the mechanisms of restenosis or occlusion after angioplasty; the last two occur during or in the first few weeks after the procedure. Later, neointimal hyperplasia becomes a significant factor, typically peaking around four to six months post-procedure. This process is driven by the activation, proliferation, and migration of vascular smooth muscle cells to the intima, and the production of an extracellular matrix. Patency-rates differ depending on the vascular region, type of procedure, implanted materials, and comorbidities. There is a lack of quality data on the best antiplatelet/antithrombotic treatment, which is important to optimise procedural outcome. In our clinical department, decisions about antithrombotic treatment are made based on different factors like the vascular region being treated, the implantation of devices or usage of drug-eluting techniques, the indication for anticoagulation treatment, known clopidogrel resistance and bleeding risk.

In patients without anticoagulation, low-dose (100 mg) ASA is given regardless of procedure type. Clopidogrel (75 mg) is added for one month in case of stent or stent-graft implantation, the usage of drug-coated balloon or plain old balloon angioplasty (POBA) of popliteal or tibial arteries. In case of POBA of the superficial femoral artery (SFA), low-dose RIVA is added to ASA. If there is proven clopidogrel resistance, it can be substituted with RIVA or ticagrelor.

If the patient has an indication for anticoagulation treatment, ASA is added only in case of POBA in the iliofemoral region, otherwise clopidogrel is added for one month. If bleeding risk is considered to be

high, usually only monotherapy with anticoagulant drug is continued. Bleeding risk is evaluated based on several factors, such as clinical impression, advanced age (above 75 years), prior large bleeding, anaemia, thrombocytopenia, kidney or liver failure, metastatic cancer or a history of cerebrovascular insult.

There are certain scenarios where optimal treatment choice is individual and at the discretion of the treating interventionalist or a result of a team decision-making process. Such scenarios are for example combined »triple« treatment with dual antiplatelet medication and an anticoagulant, or treatment after catheter-directed thrombolysis or other percutaneous thrombectomy intervention.

Data on patency-rates after surgical (bypass) procedures is sparse so patients usually receive antiplatelet or anticoagulant treatment based on primary indication. There is a possible benefit of dual antiplatelet medication in case of synthetic infrapopliteal bypass, whereas there is no strong indication for DOAC or VKA to improve bypass patency *(6, 7)*.

FOLLOW-UP OF PATIENTS WITH CHRONIC LIMB-THREATENING ISCHEMIA

In the follow-up process, CLTI patients should be seen on a regular basis and encouraged to take cardiovascular risk reducing medications and introduce lifestyle modifications. Patency after a revascularisation procedure should be checked with clinical examination, Doppler pressure measurements and possibly duplex ultrasound to detect restenosis or reocclusion and enable timely re-intervention if needed.

CONCLUSIONS

In summary, patients with CLTI represent a heterogeneous group endangered by a very high risk of fatal and non-fatal cardiovascular events as well as risk of amputation. Therefore, treatment is complex, also due to the lack of high-quality evidence and should be individually tailored by weighing the risks and benefits.

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