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Hellenic Society of Vascular and Endovascular Surgery

# Hellenic Journal of Vascular and Endovascular Surgery

## HOT TOPICS

**Timing of Carotid Intervention in Symptomatic Carotid Artery Stenosis**
Porto, Portugal and Utrecht, The Netherlands

**Near-infrared spectroscopy to monitor spinal cord oxygenation in open thoraco-abdominal aortic surgery. A case series.**
Milano, Italy

**Prevalence of Chronic Venous Insufficiency and Quality of Life in the Greek Population: Protocol and Study Design**
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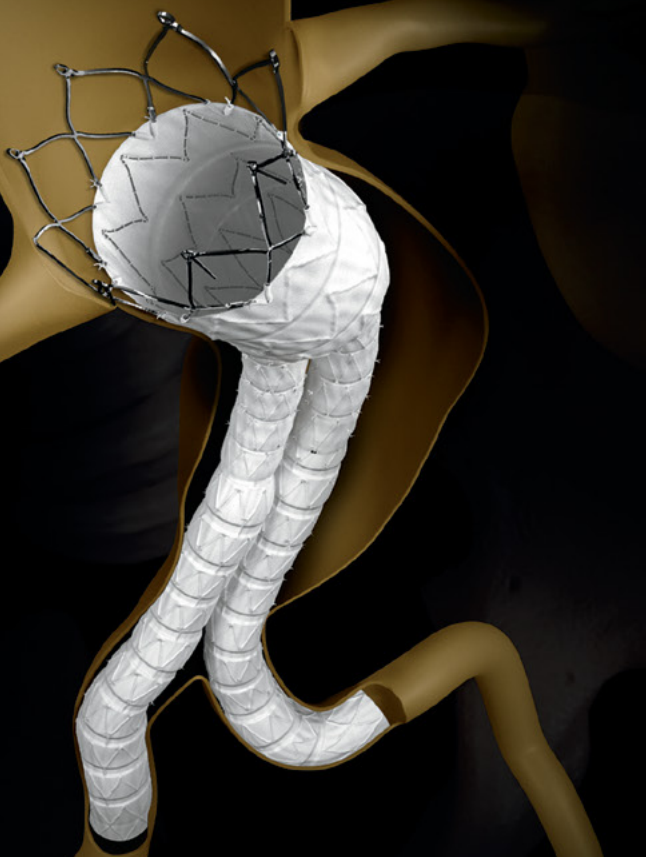

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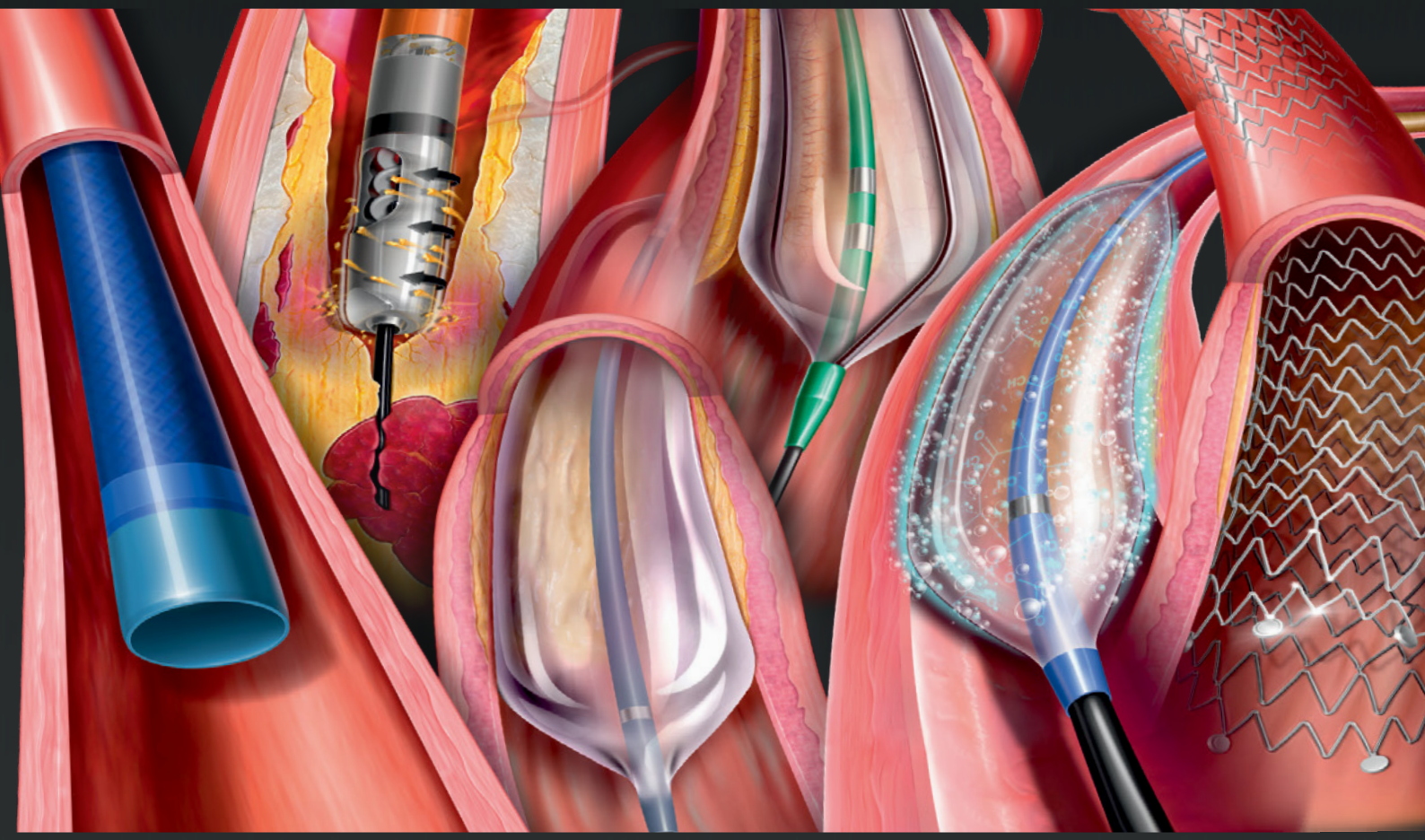

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EDITORIAL

# Timing of Carotid Intervention in Symptomatic Carotid Artery Stenosis

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A recently published systematic review and meta-analysis[1], focused on the debate regarding the optimal timing for "early" carotid intervention after transient ischemic attack (TIA) or minor stroke. The underlying concern was the challenge in balancing the natural history risk for a second (recurrent) event against the potential higher procedural risk of carotid intervention when performed very early (i.e. within 48-72 hours) after the onset of symptoms.[2]

Of relevance, this debate is even more complex when we realize something as elementary as the definition of "index event" has been applied in a highly heterogeneous manner within scientific literature. The definition has occasionally been applied ambiguously within randomized controlled trials (RCTs) developed specifically to study the outcome of carotid endarterectomy (CEA) or carotid artery stenting (CAS) in symptomatic patients. A commonly applied definition is "the most recent neurologic event" before randomization[3] and/or before revascularization[4]. Alternatively, the index neurologic event has also been defined as the very first ischemic event or as the event that lead the patient to seek medical attention[5]. From a pathophysiological point of view the latter definition seems the most relevant while the risk for a recurrent event has been shown to be highest in the early days after the initial event. Not surprisingly, these different definitions of index event can have a significant impact on the reporting of delay times.

The European Society for Vascular Surgery (ESVS) guidelines (and most other international guidelines) recommend that CEA should be performed within 14 days of the "index event" not providing, however, any guidance or reporting standard for the definition of index event. Furthermore, RCT´s and large international registry analysis revealed that (only) a minority of patients was treated within this 14-day time range (independent of the applied definition).[6] This means that RCTs can only contribute to the debate on safety of expedited CEA in small part.

It seems needless to say that ideally studies reporting delay after carotid revascularization should apply a universally accepted definition of the index event and debate to reach conformity in reporting should be encouraged.[7] In our previous review, we focused on the optimal timing for carotid intervention within the 14-day time frame. However, scrutinizing RCTs and real world data, we cannot help but wonder: are we setting up unrealistic standards?

The results of our review suggested that (at present) and considering absolute rates of 30-day stroke, mortality, and death/stroke, CEA performed within two days of the index event complies with the accepted thresholds in international guidelines. Also, at present CEA is safer than CAS when performed within 2 and 7 days of the index event.[1] In other words, we have no doubt that when a patient requires early carotid revascularization, CEA should be considered first-line therapy. The real questions are: Do these patients benefit from an early (<2 days) intervention? How can we (timely) identify patients eligible for this early intervention? And can (most) national health systems logistically provide such an expedited clinical response?

To make the interpretation more complicated, it must be highlighted that in our analysis the balance with the risk for recurrent events was not assessed due to lack of data. Best medical treatment (BMT) has been revolutionized in recent years: (1) generalization in the use of antiplatelet and statin therapy for all patients with carotid atherosclerotic disease; (2) higher rates of smoking cessation, (3) higher rates of achievement of target values for systolic and diastolic pressure and (4) stricter targets for low-density lipoproteins (LDL).[6] Also, dual antiplatelet therapy (DAPT) within 24 hours of experiencing a minor ischemic stroke or "high risk TIA" showed now compelling evidence of benefit (versus aspirin monotherapy), even though in most studies patients scheduled for carotid intervention were excluded.[8]

Overall, with BMT optimization the balance between recurrent and peri-operative events has been once more disturbed, with a potential reduction in recurrent events while awaiting for intervention. The impact of BMT may go further than reducing the risk of recurrent events while awaiting for CEA as it may actually replace carotid revascularization in a

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selected group of patients with symptomatic carotid stenosis having a low risk for recurrent events. The European Carotid Surgery Trial 2 (ECST-2) is an international RCT investigating the optimal treatment of patients with symptomatic or asymptomatic moderate or severe carotid stenosis at low or intermediate risk of future stroke (estimated 5-year risk of stroke of <20%, as calculated using the Carotid Artery Risk score). The ECST-2 trial will compare the risks and benefits of treatment by modern optimized medical management alone versus the addition of immediate carotid surgery (or stenting). The underlying hypothesis is that patients with carotid stenosis ≥50% associated with a low to intermediate risk of stroke will not benefit from additional carotid revascularization when treated with optimized BMT.[9]

While answering questions regarding the capacity of different national health systems goes beyond the scope of this editorial, the questions on "who" and "when" to intervene still remain. Patients with "crescendo TIA" or "stroke in evolution" are particularly at risk for a recurrent event and are recommended to be submitted to CEA within 24 hours.[6] Other subgroups that may benefit from a (very) early intervention may be identified from further cohort studies. Several factors have been already identified that have been associated to a higher risk of recurrence, such as hemispheric (versus ocular) symptoms, demographic patient data (co-morbidities) and plaque characteristics.[6] However, the true future challenges for the next five year will be a) to identify additional (and more specific) plaque and brain specific imaging based criteria to identify those that benefit from early carotid intervention; and b) to validate these parameters in prospective studies. Only then the question of national health systems capacity to provide treatment would become the next focus by limiting the need for invasive treatment to a specific group.

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# Near-infrared spectroscopy to monitor spinal cord oxygenation in open thoraco-abdominal aortic surgery. A case series.

**Giustiniano Enrico, MD[1], Nisi Fulvio, MD[1], Palma Sergio, MD[1], Pisciotta Walter, MD[1], Ruggieri Nadia, MD[1], Barbieri Francesca, MD[2], Civilini Efrem, MD[2,3], Cecconi Maurizio, MD, FRCA, FFICM, MD(Res)[1,3]**

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**Abstract:**

**Objectives.** We adopted the near-infra-red spectroscopy (NIRS) technology to monitor the spinal oxygen supply through the paraspinous muscles oxygenation in agreement with the concept of "collateral network" circulation. We retrospectively investigated our database of subjects who underwent Thoraco-abdominal aorta open repair assessing for the reliability of this monitoring to predict spinal cord injury.

**Methods.** Consecutive Patients who underwent elective thoraco-abdominal aorta open repair between March 2019 and September 2021. In addition to standard monitoring, patients received the monitoring of the paraspinous muscles oxygenation by NIRS.

**Results.** In one patient a significant drop of the mean arterial pressure (49 mmHg) and the spinal-cord perfusion pressure (31 mmHg) occurred after the aortic clamping, with a contemporary lowering of the left-side oxygenation of paraspinous muscles (<40%). Both the blood pressure and the spinal cord perfusion pressure were restored within 10 minutes, but the oxygenation remained at an unsafe level (<55%) until the end of the surgery. This same patient experienced a lower-limbs paralysis post-operatively. It did not happen in the other 11 cases of the sample.

**Conclusions.** The main finding of our retrospective analysis indicates reliability of this technology to monitor the spinal cord oxygenation during open thoraco-abdominal aortic surgery and possibly predict spinal cord injury. Still, several questions need to be addressed about the suitability of this technology to the anatomic and pathophysiology of the spinal cord circulation.

**Key Words:** Thoraco-abdominal aortic surgery; spinal cord injury; paraplegia.

## INTRODUCTION

Thoraco-abdominal aortic (TAA) open repair is a complex surgical procedure with a relevant impact due to the great "surgical invasiveness" and anesthesiologic issues linked to it. Consequently, the patient is at high risk for a complicated outcome (respiratory failure, acute kidney injury, severe intra- and/or post-operative bleeding, ileus, liver disfunction, cardiac adverse events, spinal cord injury) or even death.

Spinal cord injury (SCI) due to ischemia during aortic surgery still has a significant incidence (5-11%) and is one of the most distressing complications in this surgical setting[1,2]. It impacts on patients' quality of life because of the paraplegia *per se* and the psychological aftermath.

Spinal cord (SC) viability during thoracic aortic surgery can be monitored by motor evoked potentials (MEP) or somato-sensory evoked potentials (SSEP), two systems requiring invasive applications, dedicated personnel, and technical skills[3]. Therefore, MEP and SSEP are not routinely employed. The most widely adopted estimation of SC perfusion is the Spinal-cord perfusion pressure (SC-PP) resulting from the difference between the mean arterial pressure (MAP) and the sub-arachnoid pressure (sAP). In addition, the catheter that permits the monitoring of sAP allows the anesthetist to drain the cerebro-spinal fluid (CSF). This action, causing the sAP reduction, contributes to increase the SC-PP, if MAP does not change or increase.

A decade ago, Etz *et al.* described the "Collateral Network", a concept whereby the blood circulation of paraspinous muscles should provide blood supply to the spinal cord too[4].

Following this assumption and considering the anatomic characteristics of the spinal cord circulation (as also described

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by Melissano *et al*. - Figure 1)[5], we started to monitor the near-infra-red spectroscopy (NIRS) of the paraspinous muscles oxygenation during open thoracic and thoraco-abdominal aortic surgery. The present study reports the results of the retrospective analysis of a small case series.

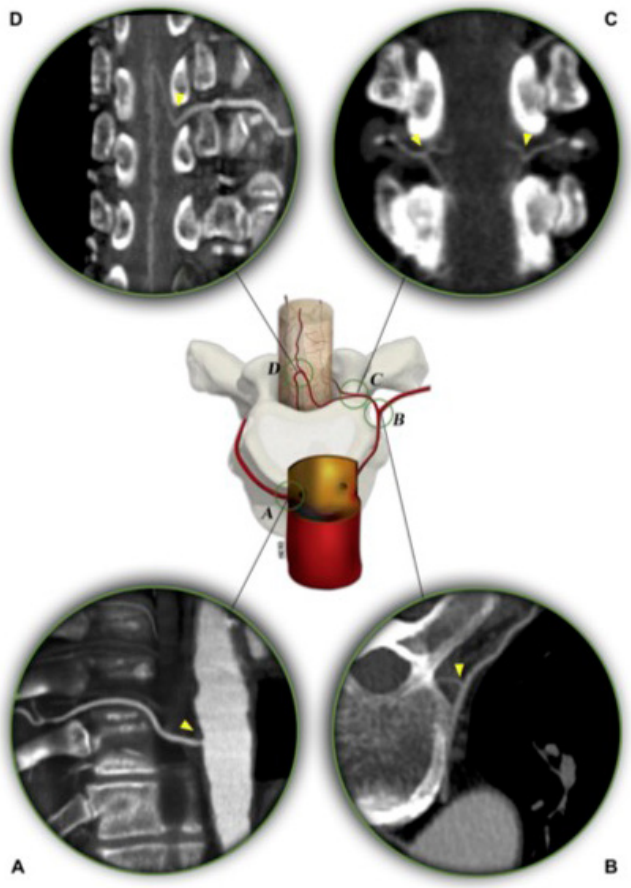


**Figure 1.** The spinal cord circulation

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## METHODS

Between March 2019 and September 2021 we collected the perioperative data of consecutive patients who underwent elective open surgery repair of thoraco-abdominal aorta, at Humanitas Research Hospital in Milan, (Italy). The open approach was indicated and consequently performed upon multidisciplinary consultation.

Emergent operations and endovascular procedures were not included.

This retrospective observational study received the permission of the local Ethical Committee (CE n. 39/21).

STROBE guidelines, and the STROBE checklist were used (http://strobe-statement.org/index.php?id=strobe-home).

The type of TAA in our Hospital is classified according to the Crawford classification[6].

Lower limbs palsy was defined by ASIA classification (America Spinal Injury Association; see https://asia-spinalinjury.org).

Before general anesthesia, we inserted a sub-arachnoid catheter (Hermetic™ Lumbar Catheter Open Tip, 80 cm, Integra NeuroSciences, Plainsboro, NJ, USA) at lumbar level (L3-L4) aimed at monitoring and managing the sub-arachnoid pressure (sAP) and measuring the cerebro-spinal fluid lactate concentration ($Lac_{CSF}$) by a point-of-care machine (GEM Premier 3500-Instrumentation Laboratory Company, Bedford, MA, USA). Then, we placed two NIRS sensors (INVOS™ 5100 Somanetics - Medtronic, Minneapolis, MN, USA) at the thoraco-lumbar region (T9-L2) over paraspinous muscles, (Figure 2).

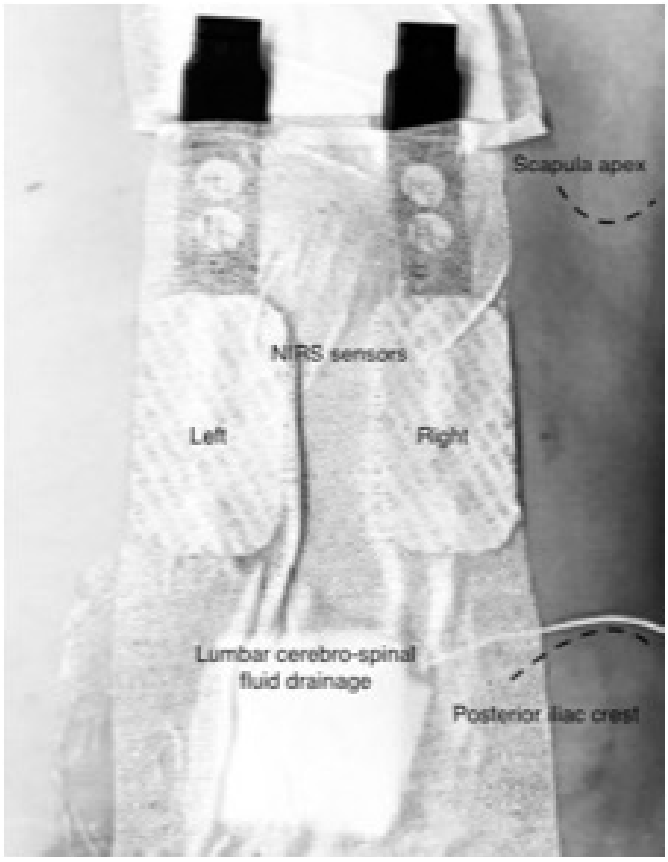


**Figure 2.** NIRS sensors placement

NIRS=Near Infra-Red Spectroscopy

An arterial line had been placed into the radial artery to monitor the invasive blood pressure ($IBP_{rad}$). Moreover, a four-lines central venous catheter was inserted into the left internal jugular vein for drugs and fluids administration, while another 8Fr-central venous catheter was inserted into the right internal jugular vein for fluids and blood products at high-flow rate.

The surgeon provided a second arterial line into the right femoral artery to monitor the blood pressure ($IBP_{fem}$) supplied by the by-pass pump (Bioconsole560-Medtronic, Minneapolis, MN, USA) draining blood from the left atrium and returning it into the left femoral artery.

The patient is placed in the left lateral decubitus position. Incision, aortic dissection, proximal and distal cross-clamping and anastomosis, and need for arterial reattachment, depend on aneurysm type.

For type 1 and 2 aneurysms, we perform the incision at the 5th intercostal space level, with posterior displacement of the ribs; extension of the incision anteriorly and along the median line of the abdomen is required for type 2 aneurysms. It allows the exposure of the abdominal aorta in the retroperitoneum by mobilizing spleen, left kidney, and left colon to the left side.

For type 3 and 4 aneurysms, we chose the skin incision at the 8th or 9th intercostal space.

For type 2 and 3, the diaphragm is sectioned.

Once the exposure is complete and the aorta is adequately isolated, we perform proximal cross-clamping after the left-bypass pump started.

Regarding the distal clamping, a fixed or a sequential clamp technique can be chosen depending on the level of the distal aneurysmal neck.

Sometimes, we use Fogarty balloon catheters to aid in occluding intercostal, visceral, or renal arteries. Considering ischemic time might be lengthy, we generally provide these arteries with a cooled perfusion solution.

When needed, we adopt a Carrel patch technique for visceral and renal arteries reattachment: most commonly, the celiac trunk, the superior mesenteric artery and the right renal artery are kept on the same patch, while the left renal artery is reimplanted individually. Sometimes, endoarterectomy of the arterial ostia might be required. Typically, the inferior mesenteric artery can be safely ligated after ensuring colonic perfusion is maintained by the arc of Riolan.

Thereafter, we perform the distal anastomosis at a level depending on the extension of the aneurysm. If the abdominal aorta is involved, we prefer to execute it at the level of the iliac bifurcation. Eventually, some previously selected intercostal arteries can be reattached to the aortic graft using a patch - if they are anatomically close enough - or a button technique - if they are too far to be positioned on a unique patch[7].

Intra-operative monitoring included standard measurements (non-invasive blood pressure, NIBP; Electrocardiogram of D2 and V5 lines; heart rate, HR; end-tidal $CO_2$, $etCO_2$; peripheral oxygen saturation, $SpO_2$), mean invasive blood pressure from both lines ($mIBP_{rad}$ and $mIBP_{fem}$) and blood-gas analysis. Further monitoring included cerebro-spinal lactate concentration ($Lac_{CSF}$), spinal-cord perfusion pressure (i.e., SC-PP=$mIBP_{rad}$ - sAP) and spinal-cord oxygenation derived from the NIRS ($rSO_2$) sensors.

All patients received general anesthesia (Propofol+Fentanyl for the induction; $O_2$+Air+Sevoflurane for maintenance; Rocuronium for neuromuscular blockade).

Our monitoring targets consisted of $mIBP_{rad}$ >65 mmHg, sAP ≤15 mmHg, SC-PP ≥50 mmHg and $mIBP_{fem}$ 60-80 mmHg. Despite Literature suggests a $mIBP_{fem}$ >80 mmHg[8], in agreement with surgeons, we adopted a little lower level as a safe compromise between providing the spinal cord perfusion and the limitation of intraoperative blood loss.

In case of $mIBP_{rad}$<65 mmHg, Norepinephrine was the first-choice drug. When inotropic support needed, we administered Dobutamine. To reach the target SC-PP we increased $mIBP_{rad}$ and/or reduced sAP by CSF drainage as appropriate: 5-10 ml of CSF within 1-2 minutes.

Alongside spinal-cord perfusion pressure, $Lac_{CSF}$ and $rSO_2$ were used as warnings of SC hypoperfusion/ischemia. Particularly, CSF lactate concentration ≥4 mmol/L was the cutoff value, since $Lac_{CSF}$ >3 mmol/L had been described to be associated with SCI[9].

All the patients were actively warmed. Nevertheless, mild intra-operative hypothermia (34.5-35.5 °C) was tolerated.

Baseline data were recorded before the aortic clamping and subsequently collected at standardized times: T1, upon starting of the extracorporeal by-pass; T2, just after clamping at the thoracic level; T3, 15 minutes after thoracic aorta clamping; T4, passing from thoracic aorta clamping to aortic prosthesis clamping; T5, final aortic unclamping; T6, end of the operation and starting wound closure. Generally, 1-3 minutes were spent between T1 and T2.

After the operation, patients were admitted to intensive care unit (ICU) sedated and mechanically ventilated. When normal body temperature had been reached (36°C), the intensivist performed a basic neurological assessment (awareness and legs' motility and sensitivity) during a free-of-sedation time--window. Then, sedation restarted along with respiratory support ventilation. The weaning from mechanical ventilation was generally achieved within the following 12 hours if no complications occurred.

In case of lower limbs paralysis, after the provisional diagnosis of SCI, patients would have received a magnetic resonance imaging (MRI).

Upon discharge from our hospital, all the patients were sent to a specialized rehabilitation center.

### *Statistics*

Data are reported as either mean ± standard deviation, median and range, or number and percentage, as appropriate.

The Pearson correlation test was used to explore linear association between parameters. Pearson's coefficient (r) between variables has been reported as value within the Confidence Interval 95%.

We assumed $p<0.05$ for statistical significance.

Analysis was performed with Prism 8.2.1 Software - GraphPad 2356 Northside Dr. Suite 560 - San Diego, CA 92108 United States.

## RESULTS

We retrospectively analyzed 12 cases admitted to our hospital for open repair of thoraco-abdominal aorta (TAA).

The sample age was 67 ± 9.5 yrs (median 68 yrs; range 49

÷ 82 yrs) and according to the Crawford classification[6], their aneurysm resulted as follows: 4 type-1, 6 type-2, 1 type-3 and 1 type-4. Preoperative ASA (American Society of Anesthesiology physical status classification) score resulted as follows: six subjects in class 2 and six in class 3. Nine of them were males, (Table 1).

The mean total duration of the aortic clamping was 101 ± 46 min. The average intraoperative CSF drainage was 73 ± 29 ml.

Before the aortic clamping, the baseline data (T0) are summarized in Table 2.

The type-4 case that had not been considered at a risk for SCI and then the surgeon did not perform any intercostal artery reimplantation to the prosthesis. Conversely, 6 patients received at least two paired intercostal arterial branches reimplantation, and 2 patients received a single pair of intercostal arteries reattached to the aortic graft (one of these two patients experienced SCI).

Out of the 12 patients, one case (Crawford type 2), indicated as Pt2, showed a reduction of $rSO_2$ to <40% on the left side at T1 and only at T6 it reached a value >50%. In this case a significant hypotensive event ($mIBP_{rad}$ = 49 mmHg; duration 5-10 minutes) occurred at T1 and was promptly and successfully treated by fluids and NE administration.

Except for Pt2 case, the whole-sample average of $mIBP_{rad}$ was always >70mmHg and the SC-PP had been maintained >50mmHg. Pt2 showed a SC-PP = 31 mmHg at T1, with both $mIBP_{rad}$ and SC-PP restored during the interval T2-T3 ($mIBP_{rad}$ >80 mmHg and SC-PP >60 mmHg).

In Pt2 we observed a high serum concentration of lactate (sLac). Specifically, at T6, sLac = 7.2 mmol/L and $Lac_{CSF}$ = 2.4 mmol/L. At the same time-point the average sLac and $Lac_{CSF}$ in the whole sample were 2.7 ± 1.8 mmol/L and 2.1 ± 0.3 mmol/L, respectively.

Figure 3 shows the trends of NIRS, blood pressure and lactatemia both in the serum and CSF, of each single patient. In Pt2, the trends showed some differences. Specifically, at T1 $mIBP_{rad}$ decreased below 65 mmHg, the left-side NIRS dropped with a nadir at around 30% of oxygenation. Then we ruled out the sensor displacement since the right-side oxygenation was stable.

**Table 1.** The sample characteristics and general perioperative results

| Sex | | 9 Male, 3 Female |
|---|---|---|
| Age (years) | | 67 ± 9.5 |
| ASA | | 2-3 |
| Crawford classification (n, %) | | |
| | Type 1 | 4 (33.3) |
| | Type 2 | 6 (50.0) |
| | Type 3 | 1 (8.3) |
| | Type 4 | 1 (8.3) |
| | | |
| Aortic clamping duration (minutes) | | 101 ± 46 |
| Total intra-operative CSF drainage (ml) | | 73 ± 29 |
| Hospital length-of-stay (days) | | 15 ± 11 |
| ICU length-of-stay (days) | | 7 ± 8 |
| Duration of mechanical ventilation (hours) | | 26 ± 27 |
| Patients who experienced post-operative complications (n,%) | | 9 (75.0) |
| Deaths during hospitalization (n,%) | | 0 (0.0) |
| Deaths during rehabilitation program (n,%) | | 1 (8.3) |

**Table 2.** Baseline values

| | |
|---|---|
| Mean radial arterial pressure (mmHg) | 78 ± **14** |
| Sub-Arachnoid pressure (mmHg) | 17 ± **5** |
| Spinal-Cord Perfusion Pressure (mmHg) | 61 ± **13** |
| Serum Lactate (mmol/L) | 0.9 ± **0.3** |
| CSF - Lactate (mmol/L) | 1.5 ± **0.2** |
| NIRS right side (%) | 75 ± **7** |
| NIRS left side (%) | 77 ± **8** |
| Cardiac Index (L/min/$m^2$ body surface area) | 2.1 ± **0.5** |
| Serum Hemoglobin (g/dL) | 10 ± **2** |

CSF: Cerebro-Spinal Fluid; NIRS: Near Infra-Red Spectroscopy.

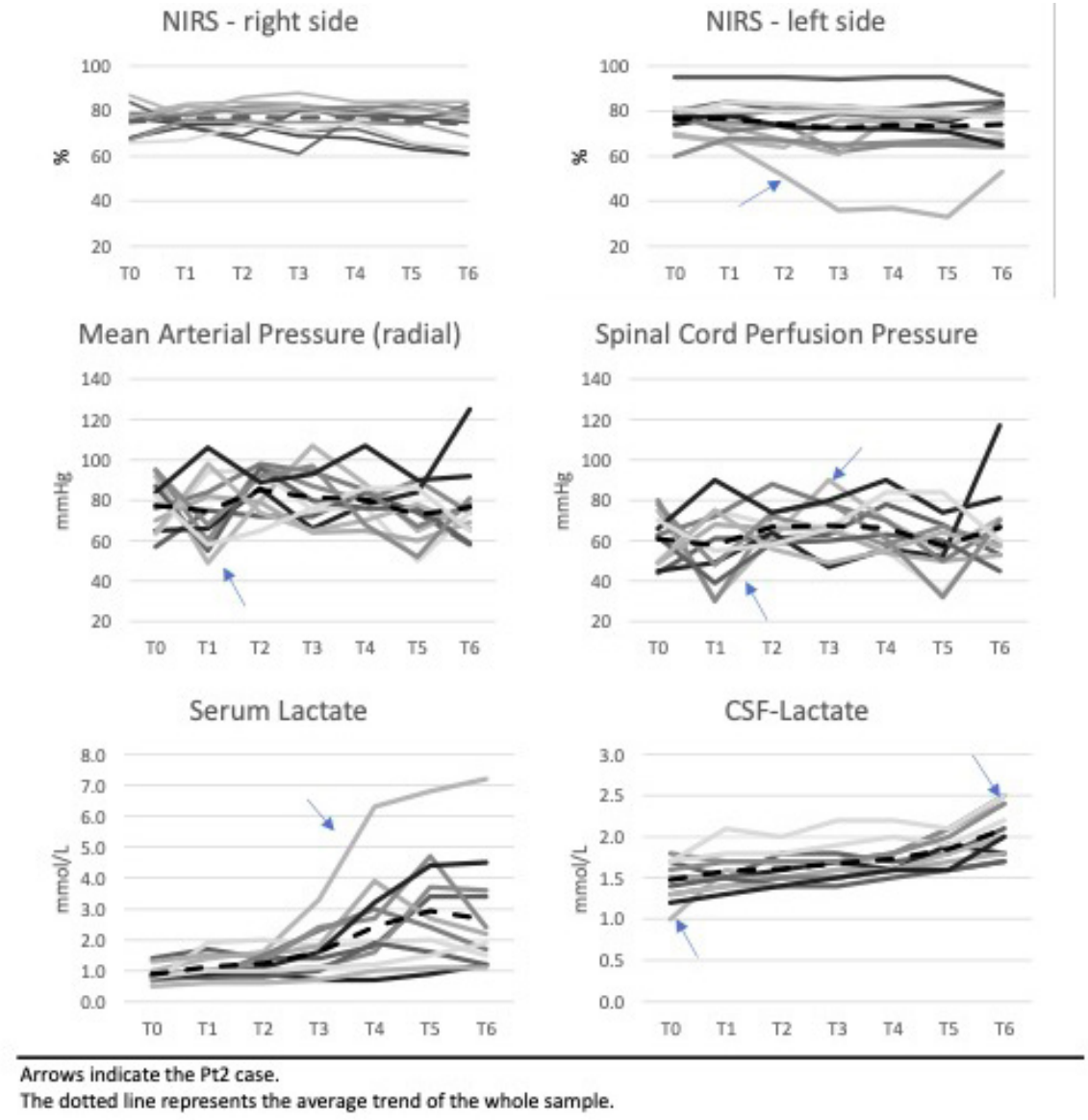


**Figure 3.** Intra-operative trends
The arrow indicates the Pt2 case

In addition, when the Pt2's blood pressure dropped (T1: 49 mmHg), the spinal-cord perfusion pressure reduced accordingly (31 mmHg) and returned to normal value as blood pressure was restored (T2: $mIBP_{rad}$ = 80 mmHg; SC-PP = 61 mmHg).

Three more patients experienced a transient hypotensive event during aortic clamping along with SC-PP dropping, but none of them showed a corresponding reduction in $rSO_2$.

We did not find any correlation between SC-PP and $Lac_{CSF}$, SC-PP and $rSO_2$, $Lac_{CSF}$ and $rSO_2$, and $rSO_2$ and sLac, from T0 to T6, except for $rSO_2$ and sLac from T3 to T6. Table 3 lists the Pearson coefficients and statistical significance of these correlations. Conversely, we observed a significant correlation between NIRS and sLac, (Figure 4).

Out of the 12 cases, three cases (25%) had an uneventful outcome. The most frequent complication was respiratory impairment: three cases of post-operative pneumonia (25%) and two cases of atelectasis were also diagnosed (16.6%). All of these had tested positive to a Covid-19 swab more than one month before and underwent surgery after two consecutive negative swabs along with a pre-operative negative chest X-ray.

One case of pneumonia needed ICU admission for 30 days and received a tracheostomy too. He died of a septic shock due to urinary tract infection during the rehabilitation phase.

Other complications consisted of one case (8.3%) of acute kidney injury (AKI) recovered after temporary continuous renal replacement therapy (CRRT), one case of acute pancreatitis (8.3%), one case of transient sub-arachnoid fistula (8.3%), and one case of hematemesis due to stress-related gastric ulcer (8.3%) and finally one case (Pt2) of post-operative paraplegia (8.3%). In addition, two patients experienced two simultaneous adverse events post-operatively (one pneumonia+AKI and the other pneumonia+stress-related gastric ulcer).

The other three patients with transient intraoperative hy-

**Table 3.** Correlation between $rSO_2$ and serum Lactate

| Time | Right side | | Left side | |
|---|---|---|---|---|
| | r | p | r | p |
| T0 | 0.2098 | 0.5127 | 0.1882 | 0.5580 |
| T1 | 0.4170 | 0.1774 | 0.1658 | 0.6065 |
| T2 | 0.1055 | 0.7717 | -0.4357 | 0.2081 |
| T3 | -0.2271 | 0.5281 | -0.7219 | 0.0184 |
| T4 | -0.1666 | 0.6684 | -0.7373 | 0.0234 |
| T5 | -0.6020 | 0.0384 | -0.7785 | 0.0029 |
| T6 | -0.7444 | 0.0055 | -0.7640 | 0.0038 |

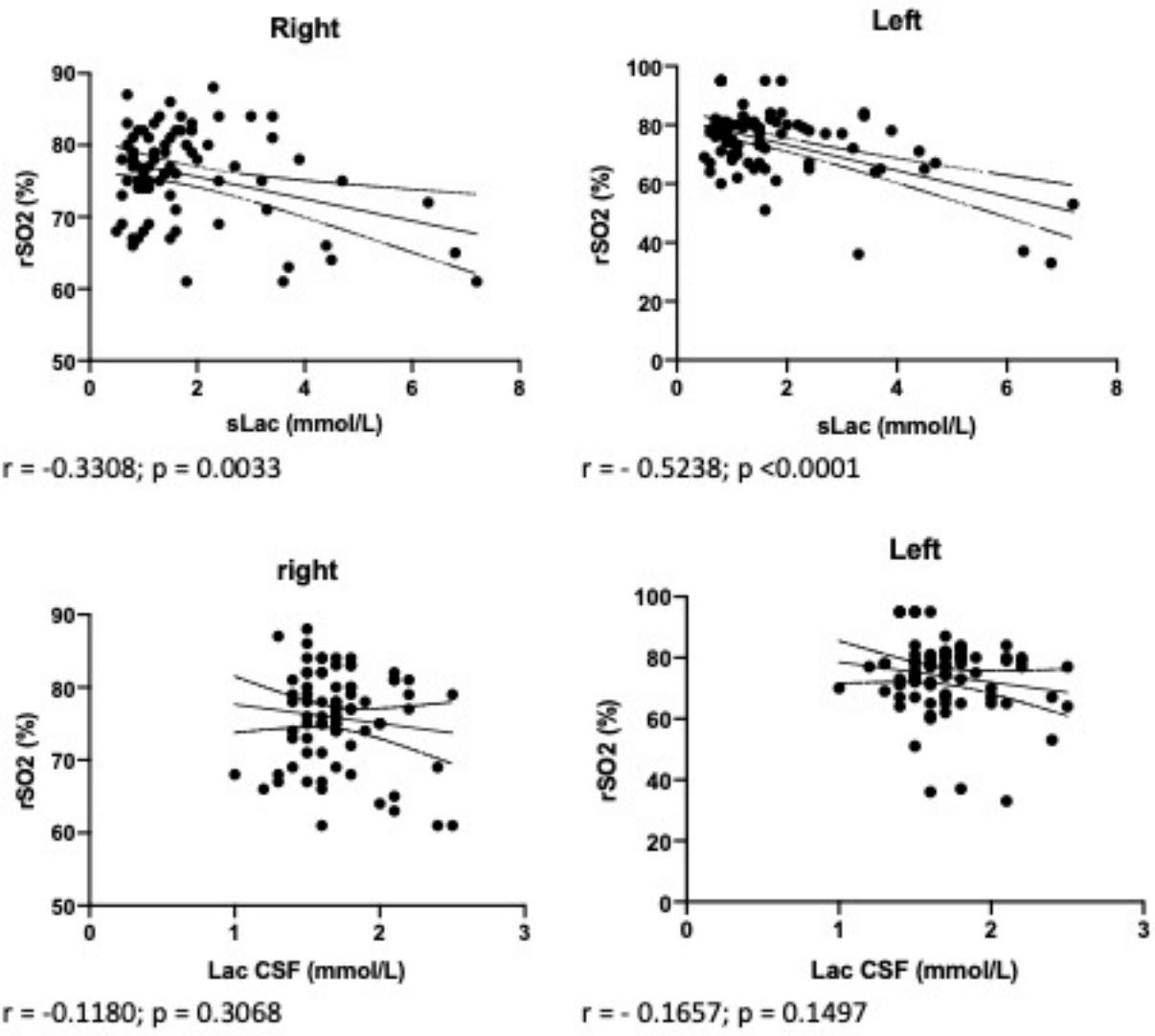


**Figure 4.** Correlation between NIRS and sLac and LacCSF

NIRS=Near Infra-Red Spectroscopy; LacCSF = Cerebro-Spinal Fluid lactate concentration.

potension did not show spinal cord injury post-operatively.

None of the twelve patients had any complication associated with the insertion of the CSF drainage.

## DISCUSSION

The main finding of our retrospective analysis indicates a possible reliability of NIRS to monitor the spinal cord oxygenation during open thoraco-abdominal aortic surgery. To corroborate this assumption, we can consider that only the patient who experienced postoperative lower limbs paralysis showed an even unilateral reduction of $rSO_2$ for most of the intraoperative time. Conversely, when $rSO_2$ drop was transient it resulted harmless.

Spinal Cord Injury in TAA repair may occur in a percentage that reach 11% or even more depending on the type of procedure (endovascular or open surgery), the extension of the

aorta substitution and the type of the aneurysm[1,2]. Aiming at limiting the occurrence of SCI, different and combined strategies are applied: spinal fluid drainage, optimization of blood pressure, neuroprotection by drugs and/or hypothermia and arterial branches reimplantation[10]. Nevertheless, such strategies need to be supported by spinal cord oxygen supply monitoring and nowadays it may be possible only indirectly.

The oxygen saturation over paraspinous muscles has been considered as corresponding to the oxygenation of the spinal cord based on the assumption that they are supplied by the same circulatory blood flow[4,11]. Consequently, if paraspinous oxygenation reduces, a simultaneous deficit of spinal cord oxygen supply deficit would be expected.

Although some different levels of sensor positions have been described, the optimal site is under debate[12]. Nevertheless, Etz *et al.* reported that the most appropriate site to monitor the SC oxygenation should be at thoraco-lumbar region, because at this level the spinal cord circulation is the most jeopardized in terms of blood perfusion[13]. Such a report made us choose the thoraco-lumbar region for NIRS sensor placement.

Contrarily to what Vanpeteghem *et al.* reported in their review[11], after by-pass pump starting and aortic clamping, we did not observe a significant reduction of the $rSO_2$, except for the Pt2 case, in which, $rSO_2$ fell almost immediately after the aortic clamping, even if only unilaterally.

Moreover, three co-existing warning signs can be considered as consistent with hypoperfusion of the spinal cord: 1) the systemic hypotension; 2) the SC-PP drop; 3) the $rSO_2$ reduction.

Even though both blood pressure and SC-PP were promptly restored, the CSF-Lactate concentration started to rise progressively but reached a similar level of other cases.

Anyway, based on these findings, some questions arise. First, why would only unilateral rather than bilateral oxygen desaturation explains the hypoxia of the spinal cord? Second, why did $rSO_2$ not recover after blood pressure and spinal-cord perfusion pressure were restored? Third, if CSF-Lactate is a marker of spinal cord ischemia, why did it not rise to a level higher than the other cases?

To answer the first question, we could speculate that the patient developing SCI there might have been a left-side predominance in the arterial circulation supplying both spinal cord and paraspinous muscles. In such a context, we could speculate that since the neural tissue is more sensitive to hypoxia compared to muscle, neurons would suffer whilst myocells hypoxia could be clinically silent, except for the increased lactatemia. This until collateral circulation restored the muscle perfusion. It might justify the late recovery of $rSO_2$. Accondingly, Luehr *et al.* reported a delay of $rSO_2$ variation of paraspinous muscles after aortic cross-clamping[14]. Furthermore, we are aware that the serum hyperlactatemia we observed in the Pt2 case could be multifactorial in such a major surgery. Nevertheless, the paraspinous muscles ischemia-reperfusion could be the main factor. We expected a progressive clearance of serum lactate provide the hemodynamics was stable.

Moreover, Rojas *et al.*, in a study including 32 cadavers, found asymmetry of the spinal cord arterial circulation both in terms of anatomic disposition and caliber of the vessels, in up to 81.25% of the cases[15].

In few words, the single pair of arterial branches reattached to the aortic graft might have not been sufficient to sustain the spinal cord circulation.

Depending on several vascular and metabolic factors, a safe pressure level does not always ensure an adequate flow. Indeed, in animal models, spinal cord autoregulation is less robust than cerebral autoregulation and more pressure-dependent, hence SC is more sensitive to hypotension[16].

Noteworthy, Vanpeteghem *et al.*, found different effects of phenylephrine and ephedrine on cerebral oxygen saturation and paraspinal oxygen saturation. Following vasoactive drug administration resulted in a steal phenomenon: an increased blood flow to the spinal muscles, masking the spinal cord hypo-oxygenation. The authors concluded that the application of the "Collateral network" concept in case of vasoconstrictive drug use remains to be confirmed[17].

In our case, NE was able to restore blood pressure promptly, but left side $rSO_2$ remained at low levels. Then, we might assume that the phenomena observed by Luher and Vanpeteghem's could explain our findings.

With regards to the Lactate concentration, we know that if the Blood-Brain Barrier (BBB) is intact, there is no mixing of blood and CSF. The $Lac_{CSF}$ is a marker of the central nervous system anaerobic metabolism, like during an ischemic injury. When the BBB is disrupted (as in the case of prolonged ischemia) a mix of blood and CSF should occur[18,19]. In Pt2 case sLac increased more than in CSF, possibly because lactatemia was also depending on the paraspinous muscles ischemia.

When spinal cord ischemia occurred due to a transient hypotension, $rSO_2$ reduced, marking the hypoxic state on the left side. Even when blood pressure was restored on the left-side, spinal ischemia persisted. The late normalization of $rSO_2$ was only due to the muscles restored oxygenation through any collateral circulation.

In our experience, we already found a significant increase of $Lac_{CSF}$ in a patient submitted to open TAA repair who experienced SCI post-operatively[20,21]. Unfortunately, at that time we did not monitor $rSO_2$, and consequently we cannot compare the two cases.

Experimental evidence about NIRS as an index of spinal cord circulation is conflicting. Suehiro et al., reported that NIRS may be used to detect changes in spinal cord circulation following aortic clamping and de-clamping in animal model, whereas it may not reflect changes in spinal cord circulation due to cerebrospinal fluid drainage[22].

If both $rSO_2$ and $Lac_{CSF}$ are markers of spinal cord ischemia, the inconsistency between the drop of the former and the hampered rise of CSF-lactate concentration in the Pt2 patient is unexpected and difficult to explain. The lacking correlation between $rSO_2$ and $Lac_{CSF}$ may be due to the fact that dead cells (neurons in this case) do not have any metabolism and then

do not produce lactic acid.

Our case series has several limitations. First, its retrospective nature along with the small sample size do not permit definite conclusions and consequently these findings should be considered mostly speculative. Moreover, a single case of deoxygenation observed may have been accidental. Finally, as discussed above, our results leave some important open questions.

In conclusion, Near Infra-Red Spectroscopy application at the thoraco-lumbar region over paraspinous muscles may be helpful to indirectly monitor the spinal cord oxygenation during open repair of thoraco-abdominal aorta. Anyway, we are aware that further specific investigations are desirable to better understand how to interpret and integrate paraspinous muscles $rSO_2$ in the setting of thoraco-abdominal aorta open surgery.

Assessing the reliability NIRS in this field, could provide a helpful and non-invasive tool to monitor the spinal cord oxygen supply. The surgeon might use it as a tool to decide for further collateral branches re-implantation to the prosthesis. The anesthetist might use it to guide the strategies to prevent spinal cord injury.

## ACKNOWLEDGEMENTS

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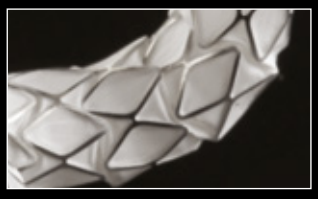

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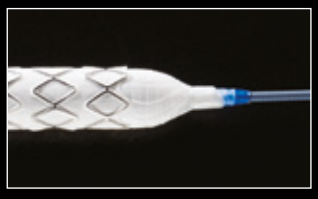

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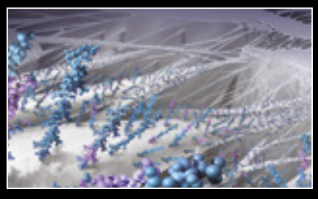

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# Prevalence of Chronic Venous Insufficiency and Quality of Life in the Greek Population: Protocol and Study Design

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**Abstract:**

Chronic venous insufficiency (CVI) is very common in the western world with various studies reporting a prevalence of 46-84%, depending on the population studied, the definition of CVI and the mode of diagnosis (ultrasound or clinical). In Greece, a few studies have focused on this chronic health problem and the findings are contradictory in terms of CVI incidence in the two genders, in different age groups and in urban or rural areas. We herein present the protocol and study design of our study targeting to assess the prevalence of CVI in Greece and the quality of life of patients at different stages of the disease (C0s-C6).

A cross-sectional study will be carried out in Greece between December 2022 and February 2023. The study will include ~2,300 adults constituting a random and representative sample of the general population in terms of geographic region of residence and gender based on the most recent census (2021). This sample will be selected from a random sample of pharmacies invited to participate in the study per geographic region; this will be proportional to the number of individuals to be included per geographic region to ensure representativeness. Each pharmacy will enroll 10 individuals.

Data collection will be carried out with the help of a questionnaire focusing on CVI symptoms. Colour photographs of lower extremities of different CVI stages will help the respondents to select whether they identify with one of these stages (C0s-C6). Their quality of life will be assessed via the CIVIQ-14 questionnaire.

## INTRODUCTION

Chronic venous insufficiency (CVI) of the lower extremities is a particularly common condition affecting the general population and includes a wide range of signs and symptoms that impact patient health and quality of life. The underlying cause is venous hypertension due to structural or functional abnormalities of the veins (venous insufficiency). The causal basis of CVI is multifactorial and is partly due to hereditary predisposition, partly due to lifestyle or other factors (e.g., pregnancy, history of thrombosis). Regardless of its causal basis, CVI has significant socio-economic consequences and significantly affects patients' quality of life.[1]

Although CVI may be asymptomatic in the very early stages, symptoms develop gradually and are increasingly worsen with age. Common symptoms are heaviness or pain, swelling, muscle cramps, burning sensation, itching sensation and restless legs. The physical signs include the appearance of telangiectasias in the initial stages, followed by venous varicosities and edema, and in the advanced stages it manifests as skin discoloration and ulcers that are difficult to heal. Due to the chronic nature of the disease, exacerbations and remissions often occur in combination with the influence of environmental factors. The clinical staging of CVI is described in the CEAP classification (Clinical condition, Etiology, Anatomic distribution and Pathophysiology).[2] In daily clinical practice, we limit ourselves to the "C", clinical condition:

- **0**: No visible or palpable signs of venous disease
- **0s**: No visible or palpable veins, without signs but with symptoms of venous disease (this subcategory has been eliminated in the 2020 revised classification)
- **I:** Telangiectasias, reticular veins
- **II:** Varicose veins
- **IIr**: Recurrent varicose veins
- **III:** Edema without skin lesions
- **IV**: Changes in and subcutaneous tissue secondary to chronic venous disease

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- **IVa:** Pigmentation or eczema
- IVb: Lipodermatosclerosis or atrophie blanche
- IVc: Corona phlebectatica
- **V**: Skin lesions as above with a healed ulcer
- **VI**: Skin lesions as above with an active ulcer
- **VIr**: Recurrent active venous ulcer

CVI is very common in the western world with various studies reporting a prevalence of 46-84%, depending on the population/sample, the exact definition of CVI (C0s-C6, C1-C6 etc.) and the mode of diagnosis (ultrasound or clinical).[1-8] Given the progressive aging of the population, the frequency is expected to increase. In Greece, a few studies have focused on this chronic health problem and the findings are contradictory in terms of CVI incidence in the two genders, in different age groups and in urban or rural areas. [9-11]

The primary objective of our study is to assess the prevalence of CVI in Greece and the quality of life of patients at different stages of the disease (C0s-C6). We herein present our study protocol and design.

## METHODOLOGY

### *Study design*

In order to serve the primary objective of this study, a cross-sectional study will be carried out in Greece between December 2022 and February 2023.

The study will include ~2,300 adults constituting a random and representative sample of the general population in terms of geographic region of residence and gender based on the most recent census (2021).

This sample will be selected from a random sample of pharmacies invited to participate in the study per geographic region; this will be proportional to the number of individuals to be included per geographic region to ensure representativeness, given that each pharmacy will enroll 10 individuals. The pharmacists who will accept to participate in the study will attend a dedicated training session for the needs of data collection.

Specifically, patients eligible for inclusion in the study will be people over 18 years of age, inhabitants of the respective geographic region, who will visit the study pharmacies between 10:00 am and 12:00 pm. In order to maintain gender representativeness of the overall Greek population in the sample, pharmacists will not target individuals of the gender for which the number of individuals has been completed, based on initial estimates. Each pharmacy will stop collecting data once they have completed the required number of questionnaires for men and women (5 questionnaires from each gender). In addition to the questionnaires, each pharmacy will record the number of people it addressed in total during the collection in order to estimate the response rate to the study.

Table 1 shows the distribution of participants by gender and geographic region. From each geographic region, one or more cities will be selected that are considered representative of the region (one of them will be its seat). In the case of more than one city selected per geographic region, the distribution of pharmacies will be proportional to the number of inhabitants of the city. The number of pharmacies - study sites per city is listed in Table 2.

### *Data collection*

Data collection, performed at pharmacies, will be carried out with the help of a questionnaire designed to serve the objectives of this study. This questionnaire includes questions about participants' general demographic data (geographic region, age, gender, height, weight), lifestyle (daily activity, smoking), family history of venous disease and personal medical history (venous thrombosis for which the participant re-

**Table 1.** Distribution of participants by gender and geographic region

| | Data by ELSTAT [Hellenic Statistical Authority] | | | | Sample size | | |
|---|---|---|---|---|---|---|---|
| Geographic Region | 2021 population | % of population | Men | % of men | Total | Men | Women |
| Eastern Macedonia And Thrace | 562,069 | 5.40% | 275,340 | 49.0% | 124 | 61 | 63 |
| Central Macedonia | 1,792,069 | 17.20% | 861,420 | 48.1% | 396 | 190 | 206 |
| Western Macedonia | 255,056 | 2.40% | 126,711 | 49.7% | 56 | 28 | 28 |
| Epirus | 319,543 | 3.10% | 157,092 | 49.2% | 71 | 35 | 36 |
| Thessaly | 687,527 | 6.60% | 336,801 | 49.0% | 152 | 74 | 77 |
| Central Greece | 505,269 | 4.80% | 252,106 | 49.9% | 112 | 56 | 56 |
| Ionian Islands | 200,726 | 1.90% | 99,139 | 49.4% | 44 | 22 | 22 |
| Western Greece | 643,349 | 6.20% | 322,242 | 50.1% | 142 | 71 | 71 |
| Peloponnese | 538,366 | 5.20% | 269,285 | 50.0% | 119 | 59 | 59 |
| Attica | 3,792,469 | 36.40% | 1,810,987 | 47.8% | 838 | 400 | 438 |
| Northern Aegean | 194,136 | 1.90% | 97,178 | 50.1% | 43 | 21 | 21 |
| Southern Aegean | 324,542 | 3.10% | 162,576 | 50.1% | 72 | 36 | 36 |
| Crete | 617,360 | 5.90% | 304,372 | 49.3% | 136 | 67 | 69 |
| Total | 10,432,481 | 100% | 5,075,249 | 48.6% | 2,305 | 1,121 | 1,184 |

**Table 2.** Identification of cities and number of pharmacies from each city

| Geographic Region | Region Seat | Number of pharmacies (N=229) |
|---|---|---|
| Eastern Macedonia And Thrace | Komotini | 2 |
| | Kavala | 5 |
| | Alexandroupoli | 5 |
| Central Macedonia | Serres | 3 |
| | Thessaloniki | 37 |
| Western Macedonia | Kozani | 3 |
| | Ptolemaida | 3 |
| Epirus | Ioannina | 6 |
| | Preveza | 1 |
| Thessaly | Larissa | 7 |
| | Karditsa | 2 |
| | Volos | 2 |
| | Trikala | 4 |
| Central Greece | Lamia | 2 |
| | Chalkida | 5 |
| | Kammena Vourla | 1 |
| | Livadeia | 1 |
| | Thiva | 2 |
| Ionian Islands | Kefalonia | 1 |
| | Lefkada | 1 |
| Western Greece | Patras | 12 |
| | Agrinio | 3 |
| Peloponnese | Korinthos | 2 |
| | Kalamata | 3 |
| | Tripoli | 1 |
| | Sparti | 1 |
| | Xilokastro | 2 |
| | Argos | 2 |
| | Messini | 1 |
| Attica | Athens | 84 |
| Northern Aegean | Mytilene | 2 |
| | Chios | 2 |
| Southern Aegean | Rodos | 6 |
| | Kos | 1 |
| Crete | Heraklion | 7 |
| | Chania | 4 |
| | Rethymno | 2 |
| | Agios Nikolaos | 1 |

ceived anticoagulation, heart/kidney/liver failure, diagnosis with lymphedema or lipedema) and focus on symptoms and signs suggestive of venous insufficiency. Colour photographs of lower extremities of different CVI stages will help the respondents to select whether they identify with one of these stages (C0s-C6). Part of the questionnaire will be the CIVIQ-14 questionnaire.[12,13] The estimation of CVI prevalence by stage (C0s-C6) will be based on patient responses. The staging will be based on the rule presented in Table 3. Participants diagnosed with any stage (C0s-C6) will also be asked about their use of elastic compression stockings, treatment for symptoms of venous insufficiency in the legs, any possible kind of vein intervention, and their quality of life via the CIVIQ-14 questionnaire. The CIVIQ questionnaire has been translated and adjusted to Greek. [14]

**Table 3.** Staging rule based on symptoms, diagnoses and photographs of lower extremities

| | Without CVI | C0s | C1 | C2 | C3 | C4 | C5 | C6 |
|---|---|---|---|---|---|---|---|---|
| **Symptoms of interest:** Heaviness, tightness, pain, itching, night cramps, numbness, burning sensation | <2 symptoms | ≥2 symptoms | regardless of the answer | regardless of the answer | regardless of the answer | regardless of the answer | regardless of the answer | regardless of the answer |
| Diagnosis of cardiac, renal, liver failure | regardless of the answer | No | regardless of the answer | regardless of the answer | no | regardless of the answer | regardless of the answer | regardless of the answer |
| Diagnosis with lymphedema or lipedema | regardless of the answer | No | regardless of the answer | regardless of the answer | no | regardless of the answer | regardless of the answer | regardless of the answer |
| Varicose veins on the leg | no | No | yes | regardless of the answer | regardless of the answer | regardless of the answer | regardless of the answer | regardless of the answer |
| Distended veins (varicose veins) on the leg | no | No | no | yes | regardless of the answer | regardless of the answer | regardless of the answer | regardless of the answer |
| Swollen leg, especially at the end of the day | no | No | no | no | yes | regardless of the answer | regardless of the answer | regardless of the answer |
| Color change on the leg to darker brown | no | No | no | no | no | yes | regardless of the answer | regardless of the answer |
| A wound on the leg that takes a long time to heal or that has healed after a long time | no | no | no | no | no | no | Yes, it has healed | Yes, open wound |

## STATISTICAL ANALYSIS

### *Calculation of the sample size*

The sample size estimate was based on the assumption that the prevalence of venous insufficiency (C0s-C6) would be about 60%, based on the available literature.[1,3,9,10] Therefore, with a statistical significance level of 5% (a) and an absolute precision (d) equal to 2%, the resulting sample size is 2,305 individuals using Lwanga's and Lemeshow's equation.[15]

### *Data analysis*

The study data will be further weighted for the age distribution of the population by sex and geographic region as derived from the latest ELSTAT census (2011 or 2021, whichever is available).

The results of the study will be presented with appropriate descriptive means: qualitative variables with absolute (n) and relative frequencies (%), and quantitative variables with mean and standard deviation (SD) or median and 1st - 3rd quartile (Q1 - Q3). Prevalence will be reported with percentages (%) and 95% confidence intervals (CIs).

Correlations between two continuous variables will be tested with Pearson's or Spearman's rho, between two categorical variables with Pearson's Chi-square test or Fisher's exact test, and between a categorical and a continuous variable with Student's t -test or the Mann - Whitney U test. In addition, generalized linear models will be applied by selecting an appropriate distribution from the family of exponential distributions and an appropriate link function to investigate demographic and clinical factors associated with venous insufficiency, its severity and the patients' quality of life of patients. All tests will consider the weights of the observations.

All tests will be performed at an $\alpha = 5\%$ significance level. Data processing and statistical analyses will be carried out with the statistical program Stata 17.

## RESEARCH ETHICS

In conducting this research, all personal data security protocols are to be followed and the confidentiality of the data collected from the sample is to be preserved. In the database that will be created, the data will be anonymized.

This study will be conducted in accordance with the principles underlying the Declaration of Helsinki, thus ensuring compliance with regulatory standards that guarantee that

the safety, rights and welfare of the participants involved in this study are protected. Written informed consent will be obtained for any individual to participate in the study. At the same time, permission to approve the research protocol will be requested from the ethics committee of the Navy Hospital of Athens (NNA), while it is also worth mentioning that the data collected from the questionnaire responses will be used exclusively for the completion of this research and not for any other purpose.

## CONFLICTS OF INTEREST

The study is sponsored by the pharmaceutical company Servier Hellas Pharmaceutique E.P.E.

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# Anatomical challenges in TEVAR and recent developments in the design of thoracic aortic stent-grafts

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**Abstract:**

Endovascular repair is the treatment of choice for the patients suffering from thoracic aortic pathologies. Nevertheless, a higher proportion of young and female patients, as well as substantially high-profile delivery systems, lead to significantly higher morbidity rates or possibly the inability to implant any endoprosthesis at all. Thoracic stent-grafts have additional challenges to overcome due to the aortic curvature. This article will review the latest developments in thoracic stent-graft designs helped to address these anatomical challenges.

## INTRODUCTION

Thoracic endovascular aneurysm repair (TEVAR), is currently preferable over open surgery for the treatment of thoracic aortic pathologies.[1] The rationale for this is the lower rates of perioperative morbidity and mortality associated with TEVAR when compared with open repair.[2, 3] However, the feasibility, as well as, the short- and long-term clinical success of this procedure fundamentally depends on the treated anatomy and the ability of the stent-graft to be accommodated to this anatomy.

In a manner analogous to the implantation of stent-graft in the abdominal segment, anchoring in a sufficiently long healthy aortic segment proximal and distal to the pathology is required in order to achieve adequate apposition of the stent-graft, allowing a secure seal and fixation. Achieving a sealing zone of ≥ 2-cm centerline length is recommended.[4] Moreover, an extremely angulated landing zone can lead to incomplete endograft apposition to the aortic lumen wall. A compromised landing zone increases the risk for endoleaks, bird-beaking configuration, retrograde aortic dissection, and even device migration or collapse.[4, 5]

Depending on the urgency, adjunctive procedures might be required to extend the landing zone and ensure a durable seal. These procedures include from the highly demanding total arch repair and the "frozen elephant trunk" procedure to other extra-anatomical arch debranching procedures, with less invasiveness (e.g transposition or bypass).[6, 7] The proximal extent of the disease guides the proximal anchoring zone and therefore, determines the extend of the repair. During the last decades stent-grafts with scallops, fenestrations or branches offer an alternative to hybrid procedures, whereas other authors also advocate the creation of in-situ fenestrations.[8, 9] Moreover, the parallel graft technique or "chimney technique", which involves deployment of stents/stent-grafts into the supra-aortic branches, with the proximal parts placed parallel to the main thoracic aortic stent-graft (between the aortic stent and the aortic wall) and extended above it to ensure perfusion, has also been used, with the advantage of immediate availability using off-the-shelf devices.[10] Laser in situ arch fenestration is a further useful adjunct that has been used successfully in expanding the proximal zone of TEVAR to obtain adequate seal.[11]

Another issue that has to be dealt with is the morphology of the access vessels and the tortuosity of the aorta. It is well known that, among patients with descending thoracic aortic aneurysms female gender and young age are more common than among patients with abdominal aortic aneurysms. [2, 12] This population of patients has smaller access vessels, which can pose challenges in the advancement of the thoracic stent-graft while and increases the risk of access related complications.[13]

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## MATERIAL AND METHODS

Aim of the present study is to list the advancements of the currently available in EU thoracic stent-grafts, which have been applied to address these anatomy-related challenges. The overview does not claim to cover all the available thoracic stent-grafts. However, it intends to illustrate the developments on the design and its impact on the results. Thus, the currently published studies on the new thoracic stent-grafts designs are presented.

### *Low-profile stent-grafts*

The delivery system has been reduced in size over the previous decade, which has been one of the most significant advancements in all aortic stent-grafts. This is especially important in

the case of larger thoracic aortic stent-grafts, as delivery system diameter has been considered as a risk factor for morbidity and mortality.[13] An overview of the available endografts with their characteristics, indicated for use in the descending thoracic aorta are included in table 1.

The Zenith Thoracic Alpha® (Cook Medical, Bloomington,IL, USA), the newer generation of the Zenith TX2®, was the first low-profile stent-graft developed for the thoracic aorta equipped with a built-in nose cone curvature (Pro Form®) to improve conformability. Medium- and long-term outcomes of this device have been reported in a single-centre, retrospective study of 44 patients with a clinical follow-up period of at least 5 years.[14, 15] The primary endpoint was continued clinical success (freedom from aneurysm-/procedure-related death, secondary intervention, type I or III endoleak, infection, thrombosis, aneurysm expansion, rupture, or conversion) according to the reporting standards for TEVAR.[16] Secondary endpoints included stent fractures and fabric erosions, as well as migration of the prosthesis. Sustained clinical success was achieved in 84.1% of the patients. Four patients died in the postoperative course, whereas 3 type I or III endoleaks, and 1 aneurysm expansion without detectable endoleak were recorded. Graft-migrations were found in 2 patients (4.5%). No stent fracture was detected during the follow-up period while three patients (7%) had access vessel complications.

It was a great concern for many years whether reducing the size of delivery system would have an impact on durability. Both the metallic skeleton and the endograft fabric have to be modified to fit within narrower introducers. In a study initiated by Cook, four migrations and one stent fracture were detected within a period of 12 months in a group of 110 patients with thoracic aortic aneurysms. To what extent these migrations could be attributed to the progression of aneurysmal degeneration in such a short time or if they were driven by the changes in design remained an unresolved topic. A second issue with the stent graft was the increased thrombus development within the device, which was described in two separate studies[17, 18]. In both cases, the stent graft had been implanted in a 24- and 29-year-old patient with blunt aortic trauma. The manufacturer then adjusted the Instructions for Use (IFU) and recommended use only for aneurysmal or ulcerative lesions.

The new generation of the Relay® platform (Relay®Pro) produced by Terumo Aortic (Inchinnan, UK), although based on the proven Relay®Plus design, offers a lower profile (3-4 F

| Company -Product | Stent - Graft Material | Length (cm) | Diameter (mm) | Sheath Compatibility (F) |
|---|---|---|---|---|
| Artivion, Inc.- E-vita Thoracic 3G Stent Graft System® | Nitinol - polyester | 10 - 23 | 24-44 | 20, 22, 24 (OD) |
| Cook Medical - Zenith Alpha® | Nitinol - Woven polyester | 14.2-21.1 (distal); 9.1-11.2 (distal extension); 10.5-23.3 (proximal straight); 10.8-23.3 (proximal 4 mm tapered | 28-46 (distal); 26-46 (distal extension); 24-46 (proximal straight); 30-46 (proximal 4 mm tapered) | 16, 18, 20 (ID) |
| Gore Ass., Conformable Thoracic Stent Graft, TAG, Active Control System® | Nitinol - ePTFE | 10, 15, 20 | 21, 26, 28, 31, 34, 37, 40, 45; tapered: 26 - 21, 31 - 26 | 18, 20, 22, 24 (ID) |
| Medtronic, Valiant Thoracic Stent Graft Captivia Delivery System® | Nitinol - Woven polyester | 10, 15, 20 | 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46; tapered: 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46 | 22, 24, 25 (OD) |
| Terumo Aortic - RelayPro® Bare Stent | Nitinol - Woven polyester | Straight: 10, 15, 20, 25; tapered: 15, 20, 25; upon request program available | Straight: 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46; tapered (4 mm): 28, 30, 32, 34, 36, 38, 40, 42, 44, 46; Custom made available | 19, 20, 21, 22, 23 (OD) |
| Terumo Aortic - RelayPro® Non Bare Stent | Nitinol - Woven polyester | Straight: 10, 15, 20, 25; tapered: 15, 20, 25; upon request program available | Straight: 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46; tapered (4 mm): 28, 30, 32, 34, 36, 38, 40, 42, 44, 46; Custom made available | 19, 20, 21, 22, 23 (OD) |
| Ankura Stent Graft system® | Nitinol - ePTFE | 4 to 20 | 20,22,24,26,28, 30, 32, 34, 36, 38, 40, 42, 44, 46 | 21,23,24 |

reduction) through optimised weave pattern and radiopaque markers as well as thinner outer sheath. The performance of this design was evaluated in an international prospective multicenter single-arm study (The Regeneration Study). A total of 31 patients with thoracic descending aortic pathologies were enrolled. The technical success rate was 90%; three patients required a proximal extension due to intraoperative type Ia endoleak. The access vessel-related complication rate was 6%, with an average minimum diameter of 9.1 mm. During the follow up period of 12 months, there was 1 (3%) type Ib and 1 (3%) type II endoleak, recorded and 1 (3%) secondary intervention (to correct type Ib endoleak) was conducted.[19]

Another very intriguing endoprosthesis is the Valiant Navion® from Medtronic (Santa Rosa, CA, USA). Azzizadeh et al. also published the first results of this prosthesis in 2019[20]. This report is interesting since it has more specific information on the access vessels. 71% of the patients had highly tortuous access vessels. 38% of the group (87 patients) were also female. In addition to achieving 100% technical success in the short term, access-related complication rate was 1%. Two patients died during the observation period of 30 days: In one case, retrograde type A dissection occurred, in the second case, a prosthesis infection led to rupture.

Similar to the COOK device concerns about the integrity of the stentgraft were raised. In the preliminary analysis of the imaging findings from the Valiant Evo Global Clinical Trial including 83 patients of the 100 patients originally enrolled in the trial, 11 patients with structural failures of the stentgraft were detected. Five patients had a type IIIb endoleak. In four of them the type III endoleak was associated with stent fractures consistent with the location of the graft seam and in one patient the type IIIb endoleak attributed to calcium erosion with no stent fracture or ring enlargement. Of the four patients with stent fracture in line with the graft seam, three underwent a relining procedure that successfully excluded the type IIIb endoleak. One of these three patients died 4 days later of suspected thoracic aortic rupture because the distal thoracic endovascular aortic repair extension had been landed in a previously dissected and fragile section of the aorta. The remaining six patients had had stent ring enlargement. One of the six patients had had persistent aneurysm expansion from the time of implantation onward and had died of unknown causes.[21] These findings led FDA at September 2021 to order a Class I recall of the device.

### *Improved release and adaptation to aortic morphology*

For aneurysms involving the aortic arch, endovascular treatment is more challenging than for those in the abdominal region. If the wall apposition of the endograft to the aorta is insufficient, the bird-beak effect occurs with a consecutively increased risk of a type I endoleak.[5] Stent-grafts of earlier generations were more prone to bird-beaking because the proximal part could not completely conform to the aortic anatomy, with an incidence as high as 40% to 57%. [22] Other associated complications such as collapse of the endoprosthesis[23] or migration during implantation[5] have also been described. Therefore, several attempts have been undertaken by the manufacturers to optimize the apposition of thoracic endografts to the curvature of the aorta. [24]

Moreover, any unintentional covering of the supraaortic ostia by the stentgraft or through manipulation in the aortic arch might result in a cerebral insult. Thus, accurate alignment of the graft in this aortic segment is of particular importance. However, the more demanding hemodynamics in aortic arch compared to other aortic segments make accurate release more challenging. Even with the stentgraft perfectly positioned, deployment of the graft can be complicated secondary to the high volume of blood flow in the thoracic aorta resulting in the "windsock effect," which describes the tendency of the graft to be migrated distally before deployment is complete. This is especially true with deployment mechanisms where the proximal end opens while the distal end remains constrained. Although several maneuvers have been suggested to reduce the cardiac output during the deployment the risk of distal migration is not completed eliminated.[25, 26]

The Gore Conformable TAG Stent Graft with ACTIVE CONTROL System® (CTAG, Gore Medical, Flagstaff, AZ, USA) was specially designed to overcome this problem. In particular, this new version of the graft introduces novel features that help to enhance deployment accuracy and stent graft apposition and to fully take advantage of the stentgraft's conformability. First, the in situ post- deployment curving ability, which allows the proximal part of stents to be curved to fit the aortic arch achieving high apposition. Secondly the two-step release mechanism: In the first step the endograft opens from proximal to distal along its entire length to its intermediate diameter, which is approximately 50% of its nominal diameter. Importantly this staged deployment reduces the wind-socking forces while repositioning is easily possible. In the second step, after ensuring precise positioning, full release of the stentgraft from the middle to the ends can follow.

Aiming to evaluate these theoretical advantages 127 patients who were treated with the CTAG with Active control were enrolled in a prospective, multi-center study between October 2017 and July 2018.[27] The primary endpoint was technical success. Secondary endpoints included clinical success and major adverse events at 30 days and 12 months. In addition, the frequency and the reasons of use of the aforementioned mechanisms were recorded. The primary endpoint was met in 124 patients (97.6%). In 3 patients the ostium of the left common carotid artery was unintentionally partially covered. In all of these patients, the landing zone was significantly shorter than 20 mm. There were 3 aorta-related deaths (due to retrograde aortic dissection, spinal cord ischemia and bowel ischemia) within 30 days and 3 further within 12 months postoperatively resulting in a 30-day clinical success rate of 97.6% and a 12-month clinical success rate of 92.9%.

The angulation feature was applied in 64 cases (50.4%) and the desired effect was achieved in 60 cases (93.8%). Rapid ventricular pacing during deployment was used only in 9 procedures (7.1%). There were no reports of device compression, bird-beak configuration, fracture, or graft occlusion. During follow-up, there were 2 type Ia endoleaks (1.6%); 1 was due

to stent-graft migration (0.8%). The access-related complication rate was 2.4%

Another interesting finding, is that the cTAG endograft with active control has a significantly lower stroke rate (0.8% vs. 11%) compared to the previous model.[28] A possible explanation is that owing to the above mentioned mechanism fewer manipulations of the stentgraft in the aortic arch as well as less frequent need for cardiac output reduction are required and thus the risk of embolism is reduced.

Recently two new stentgrafts have been initiated equipped with unique features intending to broaden the spectrum of patients can be treated endovascularly. The Ankura Stent Graft system® (Lifetech Scientific, Shenzhen, China), which consists of a dual-layer expanded polytetrafluoroethylene membrane, without suture on the main body and a nitinol skeleton with asymmetric wave design and the proximal mini-wave stent. In a single center retrospective study on 30 patients a technical success rate of 97% was reported; in one patient the deployment of the device could not be completed due to the extreme tortuosity of the descending thoracic aorta. During the first 30 days after the procedure two patients (6.8%) died (due to gastrointestinal bleeding and sepsis after pulmonary infection). Two (7%) access site complications were recorded. During a median follow-up of 31.7 (range, 38.4) months, two more patients died of non-TEVAR-related causes and two patients (7%) developed type Ia endoleak.[29]

The Cryolife E-nya ® thoracic stentgraft system, which recently receives CE mark. It is constructed of lower profile graft material and offers both bare spring and covered proximal configurations with tip capture technology, enhancing the control and predictability during deployment. Initial results with this stent-graft are to be published.

### *Limitations*

Currently there are no randomized trials, which directly compare the results of the available thoracic stent-grafts. On the other hand, a direct comparison between the thoracic stentrafts in terms of El type Ia would not be justified as the the risk for type Ia EL is associated with the intended proximal landing zone, with very low rates being more likely to be achieved when treating lesions in the descending thoracic aorta. [20, 30] Aortic curvature in zone 4 is less prominent, bird-beaking is less common in this zone. On the contrary landing in more proximal zones tends to be associated with type Ia endoleak rates of around 4%.[15, 19, 31] Moreover, because the intended landing zone is not defined with millimeter precision, but rather only very generally, as the placement at the "desired location" is provided in the published studies, a comparison among the available stentgrafts is not possible. This limitation underlines the importance of adopting more accurate reporting standards to determine the precise deployment and the wall apposition.[32]

## CONCLUSION AND OUTLOOK

All of the major manufacturers of thoracic stentgrafts have introduced new, significantly improved grafts in the last 5 to 10 years, which have been shown to be able to be used in more patients with more difficult access vessels and become more effective in dealing with challenging anatomy. In the future, further development will focus on the ascending aorta and the proximal aortic arch segments in order to be able to treat ascending and aortic arch pathologies safely and reliably using endovascular treatment.

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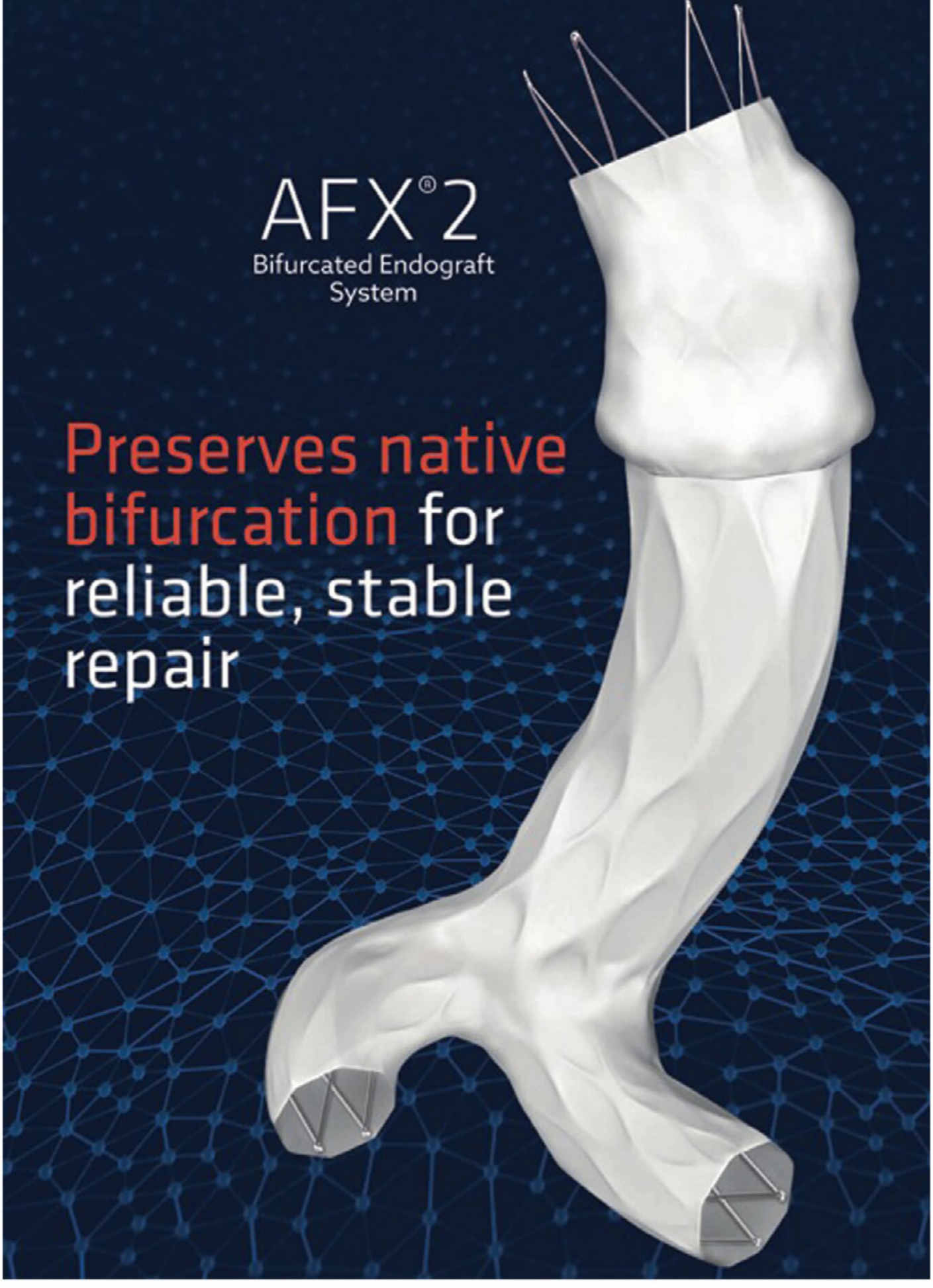


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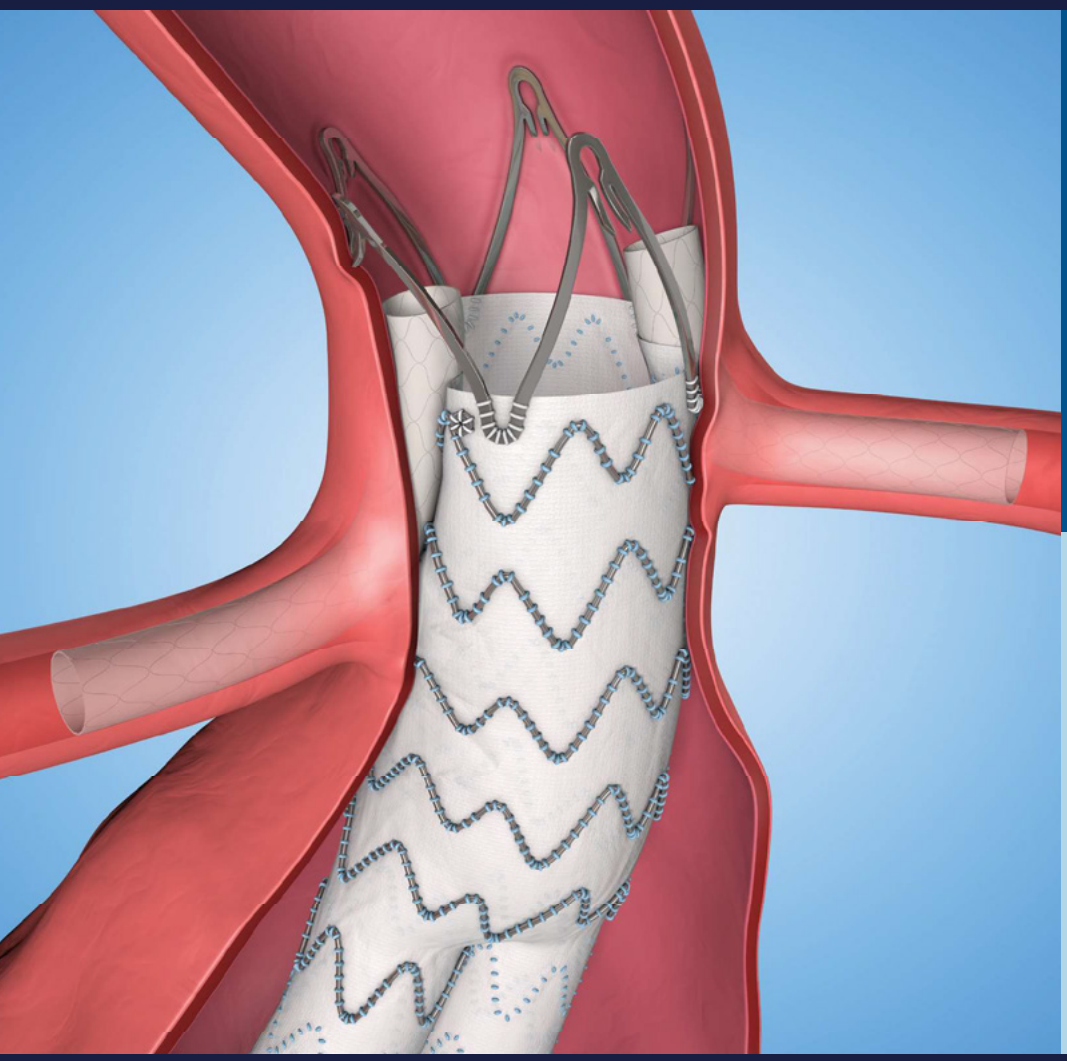

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# Biopsychosocial Assessment and Intervention on Vascular Diseases of Lower Extremities

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**Abstract:**

**Introduction:** Peripheral arterial disease (PAD), which involves one or more vessels of the lower extremities, is common in older adults due to complex genetic and environmental interactions that result in reduced peripheral perfusion. Despite being in many cases asymptomatic, early PAD is associated with reduced survival rate due to its undeniable association with atherosclerosis in other arterial areas, such as the coronary, carotid and cerebral circulations. As population worldwide grows and ages and modern lifestyle leading to obesity and Diabetes Mellitus becomes more popular the number of older adults affected by lower extremity lesions due to PAD increase. While the biological consequences of these diseases have been well-studied, the highly prevalent neuropsychiatric aftermath of vascular diseases has yet to be thoroughly investigated.

**Methods:** The conduction of this review was made possible with the use of the databases PubMed and Google Scholar and articles were included up until November 2022. Only peer-reviewed journal articles were eligible. Key words used include combinations of the terms “PAD”, “Psychiatric diseases”, “vascular diseases”, “diabetes”, “anxiety”, “depression”, “psychological status”, “cognition” and “amputation”.

**Results:** The few studies that have assessed the psychological status of patients with vascular diseases suggest that psychiatric comorbidities are common in this patient group. Further larger scale studies are needed to elucidate the exact mechanism of this phenomenon as well as the optimal diagnostic methods, treatment plan and intervention timeline for these patients.

**Conclusion:** In the present review light is shed on mental illness symptoms in PAD and their importance for disease management and course as well as the quality of life of patients.

## INTRODUCTION

Peripheral arterial disease (PAD) is a serious health care issue for older adults, the diagnosis of which not rarely is a challenging task. The most common cause of PAD is atherosclerosis while there are other less common causes including vasculitis, dysplastic syndromes, degenerative conditions, thrombosis, and thromboembolism [1]. Atherosclerotic lower extremity PAD is characterized by intermittent claudication; this symptom manifests in only 10% of patients. 50% of patients have a variety of leg symptoms other than classic claudication, and 40% have no leg symptoms at all.[2] The latter constellation pertains to higher morbidity and mortality and higher rates of lower limb amputation, due to delayed detection. Therefore, it is of utmost importance to recognize the signs of early PAD and treat these patients accordingly. One of the main diagnostic methods used to assess the hemodynamic status of lower limbs and diagnose PAD is the ankle-brachial index (ABI). According to that, an ABI of 1.0-1.3 is considered normal, 0.9-1 borderline, 0.7-0.9 mild, 0.4-0.7 moderate and below 0.4 is defined as severe PAD.

There are several classification systems for categorizing people with PAD based on disease severity and symptoms. The first classification system created was the Fontaine Classification that grades patients in 4 stages, based on clinical symptoms only. This classification is no longer used in clinical settings. The Rutherford classification system is the one which is widely used today. It does not solemnly describe the clinical presentation of the patient, but also includes laboratory and imaging findings like ABI, pulse volume recordings and Doppler ultrasound findings.[3] .

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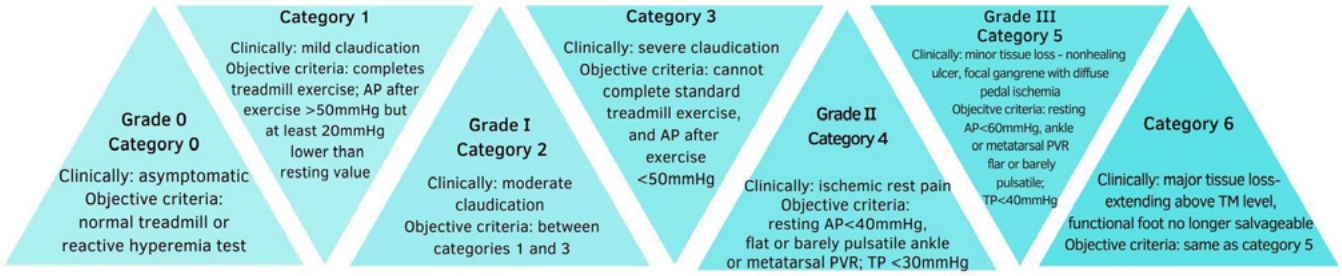
**Figure 1.** Rutherford classification for chronic limb ischemia [3]




*Abbreviations: AP, ankle pressure; PVR, pulse volume recording; TM, transmetatarsal; TP, toe pressure*

The complications of PAD, particularly in patients with DM have given rise to another classification system, i.e. WIFI (Wound, Ischemia, Foot infection) score from SVS (Society for Vascular Surgery). People are classified into five stages according to the risk of lower limb amputation. The following symptoms are considered: wounds, ischemia and foot infection, the severity of which is categorized on a scale between 0 and 3, with 0 representing absence of the respective symptom, 1 indicating mild manifestation of the symptom, 2 moderate-, and 3 severe manifestations. Following grading, the scores assigned to each symptom are pooled and assessed using two tables. The first provides an estimate of the risk of amputation at 1 year and the second an estimate of the necessity and potential benefit of revascularization. Based on the findings, the limb is categorized as having a very low, low, moderate, or high risk of amputation or potential benefit from revascularization at clinical stages 1, 2, 3, or 4, accordingly. Stage 5 is only for irreparably damaged limbs that cannot be salvaged even with revascularization.[4] Finally, it is important to note the current trends in limb amputation, where there is an increase in minor lower extremity amputation rates and a concurrent drop in major lower extremity amputation. These, along with the rise in patients' age, may indicate a shift in the treatment of PAD. [5] However, significant psychological distress can result from even small partial amputations of single digits. Therefore it is important to effectively address complications like neuromas and provide psychological support services in the post-amputation period [6]

## METHODS

This review was conducted using the databases PubMed and Google Scholar and articles were included up until November 2022. The selection of articles was based on a combination of the search terms "PAD", "Psychiatric diseases", "vascular diseases", "diabetes", "anxiety", "depression", "psychological status" and "amputation". The articles that were generated from this search were then filtered to include peer-reviewed studies with sufficient sample sizes and valid study designs that had as their central objective the study of the association between vascular diseases and psychiatric symptoms. Exclusion criteria included duplicate studies, studies with insufficient numbers of patients, articles that were not written in English and studies that diverged from the main purpose of this review. Any disagreements over inclusion criteria were resolved by an independent Reviewer.

## RESULTS

### *Mental illness symptoms*

Previous studies have shed light on the not rare coexistence of vascular diseases and mental illness symptoms. Patients with DM and complications such as ulcers and limb amputations report an overall lower quality of life and more depressive symptoms compared to people with DM but no complications[7]. Part of this problem stems from the inadequate health education and awareness of patients regarding the process of amputation, particularly in lower-middle income countries. As a result, the perceptions of patients that need to undergo amputation are centered around the feeling of fear and anxiety over their altered self-image and social acceptance after amputation. In fact, most of these patients tend to experience the stages of grief during this stage of their disease[8]. Interestingly, a review of the psychological effects of amputation: reported depressive symptoms in 10.4-63% of patients and posttraumatic stress disorder (PTSD) in 3.3%-56.3% of amputees[9]. Most studies report depressive symptoms as the most common mental illness symptoms in amputees, followed by anxiety symptoms [10].

It is important to note that there are reported differences in mental illness symptom frequency based on the cause of the amputation, with depression being particularly common among PVD-caused amputations and anxiety being more common in trauma-related amputations[11]. The strong association between traumatic injury amputation and PTSD has many implications for the mental and physical health of these patients. One notable effect is the high rate of substance misuse which includes problematic alcohol use, prescription medication overuse and illicit drug use among these patients. This link between substance abuse and PTSD further highlights the need for psychological assessment of these patients when deciding on an optimal treatment plan[12].

Mental illness symptoms in people with PAD have short- and long-term effects. Depression, being the most common mental illness in people with PAD, has been shown to be associated with poor functional and surgical outcomes in PAD[13] , even though the directionality and specific mechanisms underlying this relationship have not been thoroughly studied

yet. In addition, depression in older adults is coupled with the presence of cognitive deficits [14], while a solid basis of evidence points to the high risk that late-onset depression confers for the development of dementia [15] through inflammatory, vascular and neurodegenerative processes [16]. Moreover, higher levels of depression and anxiety pertain to worse quality of life[17] and may act synergistically in potentiating the negative impact of PVD on quality of life.

Finally, cognition is also altered by amputation. These changes can be measured by the cognitive load or the mental resources required for task completion and information processing. The cognitive load of an amputee is significantly altered due to the changes in neuronal pathways, the effects of the phantom limb and the emotional changes that take place as a result of the amputation. Therefore, one study concluded that the standard components of the cognitive load should be extended when applying it to amputees to also include emotional and neural fatigue. These two elements include the emotional response to the amputation and the prosthesis, the concentration required to perform everyday tasks, as well as the altered proprioception and neuronal connections and the phantom phenomenon. Measuring the cognitive load has important clinical implications as it could be used to assess the adjustment of the patient to the prosthesis and aid in the best rehabilitation and psychological management post-amputation in order for the patient to achieve a low cognitive load state while performing everyday activities[18].

### *Is there a need for mental health liaison services for people with PAD?*

Detecting and treating mental illness symptoms in patients with PAD (with amputation or even without) is of paramount importance. The high prevalence of mental illness symptoms in PVD and the serious risk of inducing further morbidity, they confer, highlights the importance of mental health liaison services for these patients within the frames of primary, secondary and tertiary prevention strategies. Nevertheless, very few studies have been performed to date that include a sufficient number of patients and enough follow-up time to be able to assess the potential benefits of such services in patients with PAD. One such study, which included one hundred newly amputated soldiers, found that a combination of medications and psychotherapy resulted in high rates of remission, with 62% of amputees with major depression achieving complete recovery[11]. Further, larger studies that include patients in different stages of the disease course are urgently needed in order to establish the best approach and time point of intervention.

## CONCLUSION

Mental illness is a common comorbidity in PAD. Although mounting research evidence points to a significant prevalence of mental illness symptoms in PAD and their impact in disease course and management and the quality of life of patients, the awareness among experts in vascular surgery seems to be relatively low so far. Large-scale multidisciplinary studies are needed in order to develop adequate strategies to manage such symptoms and improve quality of life of patients.

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# Symptomatic thrombus of Infrarenal Abdominal Aorta in a patient with Antiphospholipid Syndrome. A case report and review of the literature

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**Abstract:**

A previously healthy 58-year-old man presented to the emergency department with nine days history of right lower extremity rest pain (class Fontaine III, Rutherford IV). The ankle-brachial index in the right and left leg was 0.67 and 0.75, respectively. Computed tomography angiography (CTA) revealed the presence of thrombus in the infrarenal aorta, starting one centimeter below the renal arteries with occlusion of the right common iliac artery. A rheumatological workup showed antiphospholipid antibodies, and the anticardiolipin immunoglobulin G was positive. The patient underwent covered endovascular reconstruction of aortic bifurcation (CERAB). Twelve months after the procedure, he demonstrated no signs of limb ischemia, and the CTA showed excellent stent patency as well as sufficient blood flow in the infrarenal aorta and both lower limbs.

## INTRODUCTION

Antiphospholipid syndrome (APS) represents an autoimmune disorder characterized by recurrent thromboses in arterial and/or venous circulation.[1-2] Although arterial thrombosis preferentially occurs in small and medium size vessels, aortic thrombosis has been also reported.[3] Unfortunately, little is known about the optimal treatment strategy for this rare condition. We report a case of symptomatic aortic thrombus due to APS, which was successfully treated by the covered endovascular reconstruction of aortic bifurcation (CERAB) technique.

## CASE PRESENTATION

A previously healthy 58-year-old man presented to the emergency department with nine days history of right lower extremity rest pain (class Fontaine III, Rutherford IV). His medical history was unremarkable, and he also denied any tobacco use, cardiac arrhythmias, coronary artery disease or prior embolic events. The ankle-brachial index (ABI) in the right and left leg was 0.67 and 0.75, respectively.

Computed tomography angiography (CTA) revealed a heavy burden of thrombus in the infrarenal aorta starting one centimeter below the renal arteries with occlusion of the right common iliac artery (Figure 1, red arrow). Due to the unremarkable medical history, a rheumatological workup was performed. Antiphospholipid antibodies detected by enzyme-linked immunosorbent assay were 640 U/mL (positive, n.v. 0-0.9 GPL U/ml), and the anticardiolipin immunoglobulin G detected by lupus anticoagulant assays was >160 mg/mL (positive, n.v: 0-8 GPL U/ml). Additionally, an extensive hypercoagulopathy investigation (Protein C, S, Antithrombin, Factor V Leiden, Homocysteine, fibrinogen etc) was conducted. The levels of fibrinogen were slightly elevated (>400mg/dl). The patient had history of deep vein thrombosis, which had been diagnosed by Doppler ultrasound, and ischemic heart disease. He was diagnosed with symptomatic thrombus in the infrarenal aorta and occlusion in the right common iliac artery, co-occurring with antiphospholipid syndrome. The patient immediately received anticoagulant (rivaroxaban 2.5mg, twice daily) and antiplatelet (aspirin 100mg o.d) regimen. However, these conservative treatments were insufficient to resolve the patient's symptoms. A multidisciplinary team of internists, haematologists, rheumatologists, anesthesiologists and vascular surgeons recommended a surgical approach (thrombectomy or bypass grafting) or an endovascular approach (CERAB technique) to manage his condition. The patient, however, was unwilling to undergo surgical treatment, so he was scheduled for endovascular treatment (EVT) of the thrombotic lesion of the infrarenal aorta and the right common iliac artery.

The patient was placed in a supine position. The procedure was performed percutaneously using a bilateral transfemoral approach. The patient received 100 units/kg of heparin intraoperatively. A short 6Fr sheath was placed in both femoral arteries. In the right leg, the lesion was crossed intra-luminally using a 0.035 glidewire. A 12 Fr sheath was inserted via the left femoral artery, while in the right femoral artery, the 6 Fr

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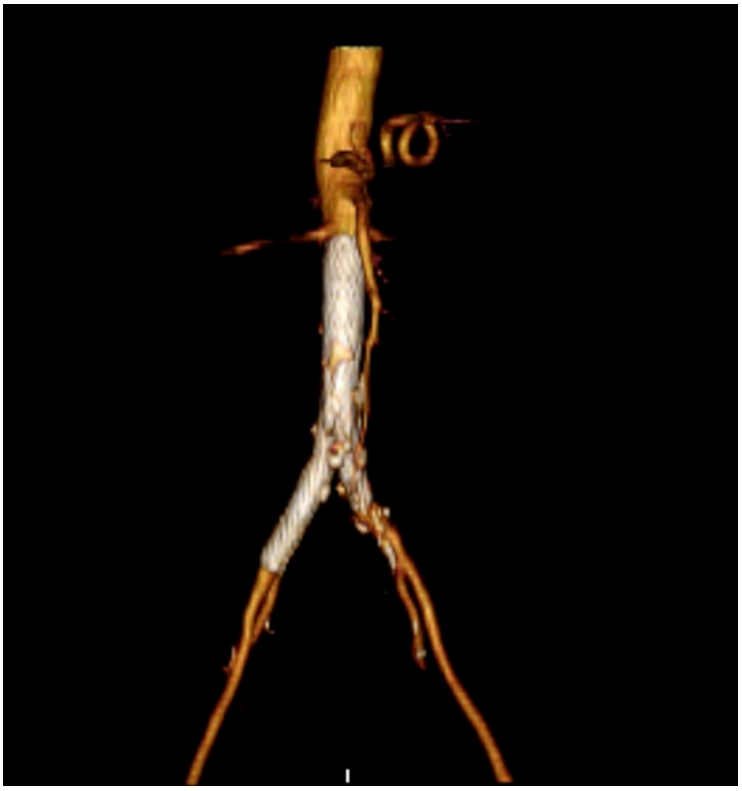

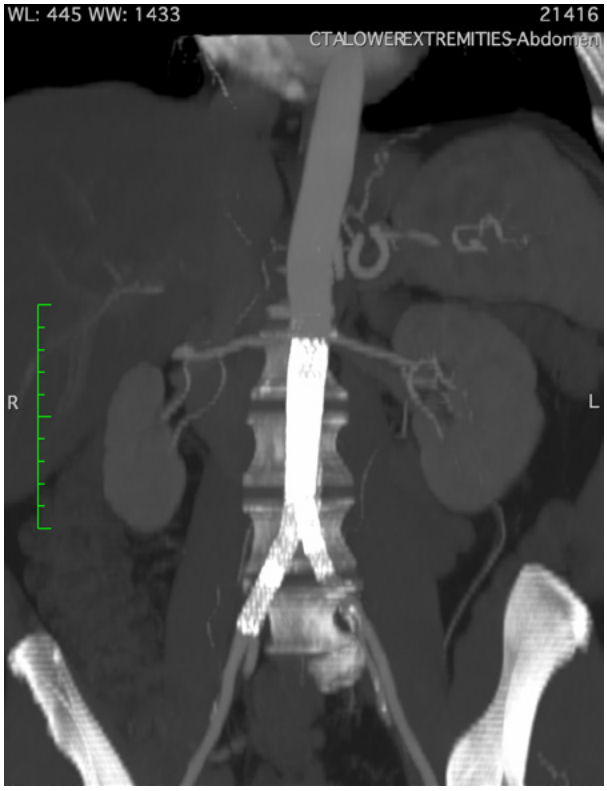


sheath was replaced with a 7 Fr sheath. Angiography through the 12 Fr sheath detected an irregular surface of the infrarenal aorta and occlusion of the right common iliac artery. A 20 mm in diameter and 48 mm in length covered balloon-expandable stent (BeGraft, Bentley, Hechingen, Germany) was deployed below the renal arteries ending approximately 20 mm above the bifurcation. The aortic stent was then molded with short semi-compliant balloons to ensure optimal aortic wall apposition.

Thereafter the iliac stents (10 x 57 mm, BeGraft, Bentley, Hechingen, Germany) were positioned in a kissing conformation, overlapping with the aortic stent for 15mm. Then ballooning with two compliant balloons was performed to adapt the parallel stents to the aortic one. Completion angiography was performed at the end of the procedure to verify the correct deployment of the stents, the apposition of the kissing stents to the aortic one, the patency of renal arteries and CERAB reconstruction.

After the removal of catheters and sheaths, a closure device (Perclose ProGlide Abbott Scientific, Abbott Park, IL) was used to close the arteriotomies in both common femoral arteries.

Postoperatively, the patient was treated with rivaroxaban (2.5mg, twice daily) and acetylsalicylic acid. Twelve months after the procedure, he demonstrated no signs of limb ischemia, with a normal ABI, whilst the CTA showed excellent stent patency as well as sufficient blood flow in the infrarenal aorta and the bilateral lower limbs. (Figure 2).

## DISCUSSION

Antiphospholipid syndrome (APS) is a disorder of coagulation that is usually manifested by arterial or venous thrombosis or pregnancy-related complications such as miscarriage, stillbirth, preterm delivery, or severe preeclampsia. The syndrome occurs due to the autoimmune production of antibodies against the cell membrane phospholipid.[1-2] When the aorta is affected, this scenario often leads to thrombosis. The management of this rare complication varies in the literature, from conservative treatment [4-5] to open [6-7] or endovascular approaches.[8] We experienced an extremely rare case of aortic thrombosis due to primary APS, which was successfully treated by the CERAB technique. According to the Sapporo criteria,[8] in patients with triple factors positivity and first unprovoked venous thrombosis, vitamin K antagonists are recommended. In our case, we preferred lifelong rivaroxaban because the patient had two positive factors. To the best of our knowledge, 11 cases have been reported in the literature (table 1), and only one was treated by endovascular means.[9] Four cases have been conservatively treated, and their late outcomes are unknown. However, these conservative treatments were insufficient to resolve the patient's symptoms, according to scarce date in the literature.[7]

The CERAB technique was introduced in 2013 for treating patients suffering from aortoiliac occlusive disease. The main goal was to reduce some negative impacts of the kissing stents technique, such as the discrepancy between the stented lumen and the aortic lumen ("radial mismatch"), that may affect their patency rate.[9] Additionally, this procedure moves

**Table 1.** Case reports of aortic thrombosis due to antiphospholipid syndrome

| Author | Year | Journal | Age/Sex | Symptoms | Location of Thrombus | Treatment Strategy |
|---|---|---|---|---|---|---|
| McGee et al | 1992 | Arch.Surgery | 26/F | Claudication | Infrarenal Aorta | Aortobifemoral grafting +Anticoagulation and Antiplatelet therapy |
| Poux et al | 1996 | Am J. Kidney Dis. | 35/M | Abdominal pain | Pararenal aorta | Anticoagulation therapy |
| Dupont et al | 2001 | Nephrol Dial Transplant | 46/F | Acute Ischemia | Suprarenal aorta | Aortic endarterectomy |
| DiCenta et al | 2002 | Annals of Vascular Surgery | 46/F | Subacute Ischemia of the lower limbs | Infrarenal aorta | Aortobifemoral grafting +Anticoagulation therapy |
| Alfayate et al | 2002 | Vascular and Endovascular Surgery | 38/F | Claudication | Pararenal aorta | Aortobifemoral grafting +Anticoagulation therapy |
| Letang et al | 2005 | Lupus | 46/F | Lumbar pain | Pararenal aorta | Anticoagulation therapy |
| Ryu et al | 2009 | J Thorac Cardiovasc Surgery | 57/M | Dyspnea | Ascending Aorta | Surgical removal of thrombus |
| Shroff et al | 2011 | The Journal of Reumatology | 39/F | Abdominal pain | Pararenal aorta | Anticoagulation therapy |
| Toffon et al | 2013 | Case Report Surgery | 68/F | Paresthesia and Pseudoclaudication in the lower limbs | Infrarenal Aorta | Aortobifemoral grafting +Anticoagulation therapy |
| Hsieh et al | 2016 | J Microbiol Immunol Infection | 52/M | Claudication | Infrarenal Aorta | Anticoagulation therapy |
| Kadoya et al | 2019 | Vascular and Endovascular Surgery | 60/M | Claudication | Infrarenal Aorta | Endovascular treatement |

the aortic bifurcation proximally, which mimics the mechanics of a bifurcated graft used in open surgery.[10]

Results from the largest CERAB series have reported a primary patency rate of about 80% at one year and no peri-procedural mortality.[10] Additionally, in cases of isolated infrarenal aortic stenosis, endovascular stenting was reported to have good long-term patency and reduced perioperative mortality rates compared to surgical options.[9] As a result, the CERAB technique seems to be a feasible treatment option for APS-associated aortic thrombosis. However, another important aspect to underline is that treating surgeons must be aware that thrombus might dislodge into the renal arteries during treatment of juxta-renal aorto-iliac occlusions or in patients with a distance shorter than 2 cm between the ostium of the renal arteries and the beginning of the aortic lesion. In this perspective, some vascular surgeons have advocated the use of protective measures such as an extra dose of heparin and the position of two guidewires in both renal arteries through the brachial route to be ready to perform prompt angioplasty and stenting if needed.[10]

## CONCLUSION

We reported a rare case of symptomatic thrombus of the infrarenal abdominal aorta due to APS. Although the relationship between APS and an isolated infrarenal aortoiliac lesion is still unclear, we speculate that APS might be one of the underlying causes of such conditions. Screening tests should be conducted in this group of patients, especially if their aorta contains a large amount of thrombus and low atherosclerotic burden.

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# Acute upper limb ischemia in a patient recently vaccinated for Covid-19

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**Abstract:**

Vascular complications of Covid-19 disease represent significant causes of morbidity and mortality, being both life- and limb-threatening. Although extremely rarely, the various vaccines against Covid-19 infection have also been associated with thromboembolic complications. We describe a patient who presented with right upper limb acute ischemia three days after her vaccination and who had a positive PCR test. Thrombosis of the axillary artery was revealed by computed tomography angiography and the patient was submitted to thrombectomy with complete restoration of upper limb perfusion. We also review the recommendations of scientific societies on the management of acute limb ischemia in the particular etiological context of Covid-19.

**Keywords**: Acute, Ischemia, Limb, Covid-19, Vaccine.

## INTRODUCTION

Vascular complications of Covid-19 disease represent significant causes of morbidity and mortality, being both life- and limb-threatening, in cases of acute limb ischemia (ALI).[1] Although much less frequently, vascular complications have also been described after Covid-19 vaccination, causing the population to be skeptical of vaccines.

Herein we describe a patient who presented with right upper limb acute ischemia three days after her vaccination and who, at the same time, had a positive PCR test at her admission. The cause of ischemia in this patient was unclear: was it the covid-19 infection or the Covid-19 vaccine? The second objective of this study was to analyse the recommendations of scientific societies on the management of ALI in the particular etiological context of Covid-19.

## OBSERVATION

A 55-year-old female presented to our hospital with acute upper limb ischemia. She was hypertensive under treatment, with no history of heart disease. She had been vaccinated with the Janssen (Johnson & Johnson) COVID-19 vaccine and had suffered from headaches, within the following 24 hours. Three days after vaccination, she experienced disabling pain in her right upper limb, with partial loss of motor function. On physical examination, the limb was cold and with no palpable pulse at the right axillary, brachial, radial and ulnar artery. There was paraesthesia of the right hand. Lab tests revealed a CRP of 27.45 mg/L, a neutrophil count of 6,600/µl and lymphocyte count of 2,000/µl. There was monocytosis of 1,400/µl and an Erythrocyte Sedimentation Rate (ESR) of 95. The patient underwent a Computed Tomography Angiography (CTA) revealing thrombosis of the right axillary artery extending to the brachial artery (Figure 1). The patient was started on unfractionated heparin and was taken to the operating room where an incision crossing the elbow crease was performed and both the radial and the ulnar artery were exposed, since the bifurcation of the brachial artery was very high at the level of the axilla. Thrombectomy of the axillary, brachial, radial and ulnar arteries with the use of a Fogarty catheter followed (Figure 1). At the end of the procedure, there was a very good reperfusion of the radial and ulnar arteries (Figure 2), verifying the patency of the inflow arteries. Palpable pulse of both the ulnar and the radial artery at the level of the wrist was restored. The patient was started on rivaroxaban 20 mg od and had an uneventful postoperative course. At the last follow-up visit, six months later, the patient remained asymptomatic and the anticoagulants were discontinued. Cardiac tests, including Holter ECG and Doppler echocardiography revealed no embologenic heart disease.

## DISCUSSION

Arterial thromboembolism is a rare complication of Covid-19 disease. In a large retrospective, multicenter study performed in California from March 2020 to March 2021, the incidence of arterial thromboembolism was found to be 0.07%.[2] Upper limb arterial thromboembolism is even less common, and the few publications in the literature are limited to reports of a single case.[1] Arterial thromboembolism after vaccination against Covid-19 is extremely rare.[3]

ALI can be a complication of pre-existing peripheral arterial disease with thrombus formation on a plaque and subsequent distal embolism. It can also occur in a healthy artery as

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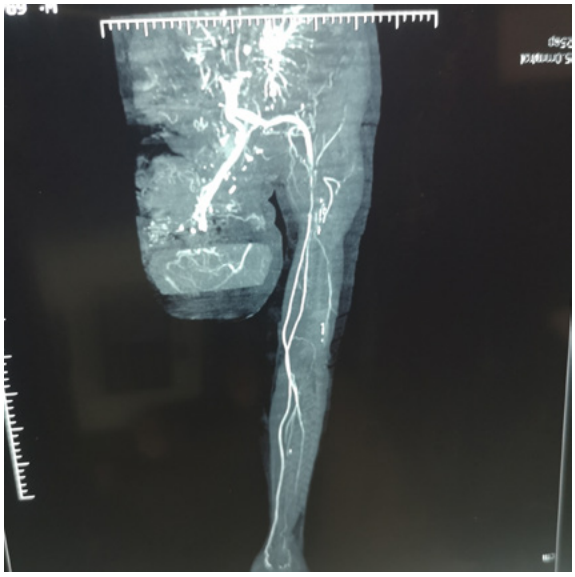

**Figure 1.** CT Angiography of the right upper limb showing thrombosis of the axillary artery. Radial and ulnar ateries arise very high.

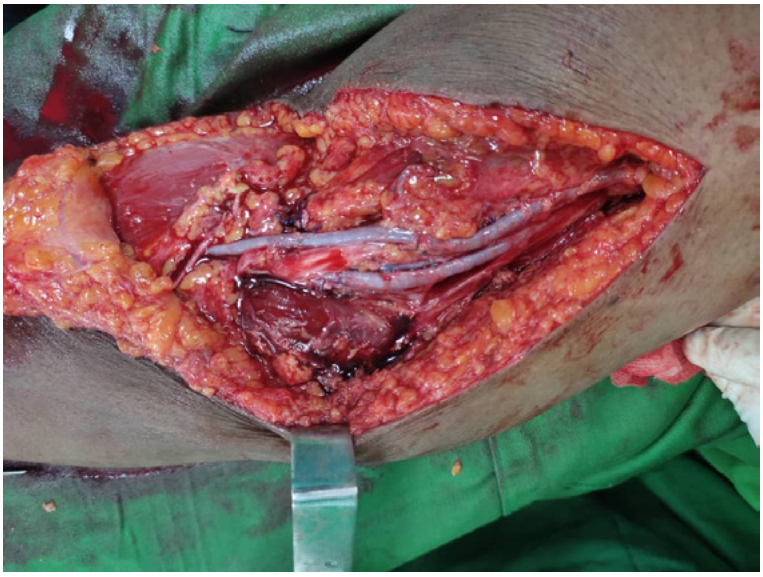

**Figure 2.** Intraoperative image after thrombectomy with restoration of normal blood flow in both the radial and ulnar ateries.

in our patient. Differential diagnosis included cardiogenic embolism or in situ thrombosis,[4,5] which was probably the case in our patient, as evidenced by the normal cardiac assessment, including a normal echocardiography, and the results of the CT angiography showing the absence of a collateral network (Figure 1).

The cause of the ischemia in our patient may be the Covid-19 infection. Indeed, in Covid-19 disease, haematological changes occur leading to hypercoagulability. Biological analyses of the blood of patients with Covid-19 show a low level of antithrombin and high levels of D-dimers, fibrinogen and fibrin/fibrinogen degradation products with a statistically significant difference from controls.[6] Oxidative stress plays a very important role, with a combination of neutrophilia and lymphopenia, elevation of CRP and reactive oxygen species (ROS) causing endothelial cell dysfunction and platelet augmentation and aggregation, resulting in clot formation.[7]

Thrombus and the resulting ischemia can also be a rare complication of the vaccine. This could be the case in our patient. Most, if not all, Covid-19 vaccines are associated with thromboembolic complications as side effects, including the Jansen vaccine. Its involvement in the occurrence of rare thromboembolic events has been established by numerous publications and accepted by the European Medicines Agency.[8,9] The accepted mechanism in the genesis of these thromboses is vaccine-induced immune thrombotic thrombocytopenia (VITT), involving anti-platelet factor IgG mimicking the mechanism of Heparin-Induced Thrombocytopenia (HIT). Apart from immunological assays, several criteria make it possible to make the diagnosis of VITT, including vaccination against Covid-19, recent thrombocytopenia, no previous exposure to unfractionated heparins and no other explanation for thrombocytopenia.[9]

Another, theoretical, explanation for the thromboembolism in our patient could be the joint action on the coagulation system of both the Covid-19 progressive infection and the recent vaccination. It has to be noted that this theory is hypothetical since there is no evidence in the literature of this mechanism neither do we have sufficient proof to support it. Yet, this is suspected due to the coincidence of the Covid-19 disease and the vaccination.

The management of acute limb ischemia is fairly well established by the various scientific societies for vascular surgery. According to the recommendations of the ESVS,[10] as soon as the diagnosis is made and awaiting operative management, if indicated, heparin is recommended by consensus. Surgical management is performed in a hydrid room with angiographic evaluation of the result at the end of the procedure.[10] Due to the lack of specific guidelines for the treatment of acute limb ischemia caused by Covid-19, these guidelines should be extended to the Covid-19 patients as well. In our case, success of the thrombectomy was verified by the resumption of adequate arterial inflow and also by the restoration of distal pulses. Postoperatively, the color and the temperature of the limb were restored to normal, the neurological signs disappeared and the arterial Doppler ultrasound signals were normal.

## CONCLUSION

Acute ischemia of the upper limb is a very rare complication of covid-19 infection and an even rarer side effect of covid-19 vaccination. When it occurs in a person who is recently vaccinated against covid-19 disease and who was already infected by coronavirus disease without knowing, it is questionable whether the cause of the arterial thromboembolism is the Covid-19 disease, the vaccine or the combination of both. Further studies are needed to clarify this issue.

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# Aortic and coeliac axis compression by the median arcuate ligament

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**Abstract:**

Median arcuate ligament syndrome is a clinical condition in which the cause of gastrointestinal symptoms is thought to be compression of the coeliac trunk by the median arcuate ligament. We report a case of a 25-year-old woman with compression of the supra-coeliac aorta and the coeliac trunk by the median arcuate ligament. The patient was successfully treated with open surgical decompression. Median arcuate ligament syndrome is poorly understood, and surgical management is highly variable in its outcome.

**Keywords:** median arcuate syndrome, Dunbar syndrome, coeliac artery compression, unintentional weight loss.

## INTRODUCTION

Median arcuate ligament syndrome (MALS) is a rare cause of chronic mesenteric ischaemia. MALS occurs when the median arcuate ligament is abnormally low and thus causes indentation on the coeliac artery. It occurs in 10-24% of the general population.[1] It typically affects young adults and rarely compresses the aorta, the superior mesenteric artery and other local structures.[2] The symptoms are variable, and include post-prandial abdominal pain, nausea, vomiting, diarrhoea, and weight loss.[3] Herein, we report a rare variation of MALS, where the compression affected not only the coeliac axis but also the supra-coeliac aorta.

## CASE REPORT

A 25-year-old female presented to our clinic with a four-year history of post-prandial abdominal pain, nausea, vomiting, diarrhoea, and a 22-kg weight loss. Her symptoms were debilitating and had a significant impact on her mental health and quality of life. Contrast-enhanced computed tomography (CT) of the abdomen and pelvis showed significant compression on the supra-coeliac aorta and coeliac artery by the median arcuate ligament (Fig 1).

The Duplex ultrasound scan showed that the Peak systolic velocity in the coeliac axis in the supine position was 263cm/s. A reduction in peak systolic velocity (PSV) was noted in all readings when obtained in the standing position confirming the diagnosis of median arcuate ligament syndrome: supine PSV 263cm/s, upright PSV 192cm/s, inspiratory PSV 292 cm/s, expiratory PSV 332 cm/s (Fig. 2).

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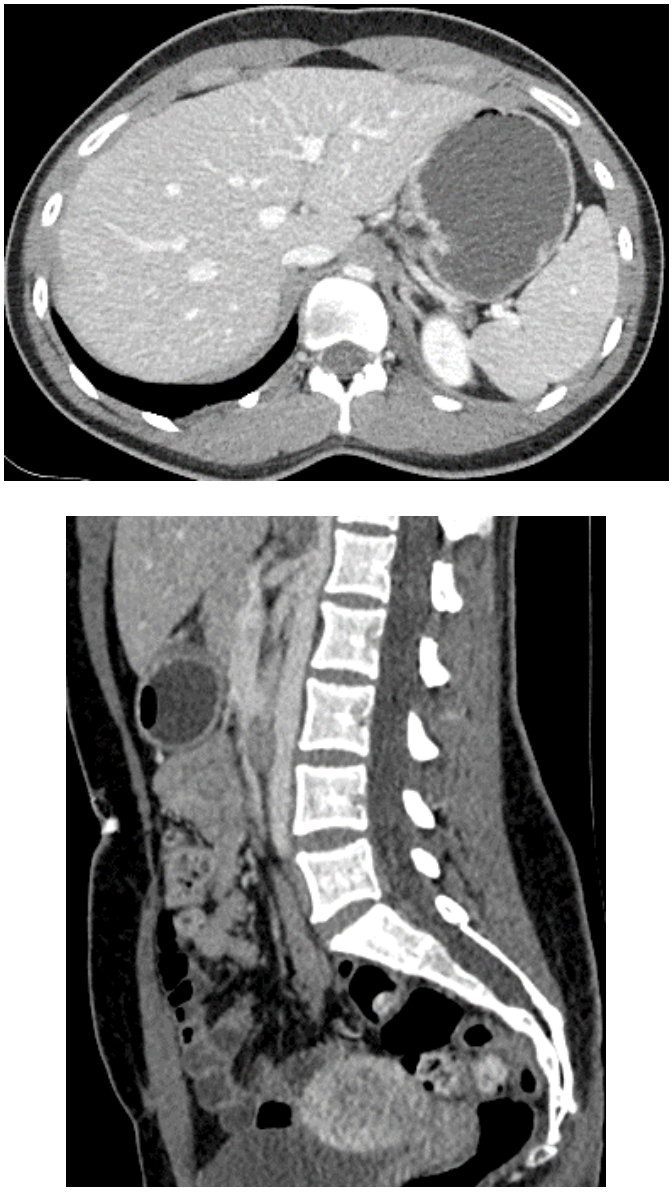

**Figure 1.** Axial (A) and sagittal view (B) of contrast enhanced CT showing compression of the supra-coeliac aorta from a hypertrophic median arcuate ligament.

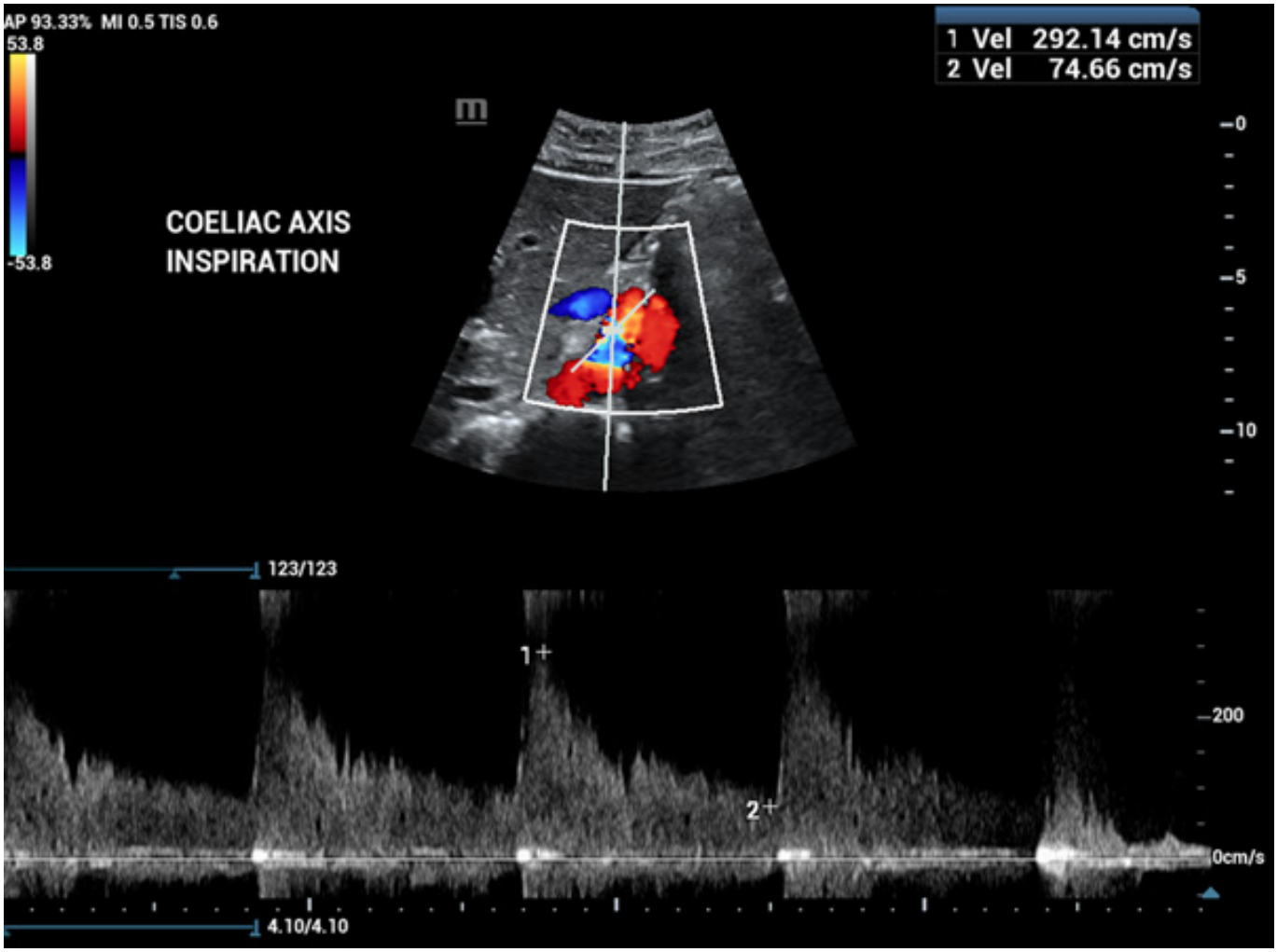


**Figure 2.** Inspiratory Duplex ultrasound image showing turbulence of the flow at the ostium of the coeliac axis and a peak systolic velocity of 292 cm/s. B: Expiratory Duplex ultrasound image showing turbulence of the flow at the ostium of the coeliac axis and a peak systolic velocity of 332 cm/s.

An open surgical division of the median arcuate ligament and surrounding fibrous bands was performed through a supra-umbilical midline abdominal incision. The superior part of abdominal aorta was dissected and freed from the ligament for around 7cm above the coeliac axis, which was skeletonised up to its bifurcation and released from the ligament and all surrounding fibrotic bands.

The patient had an uneventful post operative recovery and was discharged home on day 7.

The CT angiogram on day 2 post operatively revealed resolution of the compression of the coeliac axis and improvement of the flattened appearance of the supra-coeliac aorta.

At her five-week follow-up appointment, she reported reasonable improvement of her symptoms, and had gained 5 kgs since the surgery.

## DISCUSSION

MALS was first reported in the mid-1960s 4. The presence of compression was noted in around 34% of autopsies conducted amongst the general population with no reported symptoms, which queries the existence of the condition 5. It occurs more frequently in women (at a ratio of 4:1) 4, 6.

The characteristic anatomy in MALS is compression of the coeliac artery by the median arcuate ligament, which fluctuates during inspiration and expiration. The syndrome can also be caused by external compression of other arteries, such as the superior mesenteric artery and the aorta 7. Reilley et al. described four cases of compression of both the superior mesenteric artery and the coeliac axis 8. Coulier reported a case of a male patient who experienced chronic epigastric pain with aortic compression caused by the median arcuate ligament and no compression of the coeliac trunk or the superior mesenteric artery 9. In our case, there was compression of both the aorta and the coeliac artery.

Individuals afflicted with this condition present with gastrointestinal symptoms such as nausea, vomiting, postprandial/exercise induced abdominal pain, and weight loss. The symptoms are indicative of chronic mesenteric ischaemia, and the clinical presentation is variable in its severity 6.

In addition to a detailed clinical history, the diagnosis of

the condition is established through imaging investigations. There is no gold standard investigation or widely accepted diagnostic criteria for MALS, but the most common imaging investigations include CT angiography and dynamic Duplex ultrasonography. A typical finding on CT is the "hooked" appearance of the coeliac artery. Duplex ultrasonography usually shows elevated velocities in the coeliac axis. Invasive dynamic angiography in inspiration and expiration has been described as a diagnostic tool 10.

Treatment of the condition is achieved through surgical decompression of the artery through open, laparoscopic, or robotic release of the median arcuate ligament. The traditional treatment is open surgical decompression, although in recent years, laparoscopic approaches are being increasingly used.

Symptomatic relief post-surgery is variable and difficult to predict. Reilly et al. reported the largest series of the longest follow up of open surgical MALS in a total of 51 patients 8. At 10-year follow-up, 53% of patients who had decompression alone had resolution of symptoms compared to 76% of patients who had decompression and revascularization.

## CONCLUSION

MALS is a rare clinical condition, and its diagnosis is based on exclusion of other more common pathologies. We believe that the threshold for surgical intervention should be low in such cases as symptom relief is not always achieved, and collaborative experiences from multiple centres may help understand potential links between multi-level disease and severity of symptoms and response to treatment.

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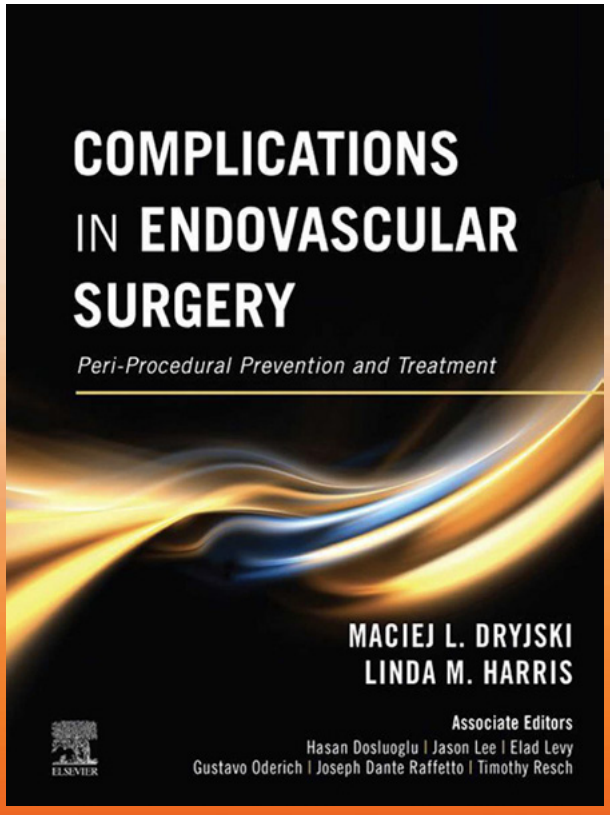


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