



REVISTA PORTUGUESA DE

# CIRURGIA CARDIO-TORÁCICA E VASCULAR

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## EDITORIALS

- Cardiac surgeons against the COVID-19 pandemic.
- Global impact of the COVID 19 Pandemic in Portuguese Thoracic Surgery.
- The impact of COVID-19 pandemic in the management of a Vascular Surgery Department.

## COMMENTS

- COVID-19 - Crisis Management in Lung Cancer Surgery.
- Thrombocytopenia after Perceval prosthesis implantation – still a mystery.
- Rare and Unpredictable inflammatory myofibroblastic tumor.
- New directions for the management of dual antiplatelet therapy in patients with coronary stents undergoing non-cardiac surgery

## ORIGINAL ARTICLES

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- Differences in anthropometric measures between critical limb ischemia and intermittent claudication.



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# MENSAGEM DO PRESIDENTE



**Adelino F. Leite-Moreira**

Professor Catedrático da Faculdade de Medicina da Universidade do Porto  
Chefe de Serviço de Cirurgia Cardiorádica,  
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## A SPCCTV em tempos de pandemia

É já um lugar comum dizer-se que, em virtude da pandemia que nos assolou, fomos obrigados a reaprender a nossa forma de viver e que temos de nos adaptar a uma nova “normalidade”. De facto, depois de termos assistido ao encerramento, sem precedentes, de múltiplos setores de atividade e ao cancelamento ou adiamento, até há uns meses impensável, de eventos nas mais variados áreas, começamos agora a retomar algumas delas e a reinventar outras. A necessidade de adaptação nos mais variados setores ao teletrabalho e ao ensino à distância permitiu evidenciar algumas mais-valias destas modalidades, a maioria das quais com o uso de tecnologia previamente existente, mas até há pouco ainda relativamente subexplorada. As circunstâncias que temos vivido, ao forçar-nos a experimentar e aclimatar a novas alternativas, levaram-nos a perceber que são demasiado valiosas para as deixar para trás e voltar exatamente ao que éramos. É nossa convicção que muitas destas modalidades seguramente sobreviverão e continuarão a proliferar na fase pós-pandémica, passando a ser encaradas de outra forma e marcando indelevelmente o nosso modo de vida.

As sociedades científicas e as atividades a elas ligadas não foram exceção, tendo todos nós assistido ao cancelamento ou adiamento de inúmeras reuniões e congressos. Sociedades, houve, contudo, que rapidamente se aperceberam que era necessário outro tipo de resposta e procederam à transformação com sucesso das suas reuniões em eventos totalmente on-line. Além desta transformação de eventos previamente existentes, assistimos à multiplicação e proliferação de ofertas formativas on-line. A Sociedade Portuguesa de Cirurgia Cardio-Torácica e Vascular (SPCCTV) também tem procurado adaptar-se à nova realidade, tendo avançado já com várias iniciativas on-line no âmbito da Academia SPCCTV, as quais, para nossa satisfação, têm atraído a atenção de profissionais e sociedades científicas nacionais e estrangeiras. Estas atividades serão fundamentais para alavancar a SPCCTV e os seus patrocínios nesta fase de crise, mas sobreviverão

seguramente à mesma e ficarão como um importante legado para o futuro.

Finalmente, uma palavra sobre o nosso congresso anual. Após aprofundada reflexão baseada em estudo e avaliação detalhados a Direção da SPCCTV decidiu avançar com a realização do seu congresso anual, que irá ter lugar na Figueira da Foz, de 27 a 29 de Novembro de 2020. Será um evento híbrido, unindo a participação presencial e online, seguindo as recomendações da Direção Geral de Saúde, de forma a realizar com segurança o Congresso da SPCCTV-4DVisions 2020.

Como previamente anunciado, este ano a SPCCTV terá como principal parceiro a Sociedade Portuguesa de Pneumologia, mas irá também contar com a colaboração do Grupo de Estudos de Doenças Valvulares da Sociedade Portuguesa de Cardiologia. Apresentando um programa diversificado, seguindo um modelo inovador, que privilegia a participação dinâmica, a discussão viva e a troca de experiências estamos convictos que iremos ter mais um evento de sucesso que tem todos os ingredientes para ser do agrado de todos.

Acreditamos que temos argumentos muito fortes para que o nível científico venha a corresponder às expectativas que nele depositamos. Mas, o sucesso desta iniciativa não se faz sem a ajuda de todos e muito especialmente sem o apoio e entusiasmo dos nossos sócios. Apelamos por isso à vossa participação para tornar este evento no sucesso que todos ambicionamos de modo a manter a vitalidade que tem marcado a SPCCTV.

Adelino Leite-Moreira | Presidente da SPCCTV





# EDITORIAL



**Miguel Guerra**

Cardiothoracic Surgeon, CHVN Gaia/Espinho  
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## Cardiac Surgeons against the COVID-19 Pandemic

*Cardiac surgeons should be actively engaged in the emergency response teams of their respective institutions during the pandemic response. We need to employ all of our skills—clinical, academic, administrative, and otherwise—to ensure optimal care for our patients while offering a safe environment for our health care teams.*

1. *The first priority of the cardiac surgery team is to be involved in regular discussions with their administrations, cardiology colleagues, and critical care colleagues to evaluate resource availability to ensure the appropriate utilization of potentially scarce resources including ward and intensive care unit beds, ventilators, ECMO circuits, operating rooms, equipment, drapes, PPE, medications, blood products, and health care personnel.*
2. *Cardiac surgeons should triage patients that are in hospital or on the elective wait list in a manner that is based not only on the patient's clinical status and risk-factor profile but also on the extent to which services are available or have been reduced in response to the COVID-19 pandemic.*
3. *Undoubtedly, there is concern that the proposed prioritization strategy will result in a surgical delay and may put patients at significantly increased risk. As such, it is critically important that cardiac surgeons ensure the presence of a robust wait-times database at their institutions that captures rates of adverse events in these patients while on the wait list so that decisions around the reallocation of resources may be made in a timely fashion.*
4. *When it is feasible, cardiac surgical programs should make every effort to maintain areas within their institutions for cardiac surgery patients that are*

*completely separate from patients with COVID-19, given the vulnerability of the average cardiac surgery patient (increased biological age and cardiovascular risk factors) were they to become infected with COVID-19.*

5. *Non-emergent cardiac surgical interventions for patients suffering from acute viral infections (such as—but not limited to—COVID-19) are largely discouraged, based on the belief that this could significantly elevate the risk of postoperative acute respiratory distress syndrome and mortality in that setting.*
6. *Cardiac surgeons and their health care teams must be aware of procedures and techniques that may potentially generate increased quantities of aerosol matter including—but not limited to—double-lumen vs single-lumen endotracheal intubation, re-operative minimally invasive surgery requiring lung dissection, and redo sternotomy vs traditional sternotomy.*
7. *Cardiac surgeons should take the necessary steps (donning and doffing PPE), as mandated by their institution and their local health authorities, to ensure their own health and well-being as well as the health and well-being of the members of the health care teams that they work with.*

Miguel Guerra | Editor-in-Chief



# EDITORIAL

**Cristina Rodrigues<sup>1</sup>, João Maciel<sup>2</sup>**

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## Global impact of the COVID 19 Pandemic in Portuguese Thoracic Surgery Centres

Mankind is now faced with an unimaginable worldwide health crisis that threatened throwing us back to the dark ages. A new virus, in a naive population, with a mortality not seen since the Spanish flue!

In Portugal, health and civil authorities tuned in to determine early confinement measures, with massive information campaigns for the public that turned Portugal into a case study of successful pandemic crisis containment.

From the moment the virus was detected in Portuguese territory, the focus of National Health authorities was preparing the Portuguese Health Service to face an epidemic spread, similar to Italy and Spain, acquiring stocks of ventilators and individual protection equipments, and reassigning and preparing health staff for covid patient care.

For a moment, all else seemed to stop!! Outpatient clinics of primary care and hospitals were closed as were Radiology clinics in public and private institutions. Operating theatres reduced activity to minimal emergent cases in preparation for the worst case scenario.

Fortunately, so far, the worst did not come! Health authorities worked alongside local hospital administrations to organize parallel pathways, for non-covid patients with urgent health issues.

Priorities had to be set for oncological patients, assuring they got the care they needed in time. Screening all candidates for invasive procedures, was the first step, but many centers ceased exams like fiberoptic bronchoscopy, rigid bronchoscopy, and pulmonary function testing, due the aerosols generated during these interventions, delaying the diagnosis and pre-operative exams of lung cancer patients.

But after the initial stand still, guidelines and recommendations started coming out, on how we could make it work for our patients.<sup>1,2</sup>

The medical oncology Council restated the importance of keeping the diagnostic exams working for the oncological patients as well as the treatment of such patients, in all stages, both with curative intent and

palliative treatment, so as not to shorten overall survival nor worsen their quality of life.<sup>3</sup>

The National Lung Cancer Group (Grupo de Estudos do Cancro do Pulmão – GECP) in a joint task force with the Pulmonology Society (SPP) reinforced these recommendations that both surgery and radiotherapy must keep their due schedule for intervention.<sup>2</sup>

The Portuguese National Health Service is mostly organized in Hospital centers that joined several hospitals under one administration for better management. This allowed for the creation of the theoretical Covid-free hospitals, like in Centro Hospitalar Universitário Lisboa Norte (CHULN), where the Pulido Valente Hospital decreased its activity, due the need for contingency plans, but kept its operating theatre (OT) working for oncology and urgent cases. Some shortage of personnel, especially Anesthesiologists, was felt due to the reassignment to reinforce the Intensive Care Unit staff, and contingency plans were devised to assure all essential tasks, but the outpatient clinics was closed, and the telephone contact became the novel modality of medical appointment. Contact was always maintained with the usual referring doctors by e-mail or postal mail, increasing an already established way for referral of distant patients for all new cases.

Like many countries, some areas were hit harder, being that the north of the country had the biggest impact.

In Centro Hospitalar Universitário de São João (CHUSJ) in Porto, the first portuguese epicentre of Covid19 Pandemic, all routine appointments and surgeries were suddenly largely reduced. The main OT (with 11 rooms for several specialities, including Thoracic Surgery) was partly set to house ventilated covid patients, only 3 rooms remained for elective surgeries. Emergency operating theatre was used for covid patients needing urgent surgeries, whereas non-covid patients requiring urgent surgery where operated in two rooms in the main Operating Theatre.

Thoracic oncological surgeries were maintained in Cardio-Thoracic Department OT (where 1 out 3 rooms

was kept in use). Although reducing the total number of thoracic non-cardiac surgeries, CHUSJ was able to operate the oncological thoracic patients with the same cadency in normal programme, but additional surgeries were also suspended during the pandemic period. Besides, a lower number of lung cancer patients were diagnosed, staged and referred for surgical treatment compared to usual.

In our national center for lung transplant, in Centro Hospitalar Universitário Lisboa Central – Santa Marta Hospital, in Lisbon, defined as a non-covid Hospital, priority was set for urgent and emergent cases only. Since the beginning of the emergency state, there was a drastic reduction of lung donors’ referral. This allied to delay of triage of the donor and recipient for covid-19 led to a 50% decrease in lung transplant.

A brief survey of the major Thoracic surgical centers in Portugal revealed a global picture of the impact on the surgical activity that during this period was restricted to oncological and urgent cases. Comparison of homologous periods of 2019 and 2020 is reflected in table 1. The two non-covid hospitals in Lisbon (H Pulido Valente-CHULN and H Santa Marta-CHULC) had a similar decrease in cases in March, but difficulties in referrals and anesthesiologists availability impacted heavily in the operative numbers of April in most centers.

In all centers, priority was given to malignancies, especially to NSCLC, in line with the recommendations of our national College of Thoracic Surgery.<sup>1</sup> Urgent patients

like empyema, pneumotoraces and trauma were resolved as they came along, but a National decrease in referral was felt, especially in April.

With May, came a trend toward deconfinement, with regulated return of normal activities, which have nothing to do with pre-covid daily activities.

Adjustments in the internal circulation paths and symptomatic triage of all patients are a limiting factor in the outpatient clinic, but added to transmit a sense of professional rigor and safety in managing this situation.

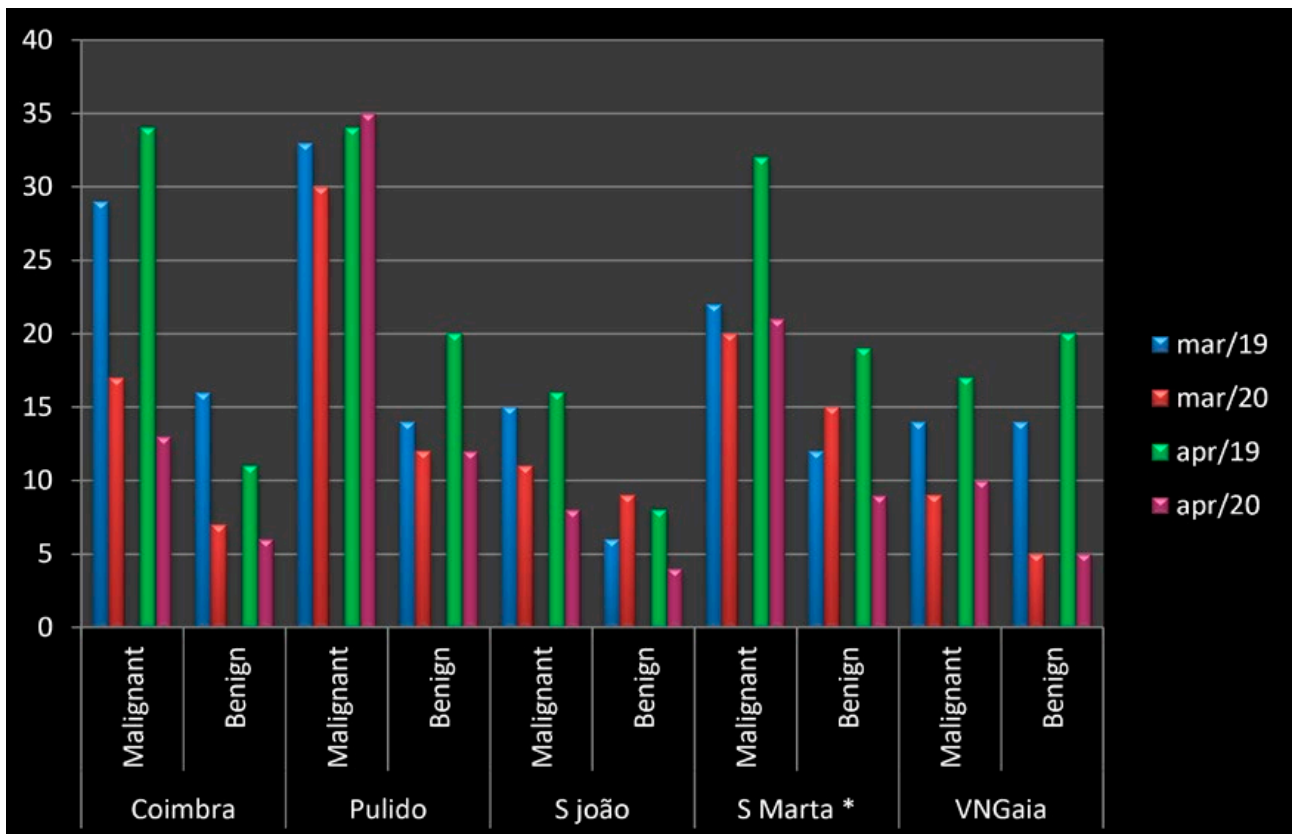
In the OR, the safety measures have not changed, with particular care being taken between patients, that invariably delays the turnover of the patients, but as routine settles in, it seems this will be our new normality.

Diagnosis of oncological cases, as many others, is underestimated, with the social confinement, and is expected to rise as the activities return to normal. On the other hand, this generated an even bigger problem with the benign pathologies waiting list.

We have now, as a community, to find ways to recover the time that was lost, while not endangering patients or professionals, but giving the best care we can.

**Acknowledgment**

The authors would like to thank Professor Miguel Guerra, Dr. Pedro Fernandes, Dr. Rita Pancas and Dr. Paulo Calvino for their help in writing this editorial



**Table1**

Operated patients (\* includes lung transplants: march 2019 - 2, April 2019 - 2, March 2020 - 0, April 2020 - 1).



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# EDITORIAL

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## The impact of COVID-19 pandemic in the management of a Vascular Surgery Department

The novel corona virus SARS-CoV-2 (COVID-19) was identified in Wuhan, China, in December 2019.<sup>1</sup> The first reported case in Europe was on the 24th January<sup>2</sup> while in Portugal it was on the 2<sup>nd</sup> of March.<sup>3</sup> COVID-19 was declared a pandemic disease by World Health Organization on the 11<sup>th</sup> of March<sup>4</sup> and national state of emergency in Portugal declared on the 18<sup>th</sup> of March.<sup>5</sup>

The impact of the pandemic on the Department of Angiology and Vascular Surgery at Centro Hospitalar e Universitário de São João (Porto, Portugal) started to be felt a week after the first national reported case, when the hospital administration implemented the initial contingency measures. Bedside teaching was immediately suspended, and visitors restricted to a pregnancies, palliative care and children. The following week, the Emergency Department (ED) was restructured creating two independent circuits - the respiratory and non-respiratory patients - and the operating room schedule was highly reduced, both to enable anaesthesiologists' relocation to the intensive care units (ICU) and to reduce the non-COVID-19 occupancy rates of ICU, forecasting the impact of the first wave of COVID-19 patients. Additionally, on the day the first case in Portugal was reported, the scientific event of the Department, "Porto Live 2020", was postponed.

Just a couple days before the wear of surgical mask became compulsory in every hospital facility, our Department was itself victim of the COVID-19 pandemic with a medical staff outbreak, detected on the 13<sup>th</sup> of March. Six specialists got infected, setting high risk contacts on a 2-week mandatory quarantine. The Department suffered a 55% reduction of medical staff, from a baseline of 16 specialists and 6 trainees to only 6 specialists and 4 trainees.

A contingency plan was implemented with the judicious use of the scarce medical human resources available, both protecting patients and surgeons - a preliminary attitude that we realized afterwards came in general accordance with the posteriorly issued recommendations of The Vascular Society for Great Britain and Ireland, released on 20th of March.<sup>6</sup> The first problem encountered were the ED

shifts, with 24/7 coverage in one of the main reference centres nationwide, located in the north of Portugal - the epicentre of COVID-19 - and which assists 2.3 million people during night and weekends. Nevertheless, with extra-shifts and good will, a specialist and a trainee were on-call at any given hour. We receive further support from district hospitals with regional units of Angiology and Vascular Surgery that instated provisional ED shifts, avoiding more patients' referrals, preventing overflow of patients and overspread of the virus. Additionally, the ED was provided with new judicious criteria for requesting our direct observation of patients. These included: cases of acute limb ischemia, ruptured or > 7.5 cm abdominal aortic aneurysms and vascular trauma. Patients with chronic peripheral artery disease were managed with the help of general surgeons present at the ED and selectively indicated for elective revascularization. Concerning suspected cases of deep vein thrombosis, the ED received indication for Wells score calculation and D-dimers measurement leaving ultrasound examination for selected cases.

The department ward has 32 beds. Owing to the shortness of medical staff, the creation of two independent teams working every other week was not an available option. Non-critical cases were promptly discharged that same weekend. Early on, patients and healthcare professionals were transferred to the plastic surgery department, as our ward became a COVID-19 ward for non-critical patients.

The 11 operating room periods of 6-hours, normally occupied by vascular elective procedures at the central operating room were reduced to solely 3 - a reduction of  $\approx$  73% operating room time (with sporadic extra-shifts). Fixed teams (usually a specialist and a trainee) were created and maintained as much as possible to avoid the risk of cross-over infection and the spread of potential new cases. Three contingency levels for the operating room criteria were established. Thankfully, there was no need to go further than level 2, in which was foreseen to intervene limb threatening ischemia's, abdominal aortic aneurysms > 7.5

cm and symptomatic carotid stenosis. The 4 periods of the ambulatory surgeries were all cancelled, as for the remaining of ambulatory surgery of all surgical departments.

At the outpatient clinic, non-urgent referrals were postponed, while the remaining appointments were performed via telemedicine or, when it was deemed mandatory, a presential consultation with adequate protective measures.

Although draconian, these measures were critically important in order to cautiously use technical resources, especially personal protective equipment which periodically has been in short supply, and to avoid exposing our vascular patients to the risk of COVID-19 infection. Moreover, all the Department planned activities were fulfilled besides the important human resource reduction. During this COVID-19 wave, no medical staff to patient cross-infection was reported. Furthermore, no additional medical staff got infected and although in the meanwhile an ICU admission was registered, all the infected colleagues had already recovered, having two negative swabs and with a minimum recovery time of 5 weeks.

Now that the peak of this COVID-19 wave is gone, with regular activities still not completely restarted, it is important to address delayed outpatient clinic visits, vascular imaging studies and surgical interventions so vascular patients don't suffer additional consequences from postponing, bearing in mind that a second pandemic wave is not ruled out. Vascular Surgery Departments will have to

adapt efficiently with the available resources at any given time while COVID-19 pandemic lasts in order to meet the demanding needs of vascular patients.

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# COMENTÁRIO EDITORIAL

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## COVID-19: Crisis Management in Lung Cancer Surgery

The COVID-19 pandemic has forced hospitals to progressively reduce surgical volumes to both minimize disease transmission within the hospital, and to preserve human and Personal Protective Equipment and other resources needed to care for COVID-19 patients. In response, many hospitals have abruptly reduced or eliminated elective surgeries. For lung cancer, failure to perform an indicated surgery in timely fashion may have long term implications on a patient's survivorship. However, thoracic oncology decisions are further complicated by the fact most of the patients would be considered to be a "high risk" group for poor outcomes with COVID-19 (advanced age, emphysema and heart disease). Further, the indicated therapeutic procedures can both impair lung function, and expose clinical teams to aerosolized viral load (bronchoscopy, double-lumen endotracheal tube placement, airway surgery and possibly parenchymal lung leaks).<sup>1-4</sup>

Transparency regarding the potential risks of deferring or proceeding with an operation remains a priority. Surgeons should discuss these decisions individually with their patients. Multidisciplinary teams are encouraged to develop alternative treatment strategies if surgical resection is declined or infeasible. Because the duration of surgical volume restriction is unknown (3 months is presumed), patients who are delayed or deferred should be carefully followed.

Although not intended for the study of patients undergoing lung cancer surgery, the first prospective study<sup>5</sup> published in the context of the treatment of cancer patients in a COVID-19 time allows us to draw some conclusions. The study by *Liang et al* monitored 1590 cases of patients hospitalized with COVID-19, of which 18 had a history of cancer (1%). Of these, 5 (28%) had a diagnosis of lung cancer, 12 (67%) were in follow-up after primary resection and 4 (25%) were in a period of convalescence after chemotherapy or surgery performed in the last month. Thus, this study compared, in infected patients, the impairment of a history of cancer, regardless of their type of treatment (chemotherapy / surgery), stage of the disease and histology.

As empirically expected, it showed that cancer patients presented more polypnea and more severe baseline CT manifestations than patients without a history of cancer. Furthermore, it was observed that cancer patients had a higher risk of severe events in intensive care, namely the need

for invasive ventilation or death. As well as a faster deterioration (median time for severe events 13 vs 43 days). Finally, patients who had undergone chemotherapy or surgery in the previous month also had a higher risk of severe clinical events than those who were at follow-up.

In line with the conclusions of the study by *Liang et al*, the Cardio-Thoracic Surgery Department of the Centro Hospitalar de Vila Nova de Gaia / Espinho proposes four main strategies in the treatment of lung cancer in the context of this pandemic:

- First, postponement of elective surgeries should be considered, except in patients where survival may be compromised if the surgery is not performed within 3 months, according to the guidelines of the *American College of Surgeons*.<sup>6</sup>
- Second, screening tests for COVID-19 should be carried out prior to surgery on all patients and not continuing with hospitalization in confirmed cases.
- Third, provide adequate personal protective equipment for surgeons and patients and apply more stringent protective measures in the first month after surgery.
- Fourth, in case of SARS-CoV-2 infection contracted after surgery, active surveillance or more intensive treatment should be considered, especially in elderly patients or those with other comorbidities.

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6. COVID 19: Elective Case Triage Guidelines for Surgical Care



# COMENTÁRIO EDITORIAL

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## Thrombocytopenia after Perceval prosthesis implantation – still a mystery

Thrombocytopenia after Perceval™ prosthesis implantation is a well-known phenomenon which, to be rigorous, don't have a clear explanation yet.<sup>1</sup> Thrombocytopenia profile, which is different when compared with other stented bioprosthesis, looks similar to the one described for Freedom SOLO™.<sup>2</sup> This makes sense, as Perceval™ combines Freedom SOLO™ design mounted in a nitinol frame. As such, it is unlikely that the frame causes the thrombocytopenia.

While many hypotheses have been raised, some common characteristic in both mentioned prostheses must be the cause of this problem. Both have no stent and have a higher leaflet coaptation area, which causes a phenomenon described as fluttering of the leaflets.<sup>3</sup> This effect is described as being more pronounced in patients with a non-circular aortic annulus, inhibiting a full expansion of the nitinol, resulting in asymmetric opening of the leaflets. This generates higher transvalvular gradients. In these patients, LDH levels were also higher – platelet destruction?

This is just another hypothesis but that warrant further investigation. Turbulent flow caused by incomplete valve opening was described as the cause for severe thrombocytopenia at least in one patient.<sup>4</sup>

Therefore, while this is mostly a transitory, self-limited and sub-clinical phenomenon, a thorough pre-operative assessment with maximum, minimum, mean diameters and perimeter of the aortic annulus may help avoiding it.

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# COMENTÁRIO EDITORIAL

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## Rare and unpredictable inflammatory myofibroblastic tumor

In this issue of the *Revista Portuguesa de Cirurgia Cardio-Torácica e Vascular*, Cabral D. *et al.* report findings based on a clinical case of inflammatory myofibroblastic tumor. This is a rare and unpredictable case that confounds diagnosis and treatment. Male, 55-year-old, admitted with pneumonia. Three months after a left lower lobectomy a new IMT nodule in left superior lobe was excised. Four months later, endobronchial involvement and liver metastases. Ten months after surgery bone lesion with histology show undifferentiated sarcoma.

Inflammatory myofibroblastic tumor (IMT) of the lung is a spindle cell proliferation of unknown etiology that is most often seen in young children, adolescents, and non-smoking adults. These tumors are relatively common in children, accounting for 20-50% of all pediatric primary lung tumors, however they comprise less than 1% of all adult lung tumors.<sup>1</sup>

There is significant controversy and confusion regarding the pathogenesis and histogenesis of these uncommon tumors or tumor-like masses. Much of the confusion has been caused by the varying degrees of inflammatory cell infiltration noted on pathologic examination and the observation that the disease process, although usually following a benign course, is sometimes invasive.<sup>2</sup>

IMT has been described in a variety of extra pulmonary sites, including the brain, orbit, thyroid, bones, spleen, and lymph nodes.

A variety of terms have been used to describe lesions falling under the category of IMT. The inflammatory infiltrate usually comprised a mixed population of lymphocytes, plasma cells, histiocytes, and occasional eosinophils. The early terminology "pulmonary plasma cell/histiocytoma complex" emphasized the histologic heterogeneity and a belief in the benign nature of the lesions. Subsequently, plasma cell granuloma was the common terminology for lung lesions, acknowledging i) the circumscribed appearance, ii) the presence of plasma cells and histiocytes, and iii) generally a benign course. The term inflammatory pseudo tumor was typically used to describe extra pulmonary lesions with similar pathology.<sup>3,4</sup>

IMTs have been divided into 3 subgroups (organizing

pneumonia, fibrous histiocytoma, and lymphoplasmacytic type) based on the predominant histopathology and cellular milieu. The plasmacytic and histiocytic varieties of IMT may mimic infections. However, whether IMTs represent a primary inflammatory process or a prominent inflammatory response to a low-grade malignancy remains a matter of debate.<sup>1</sup>

Asymptomatic disease is found coincidentally on imaging studies in approximately 70% of patients. Other patients may present with nonspecific symptoms of cough, chest pain, hemoptysis, shortness of breath, fever, and fatigue. Weight loss and associated anorexia are rare. Evidence of a preceding or concurrent respiratory infection, like in this case, is seen in 30% of the patients.

Radiographic findings in 90% of the patients include well-circumscribed, solitary peripheral lung nodules with a preference for the lower lobes, subpleural locations. Variable attenuation and echogenicity are noted at CT and ultrasonography. Nevertheless, similar to the case presented herein, multiple pulmonary nodules (5%) and endobronchial lesions (5%) have been reported. On CT, lesions may be associated with atelectasis and/or pleural effusions.<sup>5,6</sup>

A recent publication of surgical resection of 61 cases of inflammatory myofibroblastic tumor of the lung show no specific symptoms, and no specific CT imaging characteristic to distinguish from lung cancer.<sup>7</sup>

Fluorodeoxyglucose positron emission tomography (FDG-PET) demonstrates increased metabolic activity in IMT lesions, creating further challenges in distinguishing benign IMT lesions from malignant disease.<sup>8</sup>

Tissue samples obtained from fine needle aspiration and true cut biopsies are typically too small to allow a confident diagnosis. Bronchoscopically obtained tissue biopsies have also been reported to be of limited diagnostic utility due to their small size. Thus, the role of bronchoscopy in the diagnosis of IMT has been questioned in the literature and surgical biopsies are reported as the preferred diagnostic approach.

IMT profiles are typically immunoreactive to vimentin (99%), SMA (92%), muscle-specific actin (89%), desmin (69%) and negative for myoglobin and S100 protein. Spindle cell focal reactivity to epithelial markers such as

cytokeratin, epithelial membrane antigen (EMA; 36%), and CD68 (25%) is also common.<sup>9</sup>

Complete surgical resection is the treatment of choice for solitary pulmonary nodules, which confers a favourable 5 and 10-year survival in these patients of 91% and 77.7%, respectively. Medical management, using glucocorticoids, chemotherapy, and radiotherapy has been anecdotally reported.

Although IMTs are typically considered to be of benign origin, their clinical behaviour is variable and may include malignant evolution associated with locally invasive, recurrent, and metastatic disease. Metastatic spread of the disease is rare (< 5%), however loco regional spread and metastases to extra thoracic sites, including the brain, have been reported. Recurrent disease may develop years after the initial diagnosis, which highlights the need for long term surveillance of these patients.<sup>10</sup>

In a small number of patients, during the presentation or later, more malignant variants were felt to be analogous to undifferentiated "pleomorphic" sarcomas (previously termed malignant fibrous histiocytoma) arising in soft tissues. In those cases, there is a frankly sarcomatous neoplasm lacking a significant inflammatory and/or stromal component.

Approximately 50% of patients with IMT demonstrate clonal chromosomal rearrangements at band 2p23, which is the site of the ALK-1 gene in the tyrosine kinase locus. Mutations at the ALK site have been associated with constitutive overexpression of ALK and oncogenesis. ALK-1 expression is highly specific for IMT, with variation in sensitivity depending on the site of origin.<sup>11</sup>

In a recent study, Crizotinib, a competitive tyrosine kinase inhibitor of ALK, induced a sustained partial response in a patient with ALK-translocated IMT. This observation may offer a new therapeutic strategy for the subset of IMT patients with the ALK mutation phenotypes.<sup>12</sup>

By using a battery of complementary molecular techniques, Cheng et al have shown that all the thoracic IMTs harbored a tyrosine kinase abnormality, with 30% involving a kinase gene other than ALK, including ROS1, NTRK3, and RET gene fusions.<sup>13</sup>

In the near future, more definitive pathologic diagnosis and molecular characterization of locally aggressive or advanced/metastatic IMTs is quite critical, as a number of clinically available tyrosine kinase inhibitors and can be used as targeted therapeutic strategies based on the specific genomic profile of these tumors.

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# COMENTÁRIO EDITORIAL

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## New directions for the management of dual antiplatelet therapy in patients with coronary stents undergoing non-cardiac surgery

Dual antiplatelet therapy (DAPT), the combination of aspirin and a P2Y12 inhibitor, is now one of the most widely used treatments for secondary prevention in patients with coronary artery disease (CAD) suffering an acute coronary syndrome (ACS) or undergoing coronary stent implantation. A significant number of these patients undergo noncardiac surgery within the first 12 months and may require DAPT interruption. This poses a clinical dilemma because interruption exposes patients to the potential risk of stent thrombosis, perioperative myocardial infarction, or both and continuing may be associated with bleeding complications. Given the complexity of these decisions and the possible consequences of delaying the surgical procedure, a multidisciplinary approach is required to choose the best management strategy. Data in this area are conflicting.

The 2017 ESC/EACTS focused update on DAPT duration provides a novel approach to decision-making based on a four-layer scheme focusing on treatment individualization. The main factors to be considered for DAPT duration are clinical presentation (stable CAD or ACS), type of procedure (percutaneous coronary intervention [PCI], coronary artery bypass or medical treatment), device used (drug-eluting stent [DES], bare-metal stent [BMS], bioresorbable vascular scaffold [BVS], drug-eluting balloon [DEB], plain old balloon angioplasty [POBA]) and bleeding risk.

The clinical presentation at the time of the coronary event represents the first major determinant of the baseline ischaemic risk. Patients presenting with ACS are at higher ischaemic risk and remain at higher ischaemic risk for a longer period of time after the index event, hence justifying more potent and prolonged antiplatelet treatment. Guidelines now provide different recommendations for DAPT duration based on clinical presentation: 6 months of DAPT after PCI in patients with stable CAD and 12 months in patients with ACS.

Unlike in the past, the choice between a BMS and DES is no longer a driver for differences in treatment duration. In fact, a DES is recommended as the default treatment strategy and no specific preference for a BMS is based

on anticipated DAPT duration. BVSs are now recognized as more thrombogenic devices requiring longer treatment.

PCI complexity, defined as at least three stents implanted, at least three lesions treated, bifurcation stenting, total stent length >60 mm and chronic total occlusion as target lesion, has always been considered a major determinant for DAPT duration. Patients with complex PCI, prior stent thrombosis and patients with lower-extremities artery disease should be considered for prolonged DAPT duration.

A novel set of recommendations now supports specific decision-making for the timing of elective surgery and the time of withdrawal of the P2Y12 inhibitor. It is recommended to maintain treatment with aspirin perioperatively in most of the situations when surgical bleeding risk allows. The need to interrupt the P2Y12 inhibitor represents in most cases the limiting step for early elective surgery after PCI. Elective, nonemergency surgery requiring P2Y12 inhibitor interruption should be delayed for at least 1 month after stenting, and a delay of 6 months is recommended whenever possible to reduce the risk for recurrent ischaemic events. When a 6-month delay is not feasible, European guidelines recommend that early surgery (1–6 months after-PCI) should be considered in patients initially treated for stable CAD, and may be considered in those treated for an ACS.<sup>1,2</sup> American guidelines (2016)<sup>3</sup> are less permissive and differentiate between DES and BMS (Table 6<sup>4</sup>). However, such surgical procedures should be performed in hospitals where catheterization laboratories are available 24/7, so as to treat patients immediately in case of perioperative thrombotic events.<sup>1</sup>

In order to reduce intra-operative bleeding, ticagrelor should be interrupted at least 3 days, clopidogrel at least 5 days and prasugrel at least 7 days before surgery. If both oral antiplatelet agents have to be discontinued perioperatively, a bridging strategy with intravenous, reversible glycoprotein inhibitors, such as eptifibatid or tirofiban, may be considered especially if surgery has to be performed within 1 month after stent implantation

or patients with a very high risk of stent thrombosis. The P2Y12 inhibitor, when still indicated, should be restarted as soon as deemed safe and when the operative bleeding risk is controlled.<sup>1,2</sup>

Therefore, a dedicated perioperative protocol<sup>4</sup> that summarizes the evidence and provides a pragmatic guide for everyday clinical practice is welcome, showing the need for an update on Anesthesiology recommendations on this topic.<sup>5,6,7</sup> However, a multidisciplinary approach is always appropriate to determine the best individual strategy.

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# CHEST WALL TRAUMA SURGERY – REVIEW

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## Abstract

*Rib fractures are frequent in trauma patients, being most of them managed on a non-surgical way. However, in selected cases, it is advocated.*

*Chest wall stabilization (CWS) only recently has been best characterized.*

*Available data shows plenty of benefits related to CWS versus non-surgical treatment in selected cases. Even though, it is only performed in a small number of patients according to some national databases.*

*There are lots of topics to define concerning CWS such as the subgroups that benefit most, the time of surgery, which ribs should be stabilized and which incision should be performed. Most of these subjects need to be tailored for each patient.*

*So far, no guidelines for CWS are available, although some algorithms have been proposed based on a combination of clinical experience and risk factors.*

*In high-volume trauma centers it has become a common procedure. The complexity of some cases demands a careful evaluation, especially in the context of multiple injuries, and it should be taken into account in the decision.*

## INTRODUCTION

Rib fractures are frequent in trauma patients accounting up to 39% of blunt chest trauma and are present in 10% of all trauma admissions<sup>1</sup>

Sternum fractures are rare, corresponding only to 1% of all fractures and mostly associated with high energy blunt trauma, with an incidence between 3-8%.<sup>1,2</sup> These fractures are also seen in low-energy trauma, especially in older patients since the introduction of seatbelt regulations.<sup>3</sup>

Even so, there are much more trauma patients than those that actually are enrolled for surgery. Most patients are treated non-operatively.

There are no guidelines for CWS but a few interest groups have their own recommendations based on personal experience.

To date, only three randomized clinical trials (RCTs) and three meta-analyses of these and another trial have compared surgical stabilization of rib fractures (SSRF) with best medical management in those patients. Although these trials have favored the SSRF, the number of patients in each trial was low and all limited they focus to flail chest injuries due to its severity, and their conclusions and recommendations were not unanimous.<sup>4,5</sup>

They showed a reduction of the need and duration of mechanical ventilation, decreased incidence of

pneumonia, less pain, shortened ICU and hospital length of stay, earlier mobilization, faster return to active life and decreased use of narcotics in this population when early surgical intervention was performed.<sup>4,6</sup>

Flail chest is a clinical diagnosis characterized by paradoxical movement of a portion of the chest wall due to fractures of two or more consecutive ribs in at least two places. It is responsible for high morbidity and mortality, which can reach 9-16%. It is frequently associated with acute respiratory failure related with inefficient ventilator mechanics, underlying pulmonary contusion and subsequent pneumonia.<sup>1</sup> Long term consequences are chronic pain, deformity, disability and loss of quality of life. Although these are well known severe outcomes, treatment options are still poorly defined. Even with data favoring SSRF, only a small number of patients actually had surgery as treatment of choice. Data from Canada's National Trauma Bank showed that between 2007 and 2009, only 0,7% of flail chest injury patients were treated with surgical fixation of the chest wall.<sup>1</sup>

The most recent promising results of SSRF in flail-chest, the higher interest in application of techniques in patients with multiple rib fractures non-flail chest and, of course, the lack of data supporting the benefit of SSRF in those subset of patients, lead the Chest Wall Injury Society to create a multicenter randomized control trial which will try to establish indications for chest wall stabilization in patients with non-flail rib fractures.

**WHEN IS THE RIGHT TIME TO OPERATE?****Trauma patient as a complex patient**

Many researchers support intervention within a few days of the initial trauma. It is assumed that early intervention can reduce the deleterious effect of inflammation, severe hematoma, clotted hemothorax, empyema, rigidity with deformities of the chest wall, and early callous formation.<sup>5</sup>

But frequently the patient with rib and/or sternum fractures is a multi-traumatized patient. Brain, spine and bowel injury are commonly associated. Chest wall stabilization can and should be delayed until other injuries are treated, and even then its benefits can be seen.<sup>6</sup>

Patients with rib fractures and head/brain trauma are often in coma or sedated with the need for mechanical ventilation. In this kind of patients, the benefit of the SSRF when done precocious can't be seen. But after brain function has recovered and they are weaned from the ventilator, SSRF will help to reduce the need for sedation and analgesia, shorten the time needed for ventilation.<sup>6</sup>

Patients with spinal injury usually need long bed rest. SSRF can help to relieve pain, promote effective cough and so reduce respiratory complications caused by prolonged immobilization.<sup>7</sup>

Pulmonary contusion is present in 30% to 75% in patients with blunt chest trauma.<sup>7</sup> For years, patients with pulmonary contusion and rib fractures were not elected for surgery, in fact, it was thought that surgery was associated with poor outcomes. Pulmonary contusion evolves in 48 to 72 hours. Nowadays many groups consider that those patients benefit from surgery but the time of surgery still isn't well defined. Some considered operation only after the peak of contusion to avoid its effect on lung function and its negative influence in anesthesia.<sup>1</sup> Others, described the operation intervention within 72 hours of injury, and ideally within 24 hours of the injury.<sup>5,8</sup> In fact little data exist about the time of operative fixation in the setting of pulmonary contusion. There is a need to clarify the concept of lung contusion, its severity and its influence on the time of SSRF.

The impact of multiple injuries must be always carefully evaluated and taken into account in decision of CWS.

**Potential indications for surgery**

Reports reveal that the most concordant indication for CWS is uncontrolled acute pain even when treated with the best possible management, which was in 2012 considered by the Eastern Association for the Surgery of Trauma the epidural or paravertebral analgesia.<sup>9</sup> There are an increasing number of studies using pain relief as the main indication for SSRF.

Chronic pain and disability is also a main concern. Chronic non-union is defined as a lack of bone healing nine months after injury. Fractures that have not healed within 3 months have been defined as delayed union. It can occur in 5-10% of the cases and mostly remain symptomatic.<sup>10</sup> Symptoms include persistent pain and a clicking or a

**Table 1 Potential general criteria for CWS**

|  |
|--|
| 3 or more rib fractures with rib displacement of more than 1 rib cortical diameter |
| Flail chest  |
| Severe non-union, loss of continuity or deformity of the sternum                   |
| Uncontrolled acute or chronic pain   |
| Intubation/ mechanical ventilation dependent of CW deformity                       |
| Lung impalement  |
| Open chest deformity   |
| Pulmonary herniation   |
| Stabilization on the retreat of thoracotomy  |
| Symptoms associated with non-union   |

motion sensation, and is exacerbated with cough, sneezing and exercise.<sup>5,10</sup>

Table 1 resume a few indications for rib and sternum fixation.<sup>7,11</sup>

Considering age, it seems like the older ones are those who most benefit from CWS. When comparing outcomes of surgical and nonsurgical treatment in patients with age over 65 and with more than one rib fracture, those submitted to SSRF had less respiratory complications and mortality.<sup>8</sup>

In fact, some papers associate age of 65 years or older and the number of rib fractures with the outcome. Mortality increases in this population depending of the number of rib fractures.<sup>12</sup> Even if there's this kind of evidence, the selection of patients based on this criteria for CWS isn't easy and different groups use different patient age cut off.

There's no doubt that several variables must be taken into account when choosing patients to CWS. Those mentioned above are some of them.

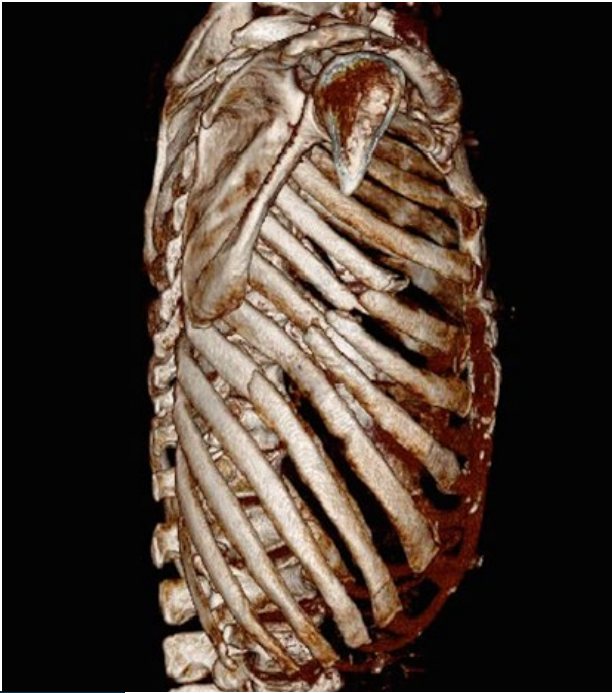
**When should surgery be performed?**

The challenge in performing rib fractures stabilization is to define which fractures must be corrected, which will be the best incision(s) to accomplish our purpose with minimal aggressiveness to the patient.

**PLANNING CHEST WALL STABILIZATION****Patient evaluation**

Patient observation is mandatory, especially in patients with severe trauma and multiple rib fractures located in different places of the thorax. It is crucial to know if there is an important and visible deformity of the thorax, paradoxical movement, rib mobilization with palpation and specific pain location.

Sometimes this observation is not as easy as it seems. Patients can be ventilated and the effect of positive

**Figure 1**

Three-dimensional reconstruction CT scan of a right lateral rib fractures.

pressure can mask the rib fractures mobility. Also, in obese patients and those with extended hematomas, palpation may be tricky.

### Complementary exams and techniques

Pre-operative thorax CT scanning combined with three-dimensional reconstruction technology helps to visualize fracture location and plan surgical positioning and incision(s) (Fig.1).<sup>13</sup>

Ultrasound examination after anesthesia further provides more accurate information regarding the incision design, assisting in determination of rib fractures on the body surface. It can also detect fine fractures and fracture hematomas.<sup>13</sup>

Video-assisted thoracoscopic surgery (VATS) in conjunction with rib fixation is commonly described. It is a useful method to precisely identify the fracture sites.<sup>13,5</sup> One trick is marking on the surface of the body the fractures placing syringe needles that can be seen inside the thorax (Fig.2). VATS can guide the placement of the incision minimizing its length, muscle division, allowing complete evacuation of hemothorax, facilitate optimal chest tube placement, aid in fracture reduction, and rule out and repair diaphragm or pulmonary laceration.<sup>5</sup>

A totally thoracoscopic approach to rib fixation is possible and has been demonstrated, but its widespread application requires further development in equipment and training.<sup>5,10,14</sup>

### Which fractures should be corrected?

A principle must be taken into account, the benefit of CWS should always be higher than the risk or damage that we can cause to the patient in surgery when attempting

**Figure 2**

Using VATS for location of rib fractures.

to correct the fractures. In multiple rib fracture injury it is not necessary fixation for all fracture sites.<sup>10</sup>

We have twelve pairs of ribs and they are not equivalent. They have different length, diameter and angulation, and contribute differently for ventilation.

The selection of fractured ribs to correct depends on: 1) which ribs are fractured; 2) how many ribs are fractured; 3) the localization of the fracture in the different ribs; 4) how many fractures exist in which rib; 5) which kind of fracture exists: aligned, uncoated or comminute; 6) the anatomic relationship around rib fractures; 7) how much the fractured ribs contribute to ventilation; 8) and how much pain and instability do they cause.

Ribs one and two are deep, have less mobility, little contribution to respiratory physiology and are in close relationship with vascular and nervous bundles. Unless those structures are damaged in trauma and surgery is needed, those ribs are usually not considered for stabilization, they're challenging to expose.<sup>5,13</sup>

Ribs from third to tenth have progressively a larger degree of motion, a higher contribute for ventilation and stability of the ribcage. When fractured, they cause more pain and can be responsible for important thorax deformity.<sup>5,13</sup> When fractured, those ribs are more actively treated, especially when the fracture is anterior or lateral.

The floating ribs are not critical to respiration and not easily accessible with standard muscle sparing incisions. Usually are not submitted to surgery unless responsible for liver or spleen damage.<sup>5,13</sup>

Antero-lateral rib fractures are easier to access but posterior fractures are much more difficult to expose because of the scapula and the incision may cause extensive muscular damage. Recent improvements in materials and techniques have helped to make this surgery less invasive. The posterior portion of the rib cage is actually more protected by these structures and so fractures located there are usually more stable and cause less pain. Posterior flail chest is difficult to evaluate, and so in these cases complementary exams can help to decide if it is necessary to SSRF.

On the left side, misaligned fractures from 5 to 9



ribs, with intrapleural tops, can drill the aorta, so SSRF is recommended.<sup>5,13</sup>

There is no apparent advantage to repairing “every other rib” to minimize dissection and tissue damage. Fixation of one rib, many times is sufficient to stabilize fractures in the rib above and below it, reestablishing the thorax configuration and minimizing the rigidity conferred by the materials used.

**Surgical approaches**

Incision is planned according to the location of rib fractures considered for stabilization. It must allow full exposure, minimal injury and aesthetic appearance. Each case is different and that’s why it is difficult to standardize the incisions.<sup>12</sup>

Although, the rib fractures can be divided into anterior (anterior axillary line), lateral (between anterior and posterior axillary lines) and posterior (posterior to the axillary line).<sup>5,13</sup>

Whenever possible we should start with minimal incision and muscle splitting. With a small incision over a fracture site the thoracic wall is exposed. Other fractures can be located by inspection or palpation to guide the extension and direction of the incision.

The rib fractures approach can be summarized as follows:

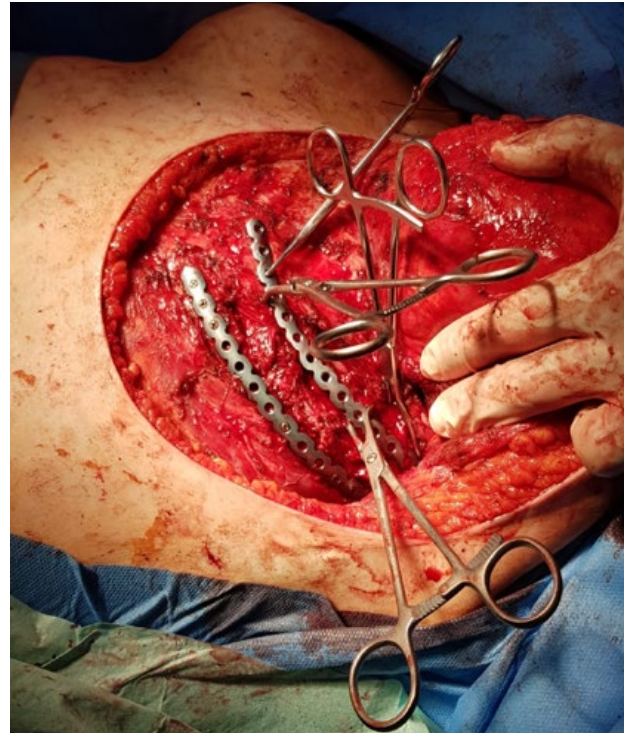
**a) Anterior chest wall fractures with or without simultaneous sternum fracture:**

With the patient in a supine position, anterior rib fractures can be exposed through a oblique incision along the submammary sulcus an then a subpectoralis major myocutaneous flap is made to expose ribs 4-6 (Fig.3(a) and (b)). Exposure of the third rib can be made through a cutaneous transverse incision above the fracture and then splitting the fibers of pectoralis major and minor (Fig.4).<sup>13</sup>

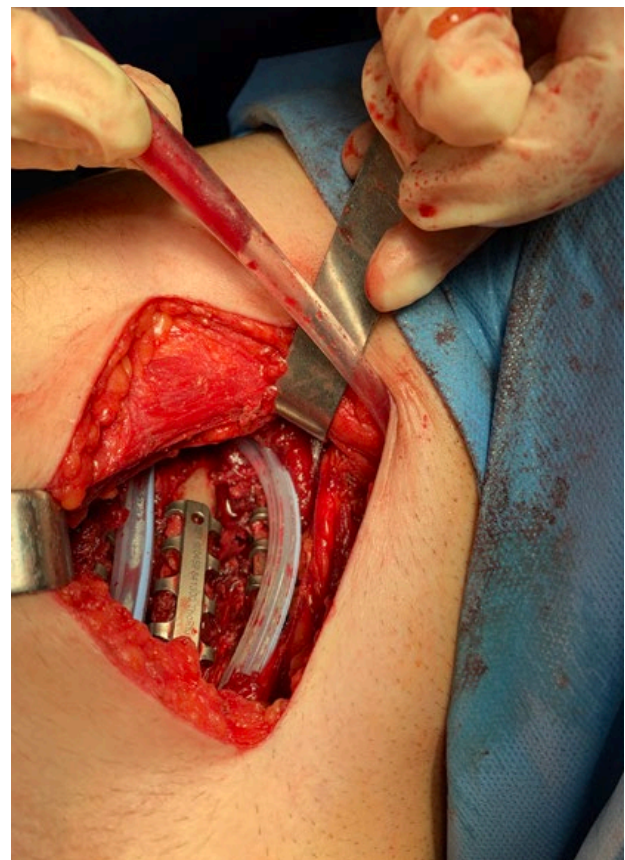
When there’s an anterior flail chest, with rib fractures on both sites of the sternum a clamshell incision can be made and both pectoralis major are dissected



**Figure 3(a)** Sub-mammary incision for anterior unilateral fourth to sixth rib fractures stabilization.



**Figure 3(b)** Anterior unilateral rib fractures stabilization with plates and bicortical screws.



**Figure 4** Antero-lateral third and fourth rib fractures. Latissimus dorsal muscle dissection through its anterior limit and incision along the pectoralis major fibers to expose the fractures. Rib fracture stabilization with clamping plates.





**Figure 5** Anterior bilateral rib fractures stabilization with plates and bicortical screws through a clamshell incision.

from their rib and sternum insertions to expose the anterior chest wall (Fig.5).

In both cases, if there's a simultaneous sternum fracture it can be corrected using both incisions, but when there are only unilateral fractures the middle incision must be prolonged upwards along the sternum to better expose the bone fracture. The incision will have an L shape.

In simple sternum fractures the incision is usually a vertical one along the bone, lateral mobilization of the myocutaneous flap just enough to expose the fracture and insert the stabilization material.

**b) Lateral chest wall fractures:**

The patient must be placed in a lateral decubitus position with the upper arm supported above the head. A vertical incision is made along the anterior edge of the latissimus dorsi muscle. The anterior edge of the muscle is dissected from the most internal muscular layer so it can be retracted backwards. Serratus anterior muscle is then exposed and can be split to access the rib fractures (Fig.6(a) e(b)). Care must be taken to not damage the long thoracic nerve.<sup>13</sup>



**Figure 6(a)** Surgical approach for lateral rib fractures..



**Figure 6(b)** Stabilization of lateral rib fractures with plates and bicortical screws.

**c) Posterior or subscapular chest wall fractures:**

The proximity to the transverse process, costal angle and subscapular location of these fractures makes them technically the most difficult to repair.

The patient can be placed in prone position and the ipsilateral arm is supported in a lower rack of the operation table. This positioning will move the scapula anteriorly allowing a better expose of the triangle of auscultation and the subtrapezius and latissimus dorsi flap. Sometimes is inevitable to make a partial division of the latissimusdorsi and trapezius muscle at the extremes of exposure in some fracture patterns and the need for scapular retraction to gain exposure to subscapular fractures (Fig.7). Traditionally postero-lateral thoracotomy can be performed.<sup>13</sup>

For multiple fractures scattered in the fracture site, deep muscular tunnels can be made by separating and retracting muscles to expose the fracture site, and 90° angle fixation device or a small incision upon the other extreme can be used for fracture fixation.<sup>13</sup>

Chest trauma can be tricky. Patient can have all kinds of fracture combinations and so many times the CWS must be done using multiple incisions (Fig.8).

**Fixation materials**

The better method for CWS is still unknown. There are several commercial available systems for rib fixation, each with advantages and deficiencies.<sup>10</sup> The development of these materials and technologies made CWS easier and



**Figure 7** *Surgical approach for stabilization of posterior rib fractures.*

with relatively few complications. The most frequently used are based in moldable metal plates with different lengths, applied on the surface of the rib and attached with bicortical screws. Alternatively, there are intra-medular splints, once again attached in one of the extremities by a bicortical screw.

There are U-shaped plates applied to the upper edge of the rib and fixed with screws. Other systems use clamping plates.

The advantage of this kind of systems is that they allow stabilization of rib fractures many of them with minimal invasive approaches, with sparing muscle incisions and minimal to the intercostal nerve.

For sternum fixation there are also similar systems, the most commonly adopted use different shapes of plates applied on the sternum surface and attached to it with bicortical screws.

All systems come with user-friendly equipment for quick and safe use.

No data are available concerning long term use of metal plates.

There are, off course, many other systems available but less is known concerning their application, like the absorbable ones.



**Figure 8** *Three-dimensional reconstruction CT scan after complex rib fractures stabilization.*

## CONCLUSIONS

There are no guidelines for CWS. Treatment algorithms have been proposed based on a combination of clinical experience and identification of the most relevant risk factors available in the published literature.

SSRF has become a common operation at most high-volume trauma centers. Increased experience with the procedure and development of new materials has spawned a variety of technical modifications to minimize incision length, muscle division, scapular retraction and general tissue trauma.

The impact of multiple injuries must be carefully evaluated and taken into account in decision of CWS.

Current available data shows benefit for a surgical approach of CWS versus non-surgical treatment. A prospective randomized control trial is now being enrolled by the Chest Wall Injury Society. We hope that it will bring us more information on this matter and validate the surgical approach of thoracic trauma patients and improvements in therapeutic strategies.

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# PLATELET COUNT DROP AFTER RAPID DEPLOYMENT AORTIC VALVE IMPLANTATION

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## Abstract

**Background:** A transient postoperative drop in platelet count is an expected finding after aortic valve replacement using extracorporeal circulation. The implantation of the Perceval valve has been associated with a more intense drop of platelet count compared to other bio-prostheses. This study analyses and compares the platelets progression associated with the Perceval and Intuity valves.

**Methods:** The data was collected retrospectively for patients submitted to isolated aortic valve replacement with the Perceval valve (80 patients) and the Intuity valve (141 patients) in our institution between March 2014 and December 2018. The groups were further divided into those who receive platelet transfusion and those who did not.

**Results:** The minimum values of platelet count were 54% and 67% of the preoperative platelet count in the patients treated with a Perceval and an Intuity valves, respectively ( $p < 0.001$ ). In the patients transfused with platelets, the minimum values were 52% and 79% of the preoperative platelet count, respectively ( $p < 0.01$ ). Recovery of the count was faster in the patients treated with an Intuity valve. Abnormal bleeding and transfusion of packed red blood cells were not significantly different between groups (without platelet transfusion:  $p = 0.71$  and  $p = 0.99$ , respectively; with platelet transfusion:  $p = 0.58$  and  $p = 0.99$ , respectively).

**Conclusion:** Compared to the Intuity valve, the Perceval valve is associated with a transient, but significant, drop in platelet count. This drop was not associated to an increased risk of bleeding. Platelet transfusion, in this setting, should be judicious and not only ruled by absolute values.

## INTRODUCTION

The biologic rapid deployment valves were developed for aortic valve replacement surgery, as an alternative for high risk patients.<sup>1</sup> At the moment, two models are available on the market: Perceval S (Sorin Group Saluggia, Italy / Livanova, London, UK) and Intuity (Edwards Lifesciences, Irvine, California, USA). By allowing a faster implantation with minimal heart and aorta manipulation, they provide shorter operative times, reduced perioperative complications and better clinical outcomes maintaining excellent hemodynamic performances.<sup>2,3,4</sup>

A transient platelet drop is an expected postoperative finding. A reduction of 30-60% of the baseline values is common between the second and third days and is generally associated to the extracorporeal circulation.<sup>5</sup> A low count of platelets, particularly if severe, has the potential for bleeding complications, among others<sup>6</sup>. Additionally, the use of the Perceval valve has

been associated with a more intense reduction and slower recovery of the platelet count and a higher need of packed red blood cells transfusion.<sup>7,8</sup>

The goals of this study were (1) to analyze the postoperative platelet response to Perceval and Intuity valves, (2) to compare the responses between the valves, and (3) identify associated adverse clinical events, such as bleeding.

## PATIENTS AND METHODS

### Population and study groups

A total of 224 consecutive patients underwent isolated Intuity or Perceval valve implantation, between March 2014 and December 2018, at our institution. The indication for surgery was the same as for conventional aortic valve replacement. The data from all the patients was retrospectively reviewed.

Multisystemic failure is a well-known factor of coagulation disturbance; for this reason, three patients were excluded due to rapid progressively multisystemic failure resulting in death.

To avoid the effect of platelet transfusion in the progression of the platelet levels, the patients that received platelet transfusion after surgery were analyzed separately. Therefore, four groups were established: (1) patients that received an Intuity valve and no postoperative platelet transfusion (IG, n=102); (2) patients that received a Perceval valve and no postoperative platelet transfusion (PG, n=60); (3) patients that received an Intuity valve and postoperative platelet transfusion (IpG, n=39); and (4) patients that received a Perceval valve and postoperative platelet transfusion (PpG, n=20).

### Valve prostheses characteristics and implantation techniques

#### INTUITY<sup>®</sup>

The Intuity valve is a bioprosthesis with three bovine pericardial leaflets. Its design was based on the Magna Ease aortic bioprosthesis (Edwards Lifesciences, Irvine, California, USA) built on a covered expandable stainless-steel frame, at the bottom side of the valve. This cloth skirt is intended to expand in the left ventricular outflow tract subjacent to the native annulus; this way, it promotes stability and sealing between the aortic annulus and the frame and host tissue in-growth.

The anticalcification technology used is ThermoFix, a combination of both thermal and chemical agents developed to remove unstable glutaraldehyde residuals, the same used in other Edwards prostheses (such as Magna and Magna Ease).

After rinsing, the valve is connected to the specialized delivery system. Three guiding sutures, placed in the annulus at the nadir of each coronary cusps, pass through sewing ring in the valve and are used to align the valve with the annulus during the descent. Once in position, the three sutures are secured using tourniquets. The balloon is inflated to the appropriate pressure (varying according to the valve size). The delivery system is removed and the guiding sutures are tied.

#### PERCEVAL S<sup>®</sup>

The Perceval S valve is a bioprosthesis with three bovine pericardial leaflets mounted on a naked nitinol self-expandable frame; this frame is coated with Carbofilm™ to improve biocompatibility. Its design was based on the Freedom SOLO (Sorin Group Saluggia, Italy / Livanova, London, UK).

The anticalcification treatment is based on homocysteic acid, the same used in other Livanova prostheses (such as Pericarbon Freedom and Freedom SOLO).

The valve is compressed by a proper collapsing device and loaded onto the delivery device. No rinsing is required. Three guiding sutures help to align the valve with the annulus during the descent into subannular position. The valve then is released from the delivery device and balloon dilatation is performed at 4 atm of pressure for 30 seconds with continuous irrigation with sterile water at 37°C. The guiding

sutures are removed afterwards. The valve is kept in position by the stent against the intra-aortic wall.

### Surgery and postoperative care

All patients were submitted to the same conventional surgical technique. The cardiopulmonary bypass was established with an arterial cannula in the ascending aorta, a double stage venous cannula through the right atrial appendage, and a left ventricle vent, placed through the right upper pulmonary vein. Cold blood cardioplegia was administered in an antegrade fashion. Complete decalcification of the aortic annulus was always performed. The choice of valve was made by the surgeon. At the end of the surgery, platelet and fresh plasma was administered, if needed, according to clinical factors (such as, the amount of bleeding, the visual absence of clotting, and diffuse bleeding with no surgical explanation) and thromboelastography. Perioperative transthoracic echocardiogram was performed in all patients to confirm valve position, hemodynamics and to exclude paravalvular leaks.

Postoperative medication was the same for all patients, and started within 24h, according to the standard protocol of the department. It includes aspirin, statin, acetaminophen, metamizole, prophylactic enoxaparin, insulin (as needed), prophylactic cefazolin (or vancomycin if allergy), furosemide, pantoprazole, ondansetron (as needed), aminergic support (epinephrine, norepinephrine and/or dobutamine, as needed).

Platelet count measurements followed the standard routine of the department: within 24h previously to the surgery, within 1h after surgery; in the mornings of the following days; and at the 1-month follow-up visit.

Abnormal bleeding was defined as > 2ml/kg/h in first 2-3 hours, > 1ml/kg/h in the next 3 hours and/or > 0.5ml/kg/h in 12 hours. A thromboelastography was performed to guide the choice of products to transfuse. If the bleeding rate was worrisome and no clot was visible in the drainage, both platelets and fresh plasma were transfused before the thromboelastography results. If the bleeding rate was great and/or causing hemodynamic instability, a surgical exploration would be quickly performed.

### Statistical analysis

Data collection and statistical analysis was carried out using SPSS v24. Continuous variables were treated as mean and standard deviation and compared with t-student tests, with a two-tailed distribution assuming unequal variances. Categorical variables were summarized as the number and/or percentage of subjects in each category and compared with Fisher's exact tests.

### RESULTS

Patients that did not received postoperative platelet transfusion

The baseline characteristics for IG and PG are presented in Table 1. Overall, the two groups were not

**Table 1** Base characteristics.

|  | No platelet transfusion |                 |       | Platelet transfusion |                 |       |
|--|-------------------------|-----------------|-------|----------------------|-----------------|-------|
|  | Intuity (n=102)         | Perceval (n=60) | p     | Intuity (n=39)       | Perceval (n=20) | p     |
| Sex (female/male)                            | 61/39 %                 | 53/47 %         | 0.411 | 41/59 %              | 40/60 %         | 0.999 |
| Age (years)                                  | 74.8 ± 5.6              | 76.6 ± 4.8      | 0.040 | 76.6 ± 6.7           | 77.7 ± 5.7      | 0.566 |
| EuroScore II (%)                             | 2.4 ± 1.4               | 2.5 ± 1.9       | 0.651 | 2.1 ± 1.2            | 2.8 ± 1.9       | 0.179 |
| Arterial hypertension                        | 94.1%                   | 93.3%           | 0.999 | 92.3%                | 100%            | 0,544 |
| Dyslipidemia                                 | 78.4%                   | 76.7%           | 0.846 | 74.4%                | 75.0%           | 0,999 |
| Impaired renal function <sup>1</sup>         | 78.4%                   | 86.7%           | 0.216 | 82.1%                | 85.0%           | 0.999 |
| Overweigh/obesity <sup>2</sup>               | 76.5%                   | 80.0%           | 0.697 | 66.7%                | 75.0%           | 0.565 |
| Coronary disease                             | 36.3%                   | 18.3%           | 0.020 | 43.6%                | 50.0%           | 0,784 |
| Diabetes Mellitus                            | 36.3%                   | 43.3%           | 0.407 | 30.8%                | 35.0%           | 0,775 |
| Insulin treated                              | 2.9%                    | 8.3%            | 0.148 | 0%                   | 0%              |       |
| Atrial fibrillation <sup>3</sup>             | 18.6%                   | 28.3%           | 0.173 | 15.4%                | 20.0%           | 0.721 |
| Smoking history <sup>4</sup>                 | 29.6%                   | 26.7%           | 0.331 | 15.4%                | 20.0%           | 0.721 |
| Thrombocytopenia <sup>5</sup>                | 7.8%                    | 10.0%           | 0.773 | 30.8%                | 30%             | 0.999 |
| Carotid disease                              | 11.8%                   | 8.3%            | 0.601 | 12,8%                | 5.0%            | 0,653 |
| Pacemaker                                    | 4.9%                    | 3.3%            | 0.999 | 5.1%                 | 5%              | 0.999 |
| Previous stroke or transient ischemic attack | 3.9%                    | 10.0%           | 0.175 | 7.7%                 | 5%              | 0.999 |

Categorical variables are presented as percentage of subjects in each category and compared with t-student tests. Continuous variables were treated as mean and standard deviation and compared with Fisher's exact tests.

1 Impaired renal function was defined as glomerular filtration rate <80%.

2 Overweigh/obesity was defined as body mass index >25.

3 Any form: paroxysmal, persistent, permanent.

4 Former or active.

5 Thrombocytopenia was defined as a platelet level <150/ml.

different. The two exceptions were the higher mean age in the PG (a difference of 1.8 years,  $p=0.04$ ) and the higher frequency of coronary disease in the IG (a difference of 18 percental points,  $p=0.02$ ).

The differences in mean aorta cross clamping, extracorporeal circulation and operative times, between the groups, were, respectively, 1.5, 3.8 and 9.0 minutes, in favor of the IG (table 2). No relevant paravalvular leaks were found in any patients, in either group. Mean post implantation mean transvalvular gradient was  $10.0 \pm 3.7$  mmHg with the Intuity valve and  $8.9 \pm 5.2$  mmHg with the Perceval valve ( $p=0.458$ ).

Platelet count progression for each group is presented in Image 1A. Preoperative means were  $225 \pm 68$ /ml in the IG and  $217 \pm 61$ /ml in the PG. In the first hour, there was a significant drop ( $p<0.001$ ), in both groups, to about 70% of the preoperative count. In the following mornings, platelet count continued to decrease in the PG to a minimum of 53.8% (at the 3<sup>rd</sup> postoperative day). In the IG, after a small increase, the numbers dropped to a minimum of 67.2% of the preoperative count, 2 days after surgery. At the follow-up visit, the IG and PG presented a mean count of 123% and 98% of the preoperative count, respectively.

No statistically significant differences occurred between IG and PG regarding abnormal bleeding, bleeding related complications, in-hospital stay, major renal dysfunction, infection or death (see Table 2 for details).

A subanalysis excluding the patients with coronary disease was conducted. No relevant baseline differences were found. The differences in platelet progression remained similar. Abnormal bleeding occurred in 3.1% and 6.1% ( $p=0.65$ ), in the patients implanted with an Intuity valve ( $n=65$ ) and a Perceval valve ( $n=49$ ), respectively; transfusion of packed red blood cells was performed in 9.2% and 12.2% ( $p=0.760$ ) and transfusion of fresh plasma occurred in 7.7% and 2.0% ( $p=0.234$ ), respectively. Major renal dysfunction was higher in the PG (10.0% vs 1.5%,  $p=0.083$ ).

#### Patients that received postoperative platelet transfusion

The IpG received a mean of 1.38 units of platelets per patient and the PpG a mean of 1.45 units per patient, within the first day. No statistically significant differences were found in baseline characteristics and surgical outcomes (tables 1 and 2).

**Table 2** Surgical and post-operative outcomes.

|  | No platelet transfusion |                    |          | Platelet transfusion |                    |          |
|--|-------------------------|--------------------|----------|----------------------|--------------------|----------|
|  | Intuity<br>(n=102)      | Perceval<br>(n=60) | <i>p</i> | Intuity<br>(n=39)    | Perceval<br>(n=20) | <i>p</i> |
| <b>Operatory times</b>                     |                         |                    |          |                      |                    |          |
| Aorta Clamping (minutes)                   | 27.2 ± 6.8              | 28.7 ± 8.4         | 0.260    | 29.9 ± 12.0          | 26.6 ± 6.0         | 0,165    |
| Cardiopulmonary bypass (minutes)           | 35.9 ± 8.7              | 39.7 ± 11.0        | 0.022    | 39.8 ± 16.4          | 36.2 ± 8.0         | 0,408    |
| Operative time (minutes)                   | 86.9 ± 20.3             | 95.9 ± 21.8        | 0.010    | 91.4 ± 26.8          | 91.2 ± 12.8        | 0,955    |
| <b>In-hospital stay</b>                    |                         |                    |          |                      |                    |          |
| ICU stay (days)                            | 2.6 ± 1.5               | 2.7 ± 1.8          | 0.518    | 4.0 ± 3.2            | 4.0 ± 2.9          | 0.953    |
| Hospital stay (days)                       | 5.6 ± 2.8               | 6.3 ± 1.8          | 0.107    | 8.2 ± 5.7            | 7.9 ± 4.6          | 0.825    |
| <b>Post-operative complications</b>        |                         |                    |          |                      |                    |          |
| Fresh plasma transfusion <sup>1</sup>      | 7.8%                    | 1.7%               | 0.156    | 69.2%                | 40.0%              | 0.049    |
| Red blood cell transfusion <sup>1</sup>    | 11.8%                   | 11.7%              | 0.999    | 69.2%                | 70.0%              | 0.999    |
| Abnormal bleeding <sup>2</sup>             | 3.9%                    | 5.0%               | 0.711    | 64.1%                | 55.0%              | 0.578    |
| Bleeding in the first 24h (ml)             | 466 ± 251               | 443 ± 363          | 0.635    | 1012 ± 466           | 1052 ± 757         | 0.829    |
| Surgical exploration for bleeding          | 2.0%                    | 0%                 | 0.531    | 10.3%                | 5.0%               | 0.653    |
| Significant renal dysfunction <sup>3</sup> | 4.9%                    | 8.3%               | 0.501    | 20.5%                | 15.0%              | 0.734    |
| Renal replacement support <sup>4</sup>     | 1.0%                    | 1.7%               | 0.999    | 2.6%                 | 5.0%               | 0.999    |
| Aminergic support <sup>5</sup> >24h        | 19.6%                   | 21.7%              | 0.840    | 38.5%                | 45%                | 0.780    |
| Infection <sup>6</sup>                     | 2.0%                    | 5.0%               | 0.360    | 12.8%                | 15.0%              | 0.999    |

ICU - Intensive care unit.

Categorical variables are presented as percentage of subjects in each category and compared with t-student tests. Continuous variables were treated as mean and standard deviation and compared with Fisher's exact tests.

1 Transfusion of at least 1 unit.

2 Abnormal bleeding was defined as > 2ml/kg/h in first 2-3 hours, > 1ml/kg/h in the next 3 hours and/or > 0.5ml/kg/h in 12 hours.

3 Significant renal dysfunction was defined as KDIGO stages 2 and 3.

4 Renal replacement support was performed through Continuous Veno-Venous Hemodiafiltration.

5 Aminergic support was performed with at least one of the following: epinephrine, norepinephrine, dobutamine.

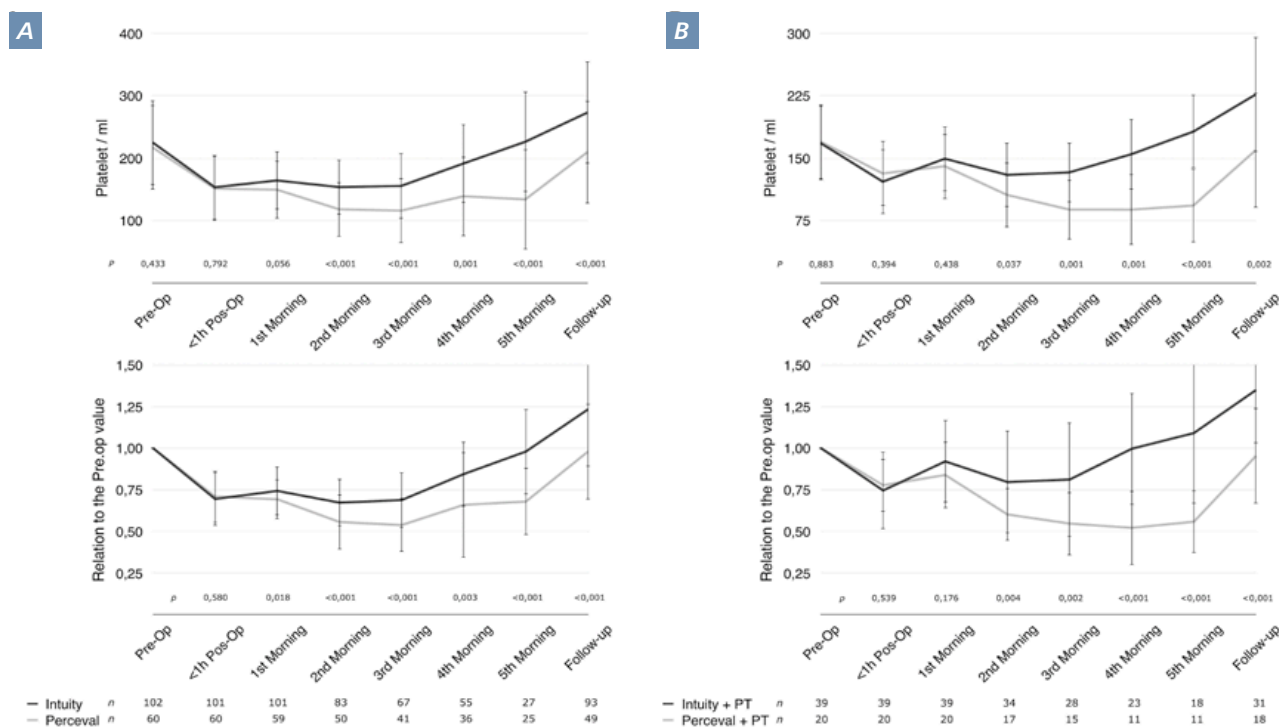
6 Respiratory, urinary and/or blood infection.

The platelet count progression for the IpG and the PpG is presented in image 1B. In the IpG, the count rose in the first morning, decreased in the second (to 79% of the preoperative count) and then increased gradually to 135% of the baseline levels, at the follow-up visit. In the PpG, the platelet levels were maintained in the first morning and then decreased gradually until the fourth morning (to 52% of the preoperative count); Afterwards, a slow recover occurred, with levels reaching 95% of the preoperative count at the follow-up visit. The differences between groups were statistically significant starting at the second morning.

## DISCUSSION

As expected, regardless of the type of valve implanted, a platelet-count drop that reached a minimum between the second and third postoperative days, was observed. This drop was statistically significant when

compared to the preoperative values. The preoperative and within 1-hour platelet count were very similar in both valves. After the first morning, and persisting at the follow-up visit (~1 month), the platelet count was higher in the IG: the lowest count was 67% and 54% of the preoperative count in the IG and the PG, respectively. Afterwards, the recovery was slower in the PG. The patients that received platelet transfusion had low baseline platelet count, but the overall progression and differences between valve groups was similar. Despite lower count in the groups that received Perceval valves (PG and PpG), bleeding and surgical exploration was not different between Perceval and Intuity groups. Platelet transfusion resulted in a significant increase in platelet count in the patients that receive an Intuity valve. This was not observed in the patients that received a Perceval valve. Higher bleeding in the PpG (5.0% vs 55.0% in PG,  $p < 0.001$ ) could result in platelet consumption and explain the "no increase" of platelets after transfusion, however, the IpG also had more bleeding than IG (3,9%



**Figure 1**

Comparison of the platelet count in the patients implanted with an Intuity valve and a Perceval valve. The patients that did not received platelet transfusion (A) and those who received platelet transfusion (B) were analyzed separately. PT – Platelet transfusion; <1h Pos-Op – Within 1-hour after surgery; Pre.Op – Preoperative.

vs 64.1%,  $p < 0.001$ ) and a significant increase was found after the transfusion. On the other hand, the low number of patients in the PpG may not be enough to represent the true response.

The results of this study suggest that, compared to those who received an Intuity valve, in the patients that received a Perceval valve: there was one (or more) factor(s) that negatively affect the postoperative platelet count; and the higher drop in platelet count was transient and not enough to increase the risk of bleeding events.

Platelet count and quality can be influenced by multiple preoperative, intraoperative and postoperative factors. Low preoperative count of platelets, intraoperative factors and postoperative renal dysfunction and infection were similar between groups (IG vs PG and IpG vs PpG). Extracorporeal circulation time was overall short in all groups and the differences were small (3.8 minutes higher in the PG [vs IG] and 3.6 minutes higher in the IpG [vs IgP]), therefore this is unlikely the cause. More patients in the IG had coronary disease (vs PG) and were under antiplatelet drugs. For this reason, preoperative antiplatelet drugs cannot explain the drop of platelets in the PG. Heparin-induced thrombocytopenia was not investigated in this study, but it is unlikely that more patients in the Perceval groups were randomly affected. As for postoperative drugs, including antiaggregant drugs, the same therapeutic protocol was applied to all patients. One possible explanation for these results is the valve itself. The Perceval valve was compared to the Intuity valve by Jiritano and colleges<sup>10</sup> and Magna Ease

by Mujtaba and colleges.<sup>11</sup> In both cases, the Perceval valve was also associated to a significant, but transient, greater reduction in platelets count, in comparison to Edward’s valves. The same was found by Stanger and colleges<sup>12</sup> when they compared Freedom, Perceval S and SOLO valves with non-Sorin valves (mechanical valves, Magna, 3f Enable). As previously mention in the Methods section, the Perceval valve is derived from the stentless Pericarbon Freedom and Freedom SOLO valves and presents the same intense postoperative platelet count drop phenomenon.<sup>13,14</sup> This phenomenon has been on study and debate over the last decade. Platelet activation by anticalcification or storage components (such as homocysteic acid)<sup>12,15</sup>, mechanical stress of the prosthesis on the platelet<sup>15</sup> and activation/rupture by the naked nitinol stent<sup>10,11</sup> have been proposed as possible causes. The last two are very unlikely, since the valve has excellent hemodynamic performances and if the stent was the problem, this phenomenon would not occur with the Pericarbon Freedom and Freedom SOLO valves, which are stentless. Strong evidences presented by Stanger and colleges<sup>12,15</sup> suggested that the underlying cause of the severe postoperative platelet count drop associated with Sorin valves was the anticalcification treatment with homocysteic acid. The hypothesis stated that after cardiopulmonary bypass some of the platelets become particularly susceptible to damage and stimulation; once in contact with valve, N-methyl-D-aspartic acid (NMDA)-type glutamate receptors on these “high sensitive” platelets were activated by the homocysteic acid, leading to its lysis. On

the other hand, the platelets not activated by the cardiopulmonary bypass were not affected and remained functionally intact, limiting the potential bleeding complications. In our study, as previously mentioned, platelet transfusion did not result in an increase in platelet count in the patients that receive a Perceval valve. Assuming this result was not a bias of small numbers, based on the previous hypothesis, we could extrapolate that the transfused platelets also became "high sensitive" during the production or delivery process and reacted to the homocysteic acid (or other unknown element). At the moment, we have no further data to support this idea; more studies are needed. Nevertheless, a reassuring fact emerges: the effect of the Perceval valve on platelets does not appear to increase the bleeding risk.

### Study limitations

The limitations of this study were linked to the use of data from a single institution, a limited number of cases and data and a different number of patients between groups. Also, it was a retrospective study and only early outcomes were studied.

### CONCLUSION

Compared to the Intuity valve, the Perceval valve is associated with a transient, but significant, drop in platelet count. This drop was not associated to an increased risk of bleeding neither in the transfuse group nor the non-transfused group. Platelet transfusion, in this setting, should be judicious and not only ruled by absolute values.

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# PROTOCOL FOR A PERIOPERATIVE APPROACH TO PATIENTS WITH CORONARY STENTS UNDERGOING NON-CARDIAC SURGERY

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## Abstract

*Patients undergoing angioplasty and stent insertion require double prophylactic anti-aggregation or monotherapy. This is a challenging procedure with a high risk of morbidity and coronary mortality. The aim of this protocol is to provide guidelines for a presurgical approach to patients with a coronary stent who will be undergoing non-coronary surgery. This protocol highlights potential complications that may occur, namely those related with the cardiac stent and the evaluation of cardiac risk, and notes the thrombotic and hemorrhagic risks associated with the surgical procedure and the decision algorithms for both elective surgery and urgent surgery involving the suspension and re-introduction of antiplatelet therapy. Our main goal is to outline an optimized approach to these cases in order to improve cardiac outcomes and to minimize the risk of complications.*

## INTRODUCTION

Percutaneous coronary interventions (PCI) are frequent, and include balloon angioplasties and stent insertion. Most patients undergo angioplasty with stent insertion, since the results of this procedure are more effective in preserving vascular permeability.<sup>1</sup> It is estimated that nearly 5-10% of patients undergo non-cardiac surgery in the first year after the insertion of their coronary stent. This percentage can rise up to 25% within the first 5 years.<sup>1</sup>

A stent is a solid scaffold that prevents vessel closure due to elastic recoil or vessel contracture.<sup>2</sup> Currently, there are two types of stents: the Bare Metal Stent (BMS) and the Drug Eluted Stent (DES), which includes the Bioresorbable Stent (BRS).<sup>2,3,4</sup>

- **BMS (Bare Metal Stent):** these stents are made of steel, cobalt chromium or platinum chromium without a pharmacological coating. The BMS ensures full endothelial coverage in averagely 12 weeks, which lowers the risk of stent thrombosis (ST). However, these stents are associated with a higher risk of restenosis due to neointimal proliferation (20% to 30%).<sup>3</sup> Currently, BMS insertion is recommended in particular contexts:
  - 1) In patients that do not comply with antiplatelet therapy;

- 2) When there is a high bleeding risk;
- 3) If surgical treatment and suspension of antiplatelet therapy are necessary within the first 6 weeks after the PCI.<sup>3,4</sup>

- **DES (Drug Eluting Stent):** The DES consists of a metallic structure with a polymer coating loaded with an antiproliferative agent. This drug is released in a gradual and controlled manner (i.e. elution), which allows for its local diffusion in the vascular tissue, preventing excessive vascular growth (neointimal hyperplasia) and vascular occlusion. Second and third generation DES have a thin cobalt or platinum chromium structure coated with polymers that reduce local inflammation and reduce interference in the reendothelialization process.<sup>3,4</sup>

- **BRS (Bioabsorbable DES):** The BRS (Bioabsorbable DES) consists of a metallic or polylactic acid alloy coated by polymers. Once the drug is eluted, both the polymer and the structure are re-absorbed throughout time, until the stent is fully absorbed.<sup>3,4</sup>

All DES(s) are loaded with two classes of antiproliferative drugs:<sup>3,4</sup>

- 1 - Sirolimus and respective derivatives with cytostatic properties (Everolimus, Zotarolimus, Myolimus e Biolimus).

2 - Paclitaxel – An antineoplastic drug that stabilizes the microtubules prior to cell division, suspending the mitotic cell cycle. Currently, it is rarely used.

**Stent-related complications**

- **Stent Restenosis** – Due to neointimal thickening. Peak incidence at 4-12 weeks after insertion, but it may occur up until 8-9 months after insertion. Suspected when there are reoccurring symptoms.<sup>2,3</sup>
- **Stent thrombosis (ST)** – Sudden occlusion where the stent is inserted resulting from the formation of a platelet-rich thrombus. This can occur at any moment after the insertion of the stent, for an indeterminate number of years (table 1). Although ST is a rare complication, it is associated with a high mortality rate.<sup>2,3</sup> The diagnosis criteria for ST are outlined in table 2.

- Previous stent thrombosis
- 2 - Patient’s drinking/smoking/toxicophilic habits, with a special focus on:
  - Cocaine use
  - Tobacco use
- 3 - Ambulatory care:
  - Type and duration of antiplatelet therapy
- 4 - PCI data:
  - Stent types
  - Number
  - Data and clinical indications for the PCI
  - Stents’ anatomical location
- 5 - Previous anesthetic/surgical history and previous hospitalizations;
- 6 - Existence of any predictive factors of MACE (Major Adverse Cardiovascular Events – table 3).<sup>2,3</sup>
- 7 - Evaluation of thrombotic and bleeding risks (table 4 and 5).<sup>5</sup>

|           |                               |
|-----------|-------------------------------|
| Acute     | 24h after insertion           |
| Subacute  | Between 1 and 30 days         |
| Late      | Between 30 days and 12 months |
| Very late | > 1 year                      |

|                      |  |
|----------------------|--|
| Definitive diagnosis | Angiographic evidence of ST and chest pain with re-occurring alterations in the ECG or the ultrasound, or elevation of biomarkers. Autopsy validation. |
| Likely               | Unexplained death within 30 days after PCI<br>Infarction in the area where the stent was placed  |
| Possible             | Unexplained death > 30 days after PCI  |

|  |
|--|
| <p><b>Clinical</b></p> <ul style="list-style-type: none"> <li>• Revised cardiac risk index &gt;2</li> <li>• Emergent/urgent surgery</li> <li>• Any stent &lt; 4-6 weeks after SCA (especially if biomarkers +)</li> <li>• DES &lt;8-12 weeks and SIHD</li> <li>• Premature discontinuation of platelet anti-aggregation</li> <li>• HTPR (High on-Treatment Platelet Reactivity)</li> <li>• Major perioperative bleeding</li> </ul> |
| <p><b>Related to the procedure</b></p> <ul style="list-style-type: none"> <li>• Incomplete revascularization after PCI</li> <li>• Persistent myocardial ischemia after PCI</li> <li>• Ostial, calcified, long and short lesions</li> </ul>   |

**PREOPERATIVE EVALUATION**

Patients with heart disease who undergo non-cardiac surgery must be evaluated with particular care. Evaluation must be done in a systematic manner and according to current guidelines, as well as in collaboration with cardiology and surgery departments.

Regarding patients who have previously undergone a PCI, pre-anesthetic evaluation must focus on the following factors:

- 1 - Existence of any of the following conditions, and, if so, evaluate how well they are controlled:
  - Diabetes Mellitus
  - Heart failure
  - Kidney disease
  - Previous myocardial infarction (MI)

**DECISION ALGORITHMS**

Currently, there are no specific or consensual recommendations regarding the perioperative care of patients on platelet anti-aggregation drugs. This approach must be multidisciplinary and seek consensus between the different medical specialties, namely cardiology, interventional cardiology, hematology, surgery and anesthesiology.

**ELECTIVE SURGERY**

The management of antiplatelet therapy in elective procedures is one of the most important and controversial issues regarding patients with coronary stents. In patients on DAPT (Dual Antiplatelet Therapy) medication, surgery and invasive procedures are the most frequent cause of temporary suspension of antiplatelet therapy, which increases the risk of MACEs during perioperative care.<sup>6</sup> The alternative is to prolong DAPT, but this would increase the risk of severe perioperative bleeding, which can also increase the risk of cardiac events.<sup>7</sup>





Table 4

|                   |  |
|-------------------|--|
| High risk         | <ul style="list-style-type: none"> <li>• BMS &lt; 6 weeks after elective PCI or &lt;6 months after PCI due to SCA</li> <li>• DES &lt; 8 weeks due to stable ischemic disease &lt; 6 months after SCA, or complex ICP associated with high thrombotic risk</li> <li>• 1st generation BRS &lt; 12 months</li> <li>• &lt;2 weeks after balloon angioplasty</li> <li>• Multiple clinical risk factors for ST</li> <li>• Previous ST (particularly if on antithrombotic therapy)</li> </ul> |
| Intermediate risk | <ul style="list-style-type: none"> <li>• BMS &gt; 6 weeks and &lt;6 months due to stable ischemic disease</li> <li>• DES &gt; 8 weeks &lt; 6 months due to stable ischemic disease</li> <li>• DES or BMS &gt;6 or &lt; 12 months after SCA or complex PCI associated with high thrombotic risk</li> <li>• 1st generation BRS - 1 to 3 years</li> <li>• Some risk factors (except previous ST)</li> </ul>   |
| Low risk          | <ul style="list-style-type: none"> <li>• BMS or DES &gt; 6 months due to stable ischemic disease</li> <li>• DES or BMS due to SCA or complex PCI &gt;12 months</li> <li>• Some risk factors</li> </ul>   |

Most guidelines only provide recommendations for the first 12 months. As a result, many doctors indiscriminately suspend DAPT and adopt procedures with a lower bleeding risk.

Regarding perioperative care, current guidelines advise as follows:<sup>1,4,8</sup>

- BMS - Minimum 4 to 6 weeks of DAPT;
- DES - Minimum of 3 to 6 months of DAPT;
- Continuation of ASA (acetylsalicylic acid) monotherapy in most cases of stable ischemic disease, except when contraindicated due to bleeding risk;
- In post-ACS (Acute Coronary Syndrome) patients or in cases of high ischemic and thrombotic risks, the guidelines recommend DAPT for a period of 12 months (minimum 6 months);
- BRSs - Require 1 year or more depending on thrombotic risk;
- For balloon angioplasties, the guidelines recommend delaying surgery in the first 14 days after the procedure.

### SUSPENSION OF ANTIPLATELET THERAPY

Due to the lack of randomized and well-designed studies that evaluate the risk-benefit ratio of perioperative antiplatelet therapy, decisions regarding this issue are made according to the balance between thrombotic and

Table 5

|   |   |
|---|---|
| Procedures that do not require suspension of platelet anti-aggregants | <ul style="list-style-type: none"> <li>• Dental procedures, including dental extraction</li> <li>• Cataract surgery</li> <li>• Gastric endoscopies, colonoscopies, with or without biopsy</li> <li>• Minor dermatologic procedures</li> </ul>   |
| Low surgical bleeding risk  | Types of surgery that allow adequate hemostasis: <ul style="list-style-type: none"> <li>• Peripheral plastic surgery</li> <li>• Minor orthopedic surgery</li> <li>• Pacemaker or ICD implantation</li> <li>• Herniorrhaphy</li> <li>• Surgical procedures for varicose veins</li> </ul>   |
| High surgical bleeding risk   | Surgeries and procedures associated with a high bleeding risk or in which bleeding is associated with a serious lesion in patients on anticoagulants/anti-aggregants: <ul style="list-style-type: none"> <li>• Urological surgery – transurethral resection of the prostate, nephrectomy, renal biopsy</li> <li>• Colonoscopic polypectomy, especially with sessile polyps with more than 1-2 cm</li> <li>• Surgeries to highly vascularized organs, such as kidneys, spleen and liver.</li> <li>• Intestinal resection surgery with possible bleeding on intestinal anastomosis</li> <li>• Major orthopedic surgery</li> <li>• Tumor resection surgery</li> <li>• Heart surgery</li> <li>• Neurosurgery and medullary procedures</li> <li>• Surgery on posterior chamber of the eyeball</li> <li>• Neuroaxis anesthesia</li> </ul> |

bleeding risks associated with each patient and each surgical procedure.

The suspension of DAPT (namely of the 2 drugs) is associated with an increase of perioperative ST as well as other ischemic myocardial events:<sup>1,3</sup>

- 1<sup>st</sup> - Many patients might not have complete stent endothelialization;
- 2<sup>nd</sup> - The sudden discontinuation of ASA or thienopyridines may generate a rebound phenomenon (platelets that are regenerated display higher responsiveness and aggregation to thrombotic stimuli);
- 3<sup>rd</sup> - Some patients show variable degrees of chronic HTPR (High on-treatment platelet reactivity), which becomes evident once the DAPT is suspended.

The discontinuation of DAPT consists of the suspension of the administration of adenosine antagonists while

Table 6

**Recommendations on whether to proceed with surgery. ACC/AHA: American college of cardiology/American Heart Association; ESC/EACTS European Society of Cardiology/ European Association For Cardio-Thoracic Surgery.**

| Stent type | ACC/AHA (2016)              |          | ESC/EACTS (2017) |                             |          |
|------------|-----------------------------|----------|------------------|-----------------------------|----------|
|            | Time range (months) ICP-CNC | Action   | Any stent        | Time range (months) ICP-CNC | Action   |
| BMS        | <1                          | Delay    | Any condition    | <1                          | Delay    |
|            | ≥ 1                         | Proceed  | No SCA/low risk  | 1-6                         | Consider |
|            |                             |          |                  | ≥ 6                         | Proceed  |
| DES        | ≥ 3                         | Delay    | SCA/high risk    | 1-6                         | Consider |
|            | 3-6                         | Consider |                  | ≥ 6                         | Proceed  |
|            | ≥ 6                         | Proceed  |                  |                             |          |

the ASA therapy is maintained – since most elective procedures can be safely performed on ASA.<sup>1,3</sup>

Certain procedures require the suspension of both drugs (e.g surgery in closed spaces), since any sort of hemorrhage can lead to serious complications.<sup>1</sup>

In practice, if one or both drugs are to be discontinued, it is recommended that clopidogrel, ticagrelor and the ASA are suspended 5 days before the surgery, and that prasugrel is suspended 7 days before.<sup>1,4,5,9</sup> Regarding ticagrelor, the most recent ESC/EACT guidelines recommend that the drug be suspended 3 days before the surgery – although the data presented are extrapolated from cardiac surgery.<sup>1</sup> Table 7 summarizes the current recommendations regarding DAPT suspension.

#### “BRIDGE” THERAPY

This strategy is aimed at patients at high thrombotic risk that will be undergoing “non-delayable” surgery associated with a high bleeding risk. In these cases, DAPT must be suspended. Antiplatelet drugs are preferable, since the formed thrombi are platelet-rich. Although heparin has been claimed to be an effective bridging agent, it has minimal benefits and can induce a prothrombotic state. Therefore, bridging therapy performed with anticoagulants, such as unfractionated heparin, low-molecular-weight heparin

or direct thrombin inhibitors is not recommended in cases where DAPT has been suspended during preoperative care.<sup>1</sup>

Currently, it is recommended that bridging therapy is performed with GIIb/IIIa inhibitors, such as Tirofiban and Eptifibatide, or P2Y<sub>12</sub> antagonists such as Cangrelor (table 8).

The P2Y<sub>12</sub> should be suspended 5 to 7 days before the procedure. The patient is then admitted to the hospital and is administered a continuous intravenous infusion (no bolus) of Tirofiban or Eptifibatide before the procedure. These drugs must be suspended 4-6h and 4-8h before the procedure, respectively. The infusion is restarted in postoperative care until DAPT may be reintroduced. Cangrelor is an alternative as it has a very short half-life – a 0.75 µg/kg/min may be prolonged until a short time after the surgery/procedure.

Although bridging therapy may be relatively safe, ST may still occur. Furthermore, bridging therapy leads to a higher bleeding risk.<sup>1,10</sup>

#### RE-INTRODUCTION OF ANTIPLATELET THERAPY

It is essential that DAPT is re-initiated, preferably within the first 24h after suspension.<sup>5</sup> The re-introduction of the P2Y<sub>12</sub> requires a loading dose, but the ASA can be re-administered at a normal maintenance dosage. Table 9

Table 7

**Perioperative management of dual anti-aggregation.<sup>4</sup>**

|                                 | Low thrombotic risk            | Intermediate thrombotic risk    | High thrombotic risk                                       |
|---------------------------------|--------------------------------|---------------------------------|--|
| Low bleeding risk               | Maintain AAS<br>Suspend iP2Y12 | Maintain AAS<br>Maintain iP2Y12 | Maintain AAS<br>Maintain iP2Y12                            |
| High bleeding risk              | Maintain AAS<br>Suspend iP2Y12 | Maintain AAS<br>Suspend iP2Y12  | Maintain AAS<br>Suspend iP2Y12<br><i>Consider bridging</i> |
| Bleeding risk for closed spaces | Suspend AAS<br>Suspend iP2Y12  | Suspend AAS<br>Suspend iP2Y12   | Suspend AAS<br>Suspend iP2Y12<br><i>Consider bridging</i>  |

**Table 8** Recommendations for bridging with GPIIb/IIIa inhibitors.

|                          | Drug         | Loading dose | Maintenance dose | Half-life | Platelet function recovery | Suspension of infusion before surgery |
|--------------------------|--------------|--------------|------------------|-----------|----------------------------|---------------------------------------|
| GPIIb/IIIa Inhibitors    | Eptifibatide | 180 µg/ kg   | 2 µg/ kg/min     | 2.5h      | 2-4h                       | 4-6h                                  |
|                          | Tirofiban    | 0.4 µg/ kg   | 0.1 µg/ kg/min   | 2h        | 2-4h                       | 4-6h                                  |
|                          | Abciximab    | 0,25 mg/kg   | 0,125mg/kg/min   | 10-15m    | 12h                        | 12h                                   |
| Inhibitor Receptor P2Y12 | Cangrelor    | 30 µg/kg     | 2-4µg/kg/min     | 3-6m      | 30-60m                     | 1-6h                                  |

**Table 9** Recommendations for management of perioperative anti-aggregants.

|                                    | Drug        | Suspension time | Re-introduction dose |              |
|------------------------------------|-------------|-----------------|----------------------|--------------|
|                                    |             |                 | Loading              | Maintenance  |
| P2Y12 Platelet receptor inhibitors | Clopidogrel | 5 days          | 300-600mg            | 75mg/day     |
|                                    | Prasugrel   | 7 days          | 60mg                 | 10mg/day     |
|                                    | Ticagrelor  | 3 to 5 days     | 180mg                | 90mg/2xday   |
| COX-1 Inhibitor                    | Aspirine    | 3 to 5 days     | 325mg                | 75-325mg/day |

displays the relevant recommendations regarding the suspension and re-introduction of platelet anti-aggregation drugs.

### URGENT SURGERY

For patients that need surgical treatment during DAPT, it is important to evaluate the risk-benefit of prolonging DAPT, such as in elective surgery.<sup>6,7</sup> In cases where there is no time to suspend DAPT due to the urgency of the surgical procedure, and where there is a higher bleeding risk, it is important to correct platelet dysfunction.<sup>1</sup>

Therapy with platelet anti-aggregation drugs is one of the most frequent causes of acquired platelet dysfunction. The incidence of thrombocytopenia associated with these agents is approximately 2 to 13%.<sup>11</sup> Given the high bleeding risk associated, it is important that the following measures are considered:

- **Platelet transfusion:** Platelet prophylactic transfusion is not currently recommended given the lack of relevant studies on this procedure. Furthermore, the guidelines indicate that prophylactic transfusion carries a high bleeding risk.<sup>11</sup> In patients on dual antiplatelet aggregation therapy and with an intracranial hemorrhage, platelet transfusion requires an individualized clinical decision based on several clinical factors, including the degree of bleeding and the patient's level of consciousness. For surgeries that involve the central nervous system, the platelets are usually prophylactically transfused if the count is lower than 80 x 10<sup>9</sup> to 100 x 10<sup>9</sup> cells/L, although this is an arguable range.<sup>11</sup>

- **Antifibrinolytic agents** (tranexamic acid or aminocaproic acid) in order to reduce the bleeding risk.
  - ✓ Tranexamic acid should be administered at a dose of 10mg/kg via intravenous infusion, followed by a dose of 1mg/kg per hour ;
  - ✓ ε-aminocaproic acid (10x less potent than tranexamic acid) should be administered at a dose of 150mg/kg via intravenous infusion, followed by a dose of 15mg/kg per hour.

### MONITORING PLATELET FUNCTION

Despite the heterogeneity in the response to platelet anti-aggregation drugs, laboratory tests aimed at evaluating the effect of antiaggregant drugs on platelet function have not been indicated as routine tests, as a solid correlation between their results and the clinical outcome in non-cardiac surgery has not yet been demonstrated.

The evaluation of coagulation tests (PT, aPTT) and the quantitative assessment of platelets do not allow for the proper ascertainment of platelet function.<sup>1,4</sup>

### LIMITATIONS IN THE CURRENT GUIDELINES

Most guidelines are based on low-quality data and on the opinions of experts, which frequently leads to a variation in recommendations. Furthermore, the current guidelines only refer to the first 12 months after the patients undergo PCI.

The most recent guidelines by the American college of cardiology/American Heart Association (ACC/AHA), the European Society of Cardiology/ European Society of Anaesthesiology (ESC/ESA) and the European Association For Cardio-Thoracic Surgery (EACTS) already make recommendations regarding the surgical procedure and perioperative management of platelet anti-aggregation in patients with a stable ischemic cardiac disease (SIHD – defined as stable angina or MI > 12 months without subsequent ischemia vs patients undergoing PCI due to ACS). The guidelines still lack a comprehensive description of specific risk factors and surgical risks.

The chart in Annex I outlines a proposed approach to cases of patients with cardiac stents who will be undergoing non-cardiac surgery.

## CONCLUSION

In recent years, several clinical studies have been conducted in order to compare different pharmacological approaches and the duration of platelet antiaggregant therapy after an acute myocardial infarction or an elective coronary angioplasty. Different strategies have been evaluated that also consider the different characteristics of patients, drugs, different drug combinations and the duration of dual anti-aggregation. As mentioned above, it seems clear that there is no consensus or general guidelines that work as an effective substitute for good judgment and an accurate clinical evaluation of each particular case.

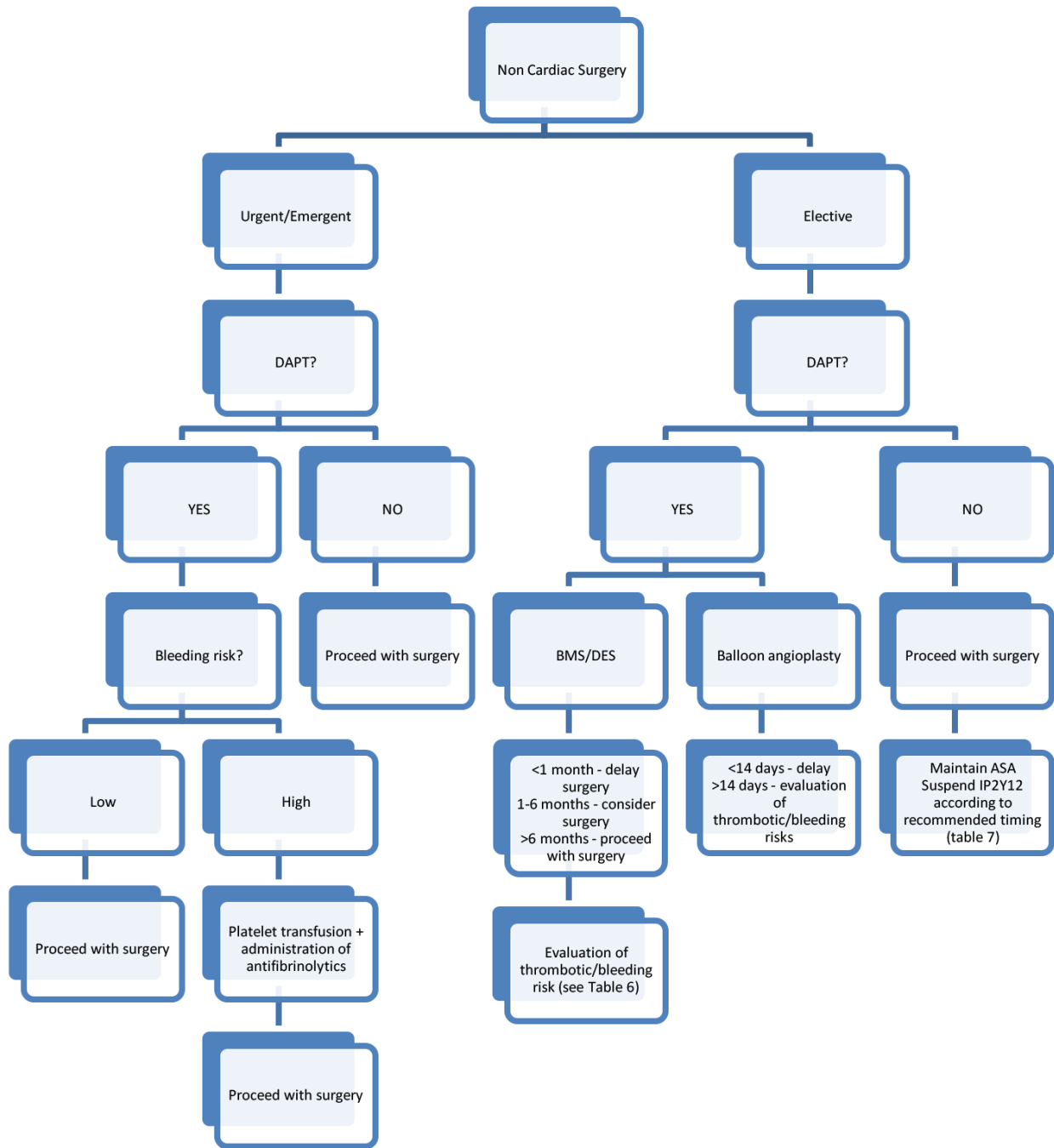
There are tools that, although not meant for patients with cardiac stents, may be useful for evaluating thrombotic and bleeding risk, such as the CHADS-VASC (thrombotic risk) and HAS-BLED (bleeding risk) risk scores.

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**ANNEX 1**

**APPROACH TO CASES OF PATIENTS WITH CARDIAC STENT WHO WILL BE UNDERGOING NON-CARDIAC SURGERY**





# DEFINITIVE TREATMENT OF PRIMARY SPONTANEOUS PNEUMOTHORAX: A 10-YEAR EXPERIENCE

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## Abstract

**Objectives:** Primary spontaneous pneumothorax (PSP) is defined as a pneumothorax without obvious underlying lung disease. Definitive treatment should be offered to patients with recurrent or persistent PSP. The aim of this study was to compare the effectiveness of medical pleurodesis (MP) with video assisted thoracic surgery (VATS) on definitive treatment of PSP.

**Methods:** 10 years' retrospective study of PSP patients that underwent VATS or MP. Baseline characteristics, perioperative and follow-up data were compared.

**Results:** A total of 133 patients were included (MP=54; VATS=79). Baseline characteristics were similar between groups, with a male predominance (MP 83.6 vs VATS 85.5%) with a mean age of 24.78 and 25.81 years old, respectively. Post interventional length of hospital stay was similar (MP 4.94 vs VATS 4.47 days,  $p=0.20$ ), but chest tube duration was longer in the VATS group (MP 2.94 vs VATS 3.56 days,  $p=0.03$ ). The overall complications rate was low with no statistically significant difference between groups (MP 5/54 vs VATS 7/79,  $p=1.00$ ). Regarding the follow-up, MP had a significant higher PSP recurrence rate (MP 11.1% vs VATS 1.3%,  $p=0.042$ ), most occurring over the first two years.

**Conclusion:** Despite both MP and VATS are safe methods with short hospital stay and few complications associated, the results of this study show that VATS had a significantly lower rate of recurrences. Overall, VATS should be offered as the first line treatment to patients with PSP.

## INTRODUCTION

Primary spontaneous pneumothorax (PSP), which is defined as a pneumothorax without obvious underlying lung disease, most commonly occurs in young (between 15-34 years old), tall, lean males.<sup>1,2</sup> This form of presentation has an incidence of 18-28 and 1-6 per 100,000 cases each year for men and women, respectively.<sup>1</sup> Furthermore, the recurrence rate is reported to range between 17% and 54% in the first year following the first episode.<sup>3</sup>

The precise pathogenesis behind PSP is not completely understood. However, blebs and bullae can be visualized ipsilaterally or bilaterally in almost all patients during surgery, medical thoracoscopy or CT scans. These changes visible on the visceral pleura have been called emphysema-like changes (ELCs), which are also recognized as a specific entity and it is generally believed that pneumothorax results from the rupture of ELCs.<sup>3</sup>

Although the management of persistent or recurrent PSP continues to be debated, it is consensual that it must include firstly, evacuation of air and secondly,

prevention of recurrences by ways of medical pleurodesis (MP) or surgical approach. The medical pleurodesis is based on instilling a chemical irritant (usually talc) to achieve a pleural symphysis. The surgical approach includes more complex procedures such as resection of bullae or blebs, partial pleurectomy or mechanical abrasion and instillation of sclerosing agents to close the pleural space and prevent relapses.<sup>1,2,4</sup>

The aim of this study was to analyze the reality of PSP treatment at a tertiary center and to compare the effectiveness of talc poudrage under medical thoracoscopy with video assisted thoracic surgery (VATS).

## METHODS

This was a retrospective single center study, in the period between January, 2008 and December, 2018. All the patients hospitalized with the diagnosis of PSP who underwent definite treatment for PSP (MP or VATS) were screened. The patients were admitted via emergency



department, either directly or referred by other hospitals.

Indications for definitive treatment were the following: recurrence of PSP, persisting air leak (>3–5 days), bilateral pneumothorax and professionals at risk (aircraft personnel, divers). Exclusion criteria included patients with evidence of lung disease, other secondary causes of pneumothorax and patients that had already been submitted to pneumothorax definitive treatment.

Simple talc poudrage was performed via single-port medical thoracoscopy under general anesthesia. Thoracoscopy was carried out in the lateral decubitus position. A 7-mm trocar was inserted into the fourth or fifth intercostal space in midaxillary line and a 0° optical telescope was inserted and connected to a video camera and monitor. The visceral pleura was carefully inspected using supplemental air insufflation when necessary. Sterile asbestos-free talc (2–4 g) was insufflated particularly to the apex. At the end of the procedure a chest drain (24 French gauge) was inserted through the sixth intercostal space in the midaxillary line and connected to underwater seal suction.

The standard surgical approach consisted of three port video-assisted intervention with lung exclusion, either by double lumen intubation or CO<sub>2</sub> inflation and general anesthesia. The procedure always included partial pleurectomy (PP). PP generally started at the level of the anterior incision using blunt dissection. The dissection is carried out until the edge of intercostal muscles posterior and one centimeter lateral of the internal thoracic artery to avoid

damage to these structures. In the apex of the pleural cavity, the pleura is carefully dissected sparing the region of the subclavian artery and vein, again to avoid harm to these structures. Lung tissue with evidence of abnormalities, fistulae or blebs was resected. In the end one chest tube was inserted and connected to a water seal system.

For both groups, criteria for drain removal included the absence of clinical signs of air leak; less than 200cc of serous fluid drainage in the last 24 hours; and complete/acceptable lung expansion.

Clinical records were retrieved and analyzed. All available clinical (medical and nursing) records were reviewed for any mention of procedural or other medical complications. Outpatient files were also reviewed, in order to identify any readmissions or pneumothorax recurrences.

The primary outcome of the study was to compare the recurrence rate of PSP after MP or VATS intervention. Secondary outcomes included: baseline characteristics (age, gender, smoking status, and comorbid conditions) and perioperative data (complications secondary to intervention, post-interventional duration of chest drainage and length of hospital stay).

Categorical variables were presented as counts and percentages, and quantitative variables as means and standard deviation (SD). For group comparison, the chi-square test or Fisher's exact test for categorical variables were used. Student's T (parametric) or Mann-Whitney (nonparametric) tests were used for continuous variables.

**Table 1** Baseline characteristics of patients.

| Variables  | MP group (n=54) | VATS group (n=79) | p value |
|--|-----------------|-------------------|---------|
| Gender, male, n (%)  | 46 (83.6)       | 71 (85.5)         | 0.811   |
| Age, mean (SD), years  | 24.7 (5.31)     | 25.8 (7.85)       | 0.401   |
| Weight, mean (SD), kilograms                                     | 66.2 (10.03)    | 64.1 (10.55)      | 0.538   |
| Height, mean (SD), meters  | 1.74 (0.08)     | 1.80 (0.06)       | 0.04    |
| <b>Risk factors</b>  |                 |                   |         |
| Tobacco smoking, n (%)   | 24 (44.4)       | 57 (72.2)         | 0.02    |
| Cannabis smoking, n (%)  | 2 (3.7)         | 11 (13.9)         | 0.07    |
| Pre-existing conditions n (%)                                    |                 |                   | 0.44    |
| Asthma   | 18,2%           | 22.9%             | 0.532   |
| Rhinitis   | 9,1%            | 22.9%             | 0.041   |
| Others   | 5 (9.3)         | 6 (7.6)           |         |
| <b>Number of PSP events prior to definitive treatment n, (%)</b> |                 |                   |         |
| 0  | 24 (44.4)       | 32 (40.5)         |         |
| 1  | 25 (46.3)       | 32 (40.5)         |         |
| 2  | 3 (5.6)         | 9 (11.4)          |         |
| 3 or more  | 2 (3.7)         | 6 (7.6)           |         |
| Time between the last and present PSP, mean (SD), months         | 11.7 (23.32)    | 16.2 (27.39)      | 0.419   |

**Table 2** Perioperative characteristics.

| Variables  | MP group (n=54) | VATS group (n=79) | p value |
|--|-----------------|-------------------|---------|
| Intervened side, right, n(%)                                 | 33 (61.1)       | 44 (55.7)         | 0.594   |
| Indication   |                 |                   |         |
| Recurrence of PSP (ipsilateral)                              | 24 (44.4)       | 10 (12.7)         | -       |
| Recurrence of PSP (contralateral)                            | 5 (9.3)         | 35 (44.3)         | -       |
| Persisting air leak (>3–5 days)                              | 24 (44.4)       | 33 (41.7)         | -       |
| First episode in professionals at risk                       | 1 (1.9)         | 1 (1.3)           | -       |
| Complications, total, n(%)                                   | 5 (9.2)         | 7 (8.9)           | 1.0     |
| Delayed lung expansion                                       | 1 (1.9)         | 3 (3.8)           | 0.646   |
| Haemothorax  | 0               | 3 (3.8)           | 0.271   |
| Nosocomial pneumonia   | 2 (3.7)         | 1 (1.3)           | 0.158   |
| Other nosocomial infections                                  | 2 (3.7)         | 0                 | 0.566   |
| Post interventional chest tube duration, mean (SD), days     | 2.94 (1.188)    | 3.56 (2.105)      | 0.033   |
| Post interventional length of hospital stay, mean (SD), days | 4.94 (2.609)    | 4.47 (2.846)      | 0.271   |

Subsequently, a multivariate analysis of the selected variables was performed. A p value of <0.05 was considered significant. Statistical analysis was performed with Statistical Package for the Social Sciences (SPSS) 25. The study was approved by the Research Ethics Committee of *Centro Hospitalar Universitário Lisboa Norte*.

## RESULTS

Between January, 2008 to December, 2018 a total of 133 patients with PSP underwent definitive treatment: 54 patients were submitted to MP and 79 underwent VATS. In the surgical group, most cases included PP with bleb resection and talc poudrage (n=75); only 2 cases were submitted to PP alone (n=2) and 2 cases of PP associated to bleb resection (n=2).

Patients' demographics are summarized in table 1. Most of the patients were young male patients (MP 83.6 vs VATS 85.5%, p=0.811) with an average age of 24.7 and 25.8 years old, respectively. Tobacco (MP 44.4 vs VATS 72.2%, p=0.02) and cannabis smoking (MP 3.7 vs VATS 13.9%, p=0.07) were more prevalent among the surgical group. Asthma was the most frequent comorbid condition in both groups (MP 18.5 vs VATS 22.8%, p=0.66), followed

by chronic rhinitis (MP 9.3 vs VATS 22.8%, p=0.06). Marfan syndrome was also found in both groups (MP n=1 vs VATS n=3). Other comorbid diseases included: Rendu-Osler-Weber syndrome (n=1), epilepsy (n=1) and systemic lupus erythematosus (n=1) in MP group; Ehlen Danlos syndrome (n=1), hepatitis C (n=1) and alpha 1 antitrypsin deficiency (n=1) in the VATS group.

Perioperative data is described in Table 2. The most frequent intervened side was the right side in both groups (p=0.594). A significant higher post interventional chest tube duration was found in patients undergoing VATS (MP 2.94 vs VATS 3.56 days, p=0.03). However, there were no significant differences in post interventional length of hospital stay (MP 4.94 vs VATS 4.47 days, p=0.271).

During the postoperative course, the overall complication rate was low and there was no statistically significant difference between groups (MP 5/54 vs VATS 7/79, p=1.0). Delayed lung expansion was found in 1.9% of MP group and 3.8% in VATS group (p=0.646); the mean of chest drain duration was 5 and 10 days, respectively. Haemothorax only occurred in the VATS group in three (3.8%) patients, two needing re-intervention for significant bleeding.

Nosocomial pneumonia was found in two patients in MP group (with one case complicated with pleural effusion and bacteremia with *Serratia marcescens* isolation)

**Table 3** Pneumothorax recurrence.

| Variables                            | MP group (n=54) | VATS group (n=79) | p value |
|--------------------------------------|-----------------|-------------------|---------|
| Recurrence rate, n(%)                | 6 (11.1)        | 1 (1.3)           | 0.042   |
| Follow-up duration, mean (SD), years | 6.57 (2.457)    | 6.47 (2.846)      | 0.832   |

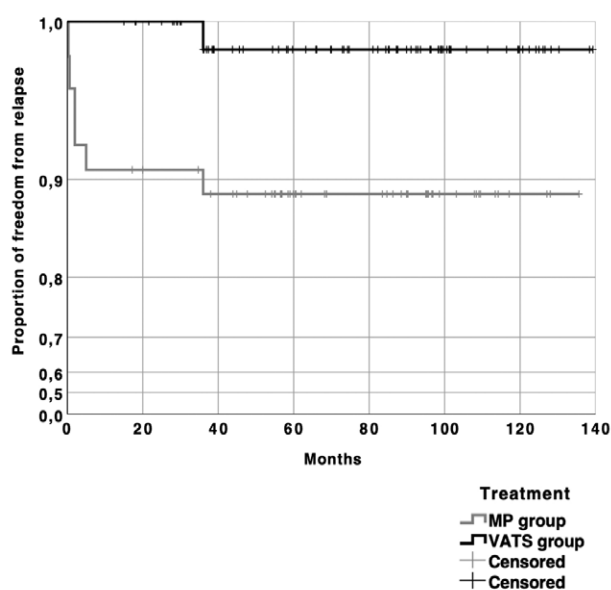


Figure 1

Freedom from pneumothorax recurrence.

and one case in the VATS group with no microbiological agent isolated. Other nosocomial infections were found in the MP group and included infection with no identified focus ( $n=1$ ) and phlebitis associated to bacteremia to *Staphylococcus aureus* ( $n=1$ ).

Regarding pneumothorax recurrence, a significant difference occurred between the groups: the MP group had 6 recurrences opposed to only one from the surgical group (MP 11.1% vs VATS 1.3%,  $p=0.042$ ), as shown in table 3. Most recurrences occurred over the first two years (Fig 1). Median follow-up period was 6.57 (SD 2.457) years in the MP and 6.47 (SD 2.846) years in the VATS group.

## DISCUSSION

The demographic characteristics present in this study were similar from those reported in the literature, with a predominance of young, tall, thin and male patients, in both groups.<sup>4-9</sup>

Asthma and chronic rhinitis were the most frequent underlying conditions. Although some studies categorized asthma to be a secondary cause of pneumothorax, in this study asthmatic patients were included, as there was no evidence of parenchymal pulmonary disease on CT scans, excepted for the presence of ELCs as the remaining cases of the study. The relationship between asthma and pneumothorax is not yet established. Also, no significant difference was found between groups regarding asthma prevalence. As asthma is a common disorder, pneumothorax and asthma can be coincidentally related rather than causally.<sup>10</sup> Further studies are needed to clarify this matter.

A large proportion of patients were active tobacco

smokers. It is known that tobacco smoking is the most important risk factor of PSP.<sup>3,9</sup> Cannabis smoke shares common pathological processes and an overlapping spectrum of lung disease with tobacco smoking; nevertheless, cannabis has been demonstrated to be particularly associated with bullous disease.<sup>11-13</sup>

The main finding of our study is related to recurrence rates. Patients with PSP submitted to MP have a significantly higher recurrence rate comparing to surgery. These results are in line with previous studies that have already demonstrated recurrence rates around 5-7% for simple talc poudrage under medical thoracoscopy<sup>14-17</sup> and 1-2% for surgical treatment of lung lesions and pleuroctomy.<sup>18,19</sup>

Although surgical treatment with VATS is the recommended first line for the definitive treatment of PSP in international guidelines<sup>1,4</sup>, direct comparative trials are lacking. In clinical practice, a large proportion of patients are still submitted to MP. Talc poudrage under thoracoscopy is a safe, cheap and very efficient agent for achieving pleurodesis with a fast recovery of the patients.<sup>18</sup> However, these arguments are surpassed by higher recurrence rates. The MP can be an acceptable approach for pneumothorax prevention in patients who wish to avoid surgery and for patients who present increased surgical risk (eg, bleeding diathesis).<sup>4</sup>

The lower rate of pneumothorax recurrence after surgery may be explained by the additional benefit of techniques such as pleuroctomy, bullectomy and/or lung apex excision, associated to pleurodesis, in the prevention of further episodes.

All surgical interventions were video-assisted. In fact, VATS is associated with reduced complication rates and morbidity, short hospital stays and fast recovery. With these obvious and recognized advantages, thoracotomy is no longer acceptable for these procedures. The use of VATS, can explain the almost similar post-operative results between the two groups in terms of complications, and hospital stay. However, a significant difference was observed in chest tube duration in favor of MP.

Complications were minor and, even though two cases of pneumonia were observed in the MP group, a direct relation to the technique could not be established. No case of severe ARDS was reported.

This study has the inherent limitations of its retrospective nature. Information regarding patient refusal of surgery was not obtained but, it is also possible that MP was offered as an alternative procedure.

In conclusion, despite both talc poudrage under medical thoracoscopy and VATS are safe methods with short hospital stay and few complications associated, the results of this study show that surgical intervention had a significantly lower rate of recurrences. Overall, VATS should be offered as the first line treatment to patients with PSP.<sup>1,4</sup> In patients that are either too frail or who present increased surgical risk (eg, bleeding diathesis) and in situations where thoracic surgery is inaccessible, medical pleurodesis may be appropriate.<sup>1,4</sup>

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# DIFFERENCES IN ANTHROPOMETRIC MEASURES BETWEEN CRITICAL LIMB THREATENING ISCHAEMIA AND INTERMITTENT CLAUDICATION IN PATIENTS UNDERGOING AORTO-BIFEMORAL BYPASS

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## Abstract

**Objective/Background:** Peripheral artery disease (PAD) is an important manifestation of systemic atherosclerosis. Obesity is a risk factor for atherosclerosis and for cardiovascular events. However, the relationship between obesity and PAD is unclear. We hypothesized that anthropometric measures of adiposity, in particularly of central obesity will be associated with PAD severity, in patients undergoing aorto-bifemoral bypass.

**Methods:** A prospective observation study was conducted. From 2009 and 2012 a total of 46 males who underwent aorto-bifemoral bypass were enrolled prospectively. 17 with intermittent claudication (IC) and 29 with chronic limb threatening ischemia (CLTI). They were followed for 5 years. The anthropometric measures, weight, body mass index (BMI), waist circumference (WC), waist-to-hip ratio (WHR) and the seric levels of hemoglobin, triglycerides, and albumin were recorded. The mortality and cardiovascular events in following five years were also registered.

**Results:** The groups did not differ in the mean age (IC  $60.69 \pm 7.46$  versus CLTI  $64.51 \pm 8.42$  years,  $p=0.712$ ), diabetes (IC 18% versus CLTI 45%,  $p=0.06$ ), hypertension (IC 70% versus CLTI 52%,  $p=0.21$ ), hypercholesterolemia (IC 18% versus CLTI 45%,  $p=0.47$ ) and smoking habits prevalence (IC 100% versus CLTI 86%,  $p=0.11$ ). The anthropometric measures: weight, WC and WHR were significant lower in CLTI compared to IC patients (IC  $72.74 \pm 9.84$  Kg versus CLTI  $65.92 \pm 10.89$  Kg,  $p=0.043$ ; IC  $98.65 \pm 8.19$  cm versus CLTI  $89.38 \pm 15.91$  cm,  $p=0.017$ ; IC  $1.06 \pm 0.06$  versus CLTI  $1.01 \pm 0.06$ ,  $p=0.038$ ). The serum levels of hemoglobin, albumin and triglycerides were also lower in CLTI patients (IC  $14.40 \pm 1.63$ g/dL versus CLTI  $13.3 \pm 1.89$ g/dL,  $p=0.048$ ; IC  $4.6 \pm 0.81$ g/dL versus CLTI  $4.3 \pm 0.67$ g/dL,  $p=0.007$ ; IC  $212 \pm 95.60$ mg/dl versus CLTI  $111 \pm 41.53$  mg/dL,  $p=0.001$ ). No relation was found between the anthropometric measures at admission and the cardiovascular events or mortality at five years.

**Conclusion:** CLTI patients had lower anthropometric measures of obesity, when compared to IC patients. These results could be explained by the fact that CLTI patients with severe atherosclerotic disease are in a state of chronic inflammation, with consequent cardiometabolic demands and catabolism.

## INTRODUCTION

Peripheral artery disease (PAD) is an important manifestation of systemic atherosclerosis.<sup>1,2,3</sup> It is characterized by arterial stenosis and occlusion of arteries in the lower extremities.<sup>1,2,3</sup> PAD prevalence in adults is about 20% and affects 27 millions person in Europe and US.<sup>3,4,5,6</sup> Up to

44% of symptomatic patients have atherosclerosis in the aorta and iliac arteries.<sup>3</sup>

PAD coexists with other ischemic events.<sup>3,4,7</sup> The risk of myocardial infarction, stroke or cardiovascular death is substantially increased in patients with PAD.<sup>1,3,7,8,9</sup> Obesity is a risk factor for atherosclerosis, coronary heart disease, cardiovascular events and all-cause mortality.<sup>10,11,12</sup> However,

the relationship between obesity and PAD is unclear.<sup>10</sup> It has been demonstrated that central obesity, but not generalized obesity is associated with PAD.<sup>5</sup> For others, PAD has been linked with a decreased body mass index (BMI) values, or no association was found.<sup>3</sup>

In a study conducted in patients with aortoiliac disease the authors concluded that waist-hip ratio (WHR) over 1.02 and percent of body fat over 26.5% are significant predictors of aortoiliac PAD, independent from blood pressure, cholesterol level and body mass index.

We hypothesized that anthropometric measures of adiposity, in particularly of central obesity, would be associated with PAD severity in patients submitted to aorto-bifemoral bypass. The aim of this study was to compare the anthropometric measures of IC versus CLTI patients, in subjects with indication for aorto-bifemoral bypass. The second objective was to analyze the relation between anthropometric measures at admission and the cardiovascular events and mortality in the following five years in this group of patients.

## MATERIAL AND METHODS

### Patients

#### • Inclusion criteria:

1. Male.
2. Aorto-iliac disease with indication to aorto-bifemoral bypass according to the decision of the Vascular Surgery department.

#### • Exclusion criteria:

1. Bedridden individuals.
2. Previous endovascular revascularization.
3. Other diseases that may be responsible for body composition changes or pro-inflammatory state: recent diet change, active malignancy, auto-immune disease, chronic renal failure (GFR <30 mL/min/1.73m<sup>2</sup>) or heart failure in the past 3 months.
4. Subjects who refused to participate in the protocol.

According to the inclusion and exclusion criteria, consecutive patients proposed to aorto-bifemoral bypass were included.

The study variables were collected at hospital admission before the surgical intervention, between 2009 and 2012. No clinical or interventional procedure was performed beyond what was already deemed the best treatment for the patient's condition.

Cardiovascular events and mortality occurring in the five following years were registered according to the Portuguese government database Sclinico. All the records were collected by one operator.

### Ethical considerations

Ethics approval for data collection and cohort evaluation were obtained from the Ethics Committee of the local Hospital. The study was conducted according to Helsinki declaration, national and European guidelines for

clinical research. The confidentiality of clinical records was assured for both patients' information and processing of biological samples. All the participants signed the informed consent.

### Determined variables

#### • Clinical characteristics at admission

Patients' age, co-morbidities and medication taken at admission were recorded. Arterial hypertension was defined as requiring treatment with oral antihypertensive agents or as systolic blood pressure  $\geq 140$  mmHg and/or diastolic  $\geq 90$  mmHg. Diabetes was considered if the patient was taking anti-diabetic medications, fasting glycaemia  $\geq 126$  mg/dL, or glycated haemoglobin (HbA1c)  $\geq 6.5\%$ . The diagnosis of dyslipidemia was described as requiring treatment with statins or a low density lipoprotein (LDL)  $\geq 130$  mg/dL, total cholesterol  $\geq 200$  mg/dL or plasma triglycerides  $\geq 200$  mg/dL. The smoking habits were classified as active smoker, former smoker or non-smokers and quantified in pack-years (multiplying the number of packs of cigarettes smoked per day by the number of years the person has smoked). Former smoker was defined as smoking cessation for at least six months.

CLTI was defined as ischemic rest pain or tissue loss (ulceration or gangrene). Ischemic rest pain was considered if the patient describes pain for more than for >2 weeks, affecting the forefoot, worse with recumbency, relieved by dependency and with an ankle pressure less than 40-50 mmHg (not valorized in the presence of medial calcinosis). Tissue loss to CLTI includes gangrene of any part of the foot or nonhealing ulceration and with an ankle pressure less than 50-70 mmHg (not valorized in the presence of medial calcinosis).

#### • Cardiovascular events and mortality five years later

Hospital mortality of any cause, hospital admission for carotid endarterectomy, stroke, angina and myocardial infarction were recorded in the following five years.

### Anthropometric measurements

The measurements were taken after 5 minutes of rest in a comfortable room. The subjects' height and weight were measured while they wore indoor clothes and no shoes. BMI was calculated dividing the weight by height squared (kg/m<sup>2</sup>). Waist circumference (WC) was measured at the approximate midpoint between the lower margin of the last palpable rib and the top of the iliac crest in the horizontal position, using the anthropometric tape. The hip circumference measurement was taken around the widest portion of the buttocks. WHR was calculated as waist circumference divided by hip circumference. Ankle brachial index (ABI) was determined with a handheld Doppler and an aneroid sphygmomanometer manual blood pressure. The measurements taken were the systolic pressure at the brachial artery, anterior tibial artery, posterior tibial artery and peroneal artery. Three measures in each point were recorded in each arm and foot. The ankle brachial index was calculated for each leg as the ratio of the higher systolic



pressure in the ankle by the higher systolic pressure in the arm. The blood pressure was determined with the patient seated. Three measurements, spaced 2 min apart, was recorded with an electronic sphygmomanometer in both upper limbs, using an appropriate cuff size for arm circumference.

Fasting blood was sampled to ascertain levels of hemoglobin, glucose, glycosylated hemoglobin A1c, total cholesterol, HDL-cholesterol, triglycerides, creatinine, albumin. All assessments were performed by a single laboratory.

### Statistical analysis

Results are expressed as means with standard deviations or as percentages unless otherwise stated. Continuous variables were compared using the Student t test. The X2 test was used to compare the prevalence of categorical data.  $P < 0.05$  was considered statistically significant for all test.

### RESULTS

168 patients were proposed to aorto-bifemoral bypass during the study period. 46 patients (all males) fill the inclusion criteria: 17 with IC and 29 with CLTI (Figure 1). Demographic characteristics of subjects are presented in Table 1. The groups did not differ in the average age, diabetes, hypertension, total cholesterol and smoking habits prevalence. However, the CLTI group had a lower prevalence of patients with hypertriglyceridemia (CLTI 6% versus IC 53%,  $p=0.039$ ). ABI of the studied population was  $0.346 \pm 0.23$  ( $0.45 \pm 0.17$  for IC and  $0.27 \pm 0.23$  for CLTI,  $p=0.0085$ ). At admission CLTI patients were less like

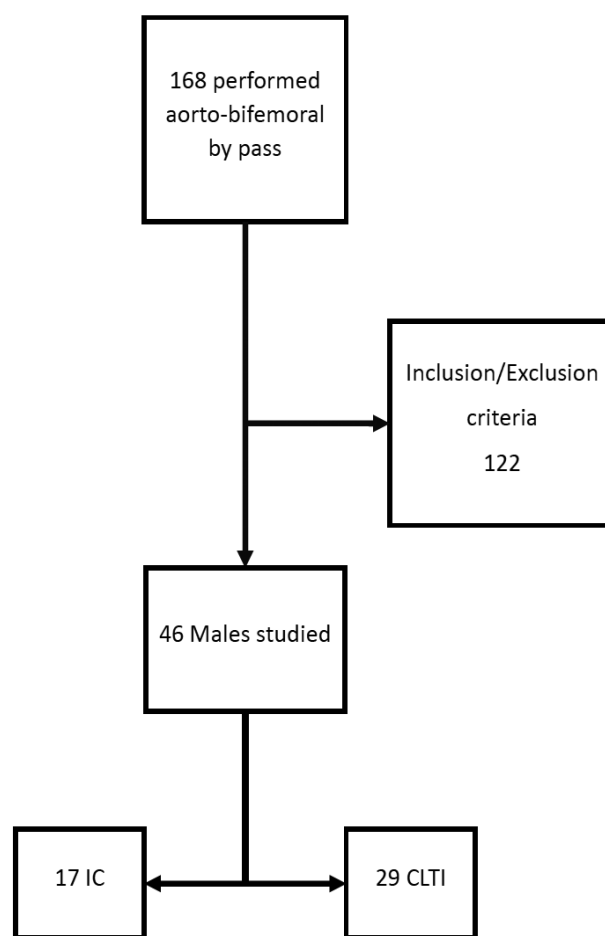


Figure 1 Patients fluxogram.

**Characterization of the population according to PAD severity. Characterization of IC and CLTI study groups according to the age, prevalence of hypertension, diabetes, smoking habits and number of patients with hypertriglyceridemia, hypercholesterolemia, taking antiplatelets and statins. The difference in ABI index is also shown.**

Table 1

|                            | IC (n=17)        | CLTI (n=29)      | P value   |
|----------------------------|------------------|------------------|-----------|
| Age (years), mean $\pm$ SD | 60.69 $\pm$ 7.46 | 64.51 $\pm$ 8.42 | $p=0.712$ |
| Hypertension, %            | 70.00            | 51.72            | 0.21      |
| Diabetes, %                | 17.60            | 44.80            | 0.06      |
| Smoker/Ex-smoker, %        | 100.00           | 86.20            | 0.11      |
| Hypertriglyceridemia, %    | 53.33            | 5.88             | 0.039*    |
| Hypercholesterolemia, %    | 33.33            | 22.22            | 0.47      |
| Antiplatelet, %            | 82.35            | 41.38            | 0.0001    |
| Statins, %                 | 64.70            | 37.93            | 0.079     |
| ABI, mean $\pm$ SD         | 0.45 $\pm$ 0.17  | 0,27 $\pm$ 0.23  | 0.0085*   |

P values denotes the results from the Student t test and from the X2 test as appropriate. \* $P < 0.05$  was considered statistically significant for all test. Abbreviation: Antiplatelet- Taking antiplatelet at hospital admission. Statins- Taking statins at hospital admission. ABI- Ankle-brachial index. SD - Standard deviation.

**Table 2** Distribution of the anthropometric measures and serum measurements, according to PAD severity

|                          | IC (n=17)    | CLTI (n=29)   | P value |
|--------------------------|--------------|---------------|---------|
| BMI (Kg/m <sup>2</sup> ) | 25.10±5.01   | 23.52±3.59    | 0.27    |
| Weight (Kg)              | 72.74±9.84   | 65.92±10.89   | 0.043*  |
| WC (cm)                  | 98.65±8.19   | 89.38±15.91   | 0.017*  |
| WHR                      | 1.06±0.06    | 1.01±0.06     | 0.038*  |
| Hb (g/dL)                | 14.40±1.63   | 13.3±1.89     | 0.048*  |
| Platelets                | 234.53±63.70 | 267.67±103.77 | 0.20    |
| Leucocytes               | 7.75±1.87    | 8.23±2.89     | 0.56    |
| NLR                      | 2.98±2.07    | 2.55±1.57     | 0.44    |
| Albumin (g/dL)           | 4.60±0.81    | 4.30± 0.67    | 0.007*  |
| Triglycerides (mg/dL)    | 212±95.60    | 111±41.53     | 0.001*  |

Values presented correspond to mean ±standard deviation. P values denotes the results from the Student t test. \* P <0.05 was considered statistically significant for all tests. Abbreviation: BMI- body mass index, WC-waist circumference, WHR- waist hip ratio, Hb- hemoglobin, NLR- neutrophil-lymphocyte ratio.

**Table 3**

**Relation between anthropometric measures and cardiovascular events and mortality at 5 years. Hospital admission due to angina, myocardial infarction, ischemic and haemorrhagic stroke, carotid endarterectomy and mortality were recorded in the following 5 years after the admission to perform aorto-bifemoral bypass.**

|                            | BMI (Kg/m <sup>2</sup> ) | Weight (Kg) | WC (cm)    | WHR       |
|----------------------------|--------------------------|-------------|------------|-----------|
| CAD                        | 27.86±2.01               | 80.5±10.47  | 107.5±6.05 | 1.05±0.05 |
| Non-CAD                    | 23.78±4.27               | 67.69±10.53 | 92±14.09   | 1.03±0.44 |
| P value                    | 0.069                    | 0.058       | 0.074      | 0.285     |
| Stroke                     | 20.59±3.12               | 56.78±2.51  | 84±8.48    | 0.94±0.05 |
| Non-stroke                 | 25.05±4.27               | 70.00±10.80 | 95±14.17   | 1.04±0.06 |
| P value                    | 0.225                    | 0.120       | 0.357      | 0.235     |
| Carotid endarterectomy     | 27.61±11.05              | 77±10.54    | 92±11.93   | 1.03±0.10 |
| Non-carotid endarterectomy | 24.44±3.55               | 70.00±10.76 | 94.5±14.48 | 1.04±0.06 |
| P value                    | 0.436                    | 0.130       | 0.740      | 0.940     |
| Mortality                  | 27.61±11.05              | 77±10.54    | 92±11.93   | 1.03±0.10 |
| Non-Mortality              | 24.44±4.36               | 70.00±10.93 | 94.0±14.69 | 1.03±0.07 |
| P value                    | 0.550                    | 0.618       | 0.807      | 0.623     |

Values presented correspond to mean ±standard deviation. P values denotes the results from the Student t test. \* P <0.05 was considered statistically significant for all tests. Abbreviation: CAD- coronary heart disease; carotid endarterectomy- patient submitted to carotid endarterectomy; BMI- body mass index, WC-waist circumference, WHR- waist hip ratio.

to be taking antiplatelets, as well as statins. The Table 2 shows the anthropometric measures and serum evaluations in the two groups. The weight, WC, WHR and the serum levels of hemoglobin, albumin and triglycerides were significant lower in CLTI compared to IC patients. No difference was found between the groups about platelets, leucocytes and neutrophil-lymphocyte ratio (NLR) levels. No relation was found between the anthropometric

measures and the cardiovascular events or mortality at 5 years (Table 3).

## DISCUSSION

Our hypothesis was not demonstrated. We hypothesized that anthropometric measures of adiposity, in

particularly of central obesity would be associated with PAD severity, in patients with aorto-iliac disease undergoing aorto-bifemoral bypass. Instead we found that BMI, weight, WC, WHR were lower in CLTI patients when compared to IC, in this sample. Patients with a more severe form of atherosclerosis had lower anthropometric measurements, including those associated with visceral obesity (WC, WHR).

Our initial hypothesis was based on the fact that obesity promotes endothelial dysfunction, systemic inflammation, and a prothrombotic state, having a role in atherosclerosis.<sup>2,12</sup> BMI and weight are a measure of overall fatness.<sup>7</sup> However, BMI and weight do not estimate body composition, do not provide information about the distribution of fat and cannot distinguish between lean and fat mass.<sup>3,4,7</sup> WC and WHR are measures of abdominal/visceral obesity and are associated with cardiovascular morbidity and mortality, including stroke, congestive heart failure, myocardial infarction cardiovascular death and PAD.<sup>2,7,10,13,14,15</sup> Visceral adipose tissue is the most metabolically active fat store, producing pro-atherogenic and inflammatory mediators and reducing the secretion of vascular-protective adipokines.<sup>4,14,15,16,17</sup> Abdominal obesity is related to metabolic changes, such as dyslipidemia, type 2 diabetes mellitus, hypertension, inflammation, oxidative stress and hypercoagulability, which are all associated with an increased cardiovascular risk.<sup>14,18</sup> Obesity, particularly abdominal adiposity is associated with PAD severity.<sup>14,19</sup>

The two groups analyzed in this study were both proposed for aorto-iliac revascularization and were relatively homogenous, in the distribution of cardiovascular risk factor (except triglycerides) and age. The groups differ in ABI, as expected.

In this study, weight, WC, WHR were significant lower in CLTI patients when compared to IC. These results agree with a previous study in aortoiliac PAD patients (only one), that showed that all anthropometric parameters (BMI, WC, WHR) strongly inverse correlated with ABI.<sup>3</sup>

In severe atherosclerotic disease, there is a state of chronic inflammation, with a higher cardiometabolic demands and consequently lower body fatness.<sup>20,21</sup> CLTI patients have a reduction in their mobility with muscle atrophy and consequently lower mean mass[18]. These changes are associated with low albumin, nutritional dysfunction and immunity compromise.<sup>20</sup> In this study, we found lower seric levels of albumin, triglycerides and hemoglobin in CLTI group (and these differences were statistically significant between the groups). In fact, the literature reports that BMI also had significant positive correlations with triglyceride and albumin.<sup>9</sup> Shah also reported that anemia and malnutrition are common in CLTI patients.<sup>22</sup> CLTI patients also suffer from chronic inflammation, ulceration and gangrene that contribute to chronic anaemia.<sup>22</sup> Salomom realized that in 106 patient with CLTI, the prevalence of malnutrition was 75.5%.<sup>23</sup> Due to this data the management of PAD patients includes the evaluation of the patient nutritional status and prevention of protein waste.<sup>21</sup>

We did not find any differences in platelets or leucocytes count or neutrophil-lymphocyte ratio (NLR) between

the groups. We would expect increased leucocytes in CLTI patients, as reported by other authors, due to an increased in inflammation, endothelial damage, procoagulant effect and microvascular damage.<sup>24</sup> It was also described that NLR is significantly associated with the presence of CLTI in 2121 patients with PAD.<sup>25</sup>

We noted that CLTI patients were less likely to be taking antiplatelets as well as statins. These differences could be explained by the fact that IC patients were already followed by a vascular surgeon before the hospital admission. The majority of CLTI were admitted from the emergency room and were not properly medicated.

In this study there was no association between anthropometric data and the incidence of stroke, carotid endarterectomy, coronary heart disease and mortality. The lack of results could be explained by the sample size and by the fact that just hospital data was taken in account. In the literature, the association between anthropometric measures of obesity and cardiovascular events in PAD patients is controversial. Kumakura demonstrated that low BMI is risk factor for mortality in PAD patients.<sup>9</sup> Murata proved that, in CLTI patients who underwent endovascular therapy, the low weight was related with poorer prognosis at 3 years.<sup>9,26</sup> Some authors showed that abdominal obesity is a strongly predictor of cardiovascular events.<sup>4,27</sup> Cronin and other authors did not find an association between visceral adipose volume and cardiovascular events in the PAD population.<sup>18,27</sup>

## LIMITATIONS

The sample size is small. The anthropometric measures do not rigorously determine the body composition, which would be better determined with a CT scan or MRI. The study cannot be applied to atherosclerotic disease in other anatomic locations, because it is limited to PAD patients with aorto-iliac disease. The inclusion of surgical patients may introduce bias. BMI increases the risk of postoperative surgical site infections, pneumonia and prolonged ventilation. The surgeons tend to propose obese patients to endovascular repair. The anthropometric measures were determined at baseline and could have changed during follow-up. Dietary habits, alcohol consumption, physical activity were not determined.

## CONCLUSION

In this small series of patients who underwent aorto-bifemoral bypass, the CLTI had lower anthropometric measures of obesity (BMI, weight, WC, WHR), when compared to IC patients. There is no association between the anthropometric data at admission and the incidence of stroke, carotid endarterectomy, coronary heart disease and mortality. Further studies are needed to corroborate this data. However, this study calls attention to importance of the metabolic optimization of the PAD patients.

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# RIGHT VENTRICULAR OUTFLOW TRACT PSEUDO-ANEURYSM AFTER RECONSTRUCTION WITH SMALL INTESTINAL SUBMUCOSAL (CORMATRIX) PATCH – A WORD OF CAUTION

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## Abstract

*Tetralogy of Fallot is very prevalent with correction techniques well standardized. Whenever infundibular incisions are needed, patch reconstruction seems mandatory. Recently, the small intestinal submucosal (CorMatrix, MAC's Medical Group,) patch was introduced, with optimal results in pre-clinical studies. However, clinical results do not match its pre-clinical promises, particularly when used in right ventricular outflow tract and pulmonary artery reconstructions. We describe a case of Tetralogy of Fallot for which small intestinal submucosal (CorMatrix) patch was used as a trans-annular patch, with development of a massive pseudo-aneurysm.*

## INTRODUCTION

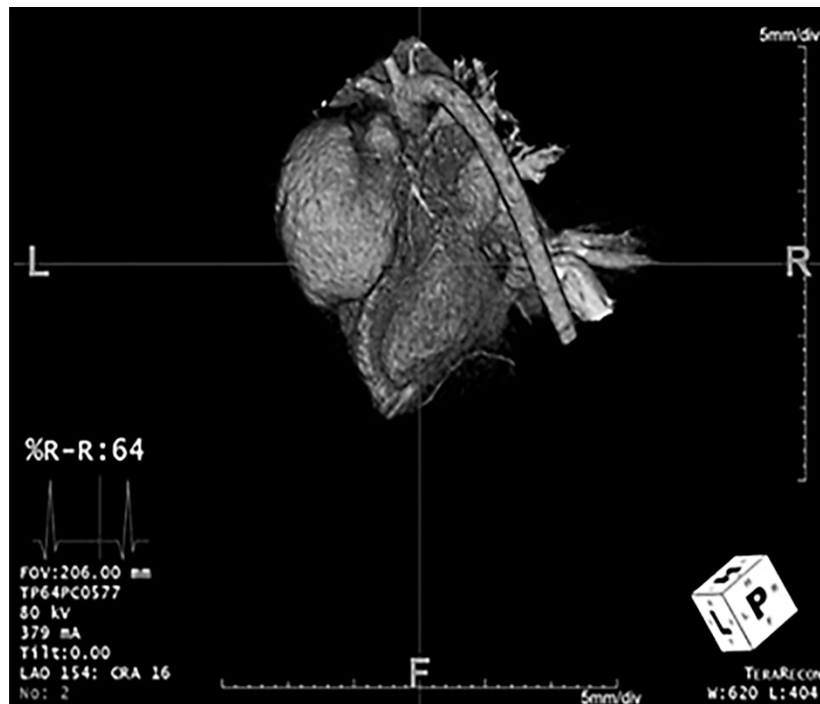
Tetralogy of Fallot (TOF) is very prevalent with correction techniques that are well standardized - all producing predictable results with an immediate mortality risk below 2%.<sup>1</sup> Whenever infundibular incisions are needed, patch reconstruction seems mandatory and options vary between synthetic and biological materials.<sup>2</sup> Recently, small intestinal submucosal (CorMatrix) patch was introduced and claimed having perfect stability and low incidence of retraction and calcification, given its decellularization process.<sup>3</sup> We describe a case of TOF for which small intestinal submucosal (CorMatrix) patch was used as a trans-annular patch, with apparent immediate good results but soon developing a massive pseudo-aneurysm and severe right ventricle out-flow tract obstruction (RVOTO).

## MATERIAL AND METHODS

A 5 years old patient with TOF and hypoplastic intrapulmonary pulmonary arteries was initially submitted to a right modified Blalock Taussig shunt in 2013. Five years later, he underwent total correction, consisting of trans-atrial ventricular septal defect closure with a Dacron

patch and RVOTO relieve by muscular section and extended infundibular, main pulmonary trunk and bifurcation enlargement, using a trans-annular single small intestinal submucosal (CorMatrix) patch. Taking into consideration the hypoplastic pulmonary arteries, we created a 3mm atrial septal defect. Weaning of bypass was uneventful with direct systolic right ventricle pressure measurement of 38 mm Hg. We collected blood samples at the pulmonary artery, superior vena cava and aorta and performed gasometric analyze. There was no evidence of intra-cardiac shunt, despite the presence of an iatrogenic atrial septal defect. Immediate postoperative period was uneventful. An echocardiogram at discharge revealed no residual pressure gradient across RVOT, but a residual gradient of 70 mmHg was present at the level of pulmonary artery (PA) origin, bilaterally. There was mild pulmonary valve regurgitation. Taking into consideration that the patient was clinically asymptomatic, with pulse oximetry values of 99-100%, he was discharged home, with indication of echocardiographic reevaluation one month later. The echocardiogram revealed systemic right ventricle pressure and stenosis at the origin of right PA (5,7 mm) and left PA (3 mm). Pulmonary regurgitation was now free. There were no signs of infection. An angio-CT scan evidenced a giant RVOT pseudo-aneurysm (66 x 46 mm) compressing pulmonary

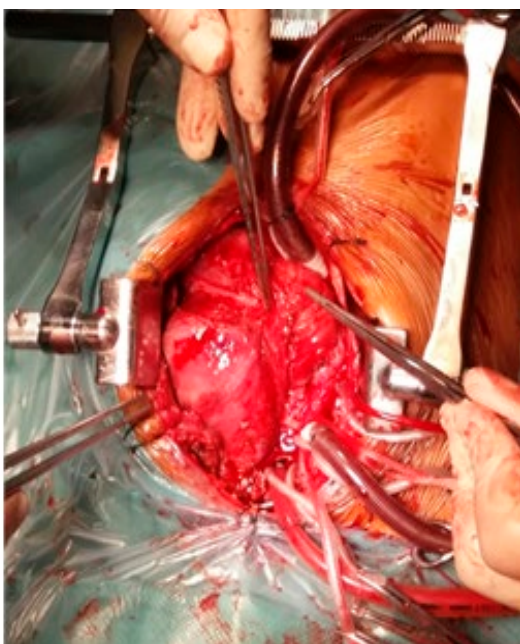




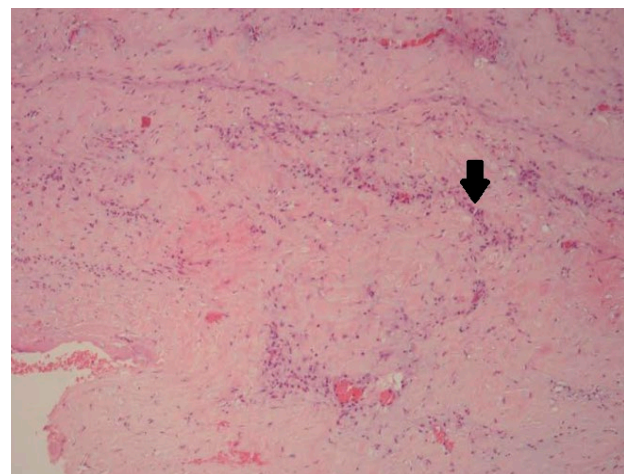
**Figure 1** Angio-TC showing pseudo-aneurysm dimension and space relationship.

bifurcation and producing bilateral branch stenosis (Figure 1). Patient was scheduled for urgent reoperation. RVOT area was dissected, revealing a massive pseudo-aneurysm (Figure 2), the wall consisting of patch remains and organized clots. Visually, the patch seemed to have been disintegrated. There was no evidence of rupture of the suture lines. There was massive inflammation and adhesions, the

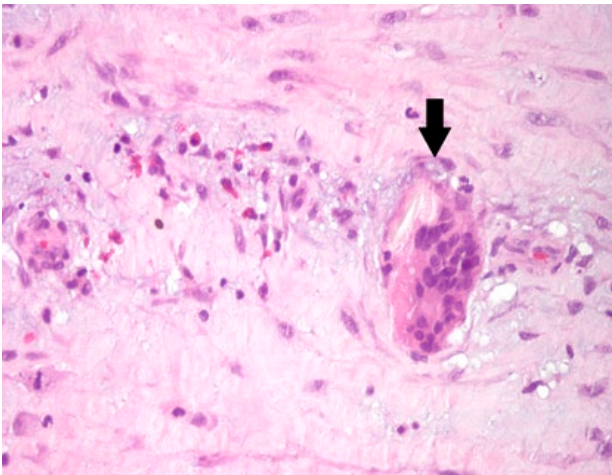
PA bifurcation was compressed and grossly distorted by the pseudo-aneurysm. The pseudo-aneurysm was resected and RVOT continuity was re-established using a Contegra 16 graft interposed between the slit open bifurcation and the ventricular incision. A patch of pericardium was used to augment the origin of both PA's. Post-operative period was uneventful. A fragment of the pseudo-aneurysm wall was sent for pathology, showing small fragments of residual patch material, engulfed in fibrosis, hemorrhage and mononuclear cell infiltrate consisting on eosinophils and giant multinuclear cells in a foreign body reaction (Figure 3 and 4).



**Figure 2** Intra-operative appearance of the pseudo-aneurysm.



**Figure 3** Histological exam of pseudo-aneurysm wall with a small amplification with H&E showing marked eosinophilic infiltration (arrow).



**Figure 4**

*Histological exam of pseudo-aneurysm wall with a great amplification with H&E showing a giant multinucleated cell in a foreign body reaction (arrow).*

## RESULTS

We describe a case of TOF and hypoplastic arteries, corrected by a trans annular patch using small intestinal submucosal (CorMatrix) patch. One month later, the patch material was disintegrated leaving place to a massive and fast-growing pseudo-aneurysm, compressing PA bifurcation. There was no infection by clinical and laboratory methods and no evidence of rupture of the suture lines.

## DISCUSSION

Small intestinal submucosal (CorMatrix) patch was firstly used in 2010 and received FDA approval as a pericardial substitute and for intra cardiac corrections. This is a de-cellularized patch having the needed protein structure to ensure constructive remodelling. The reabsorption process starts early but extends till 3-6 months, in pre-clinical studies. Supposedly the host tissue would replace the patch material between 3 and 6 months. Previous reports showed conflicting results regarding the use of this type of patch for RVOT and or pulmonary reconstruction, namely in the paediatric group, with a very high rate of reoperations. Among these, there are two cases reporting TOF repair, both needing reoperation, at 2 months and 13 months,

and showing similar pathology findings, as for our case.<sup>4</sup> The only multicentric study evolving over 100 cases with small intestinal submucosal (CorMatrix) patch also revealed a high incidence of reoperation, particularly on the right side of the heart.<sup>5</sup> Clinical results regarding the use of small intestinal submucosal (CorMatrix) patch do not match its pre-clinical promises, particularly for use in the RVOT and pulmonary artery reconstructions.<sup>6</sup>

In our case, the absence of signs or symptoms of infection and the integrity of the suture lines suggest that the pseudo-aneurysm resulted of the characteristics of the patch material, in the context of residual right ventricular hypertension.

## CONCLUSION

We understand it is a single case report. However, in view to literature evidence and our present case, small intestinal submucosal (CorMatrix) patch should be used carefully for right heart reconstructions.

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# AORTIC VALVE REPLACEMENT IN ALKAPTONURIC OCHRONOSIS

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## Abstract

*Alkaptonuria is an autosomal recessive inborn error of metabolism of the aromatic amino acids. Deficiency of the homogentisate 1,2-dioxygenase leads to an increased blood and urinary concentration of homogentisic acid resulting in a slow accumulation of its oxidation products in the connective tissues (ochronosis). The most common clinical manifestation of ochronosis is arthropathy whereas cardiac involvement is very infrequent. We report the case of a patient with ochronotic involvement of the aortic valve who underwent a valve replacement. Some aspects of pathogenesis, and treatment are discussed.*

## INTRODUCTION

Alkaptonuria is a rare autosomal recessive inborn error of metabolism of aromatic amino acids caused by a deficiency of homogentisate 1,2-dioxygenase (HGO) activity. The deficiency of HGO activity has been linked to chromosome 3q21-q23 with over 80 mutations discovered. The inability to break down the homogentisic acid (HGA) leads to the accumulation of HGA and its oxidized product benzoquinone in various tissues and fluids. Cell damage results from the deposition of a melanin-like pigment - a polymerized form of benzoquinone with high affinity for connective tissues- leading to characteristic bluish-black pigmentation known as ochronosis.<sup>1,2</sup>

The birth prevalence of alkaptonuria is estimated at around 1/250.000 to 1/1000.000 individuals. The condition is more common in the Dominican Republic and Slovakia where it affects up to 1 in 19.000 individuals.<sup>1</sup>

Alkaptonuria causes a triad of HGA aciduria, ochronotic connective tissue pigmentation and degenerative arthritis of axial and peripheral joints. Alkaptonuric ochronosis of the cardiovascular system is rare. The heart valves, aorta, endocardium, pericardium and coronary arteries may be affected, with the aortic valve more frequently involved.<sup>1,2</sup>

We report the case of a patient with alkaptonuric ochronosis of the aortic valve who underwent a bioprosthetic valve replacement.

## CASE REPORT

A 71-year old woman with symptomatic severe aortic valve stenosis was referred to our Cardiac Surgery Unit. The previous history included congenital deafness, thyroid adenoma, bilateral hip joint and right knee replacement. She had been diagnosed with alkaptonuria six years before. The urinary excretion rate of HGA was 6098 mg/24h (upper normal limit 10mg/24h).

On admission physical examination revealed a bluish-black pigmentation of the sclerae and ears (figure 1). An electrocardiogram displayed a sinus rhythm and left ventricular hypertrophy. A chest x-ray revealed cardiomegaly and calcification of intervertebral discs. A transthoracic echocardiogram confirmed the presence of calcified aortic valve stenosis with a maximum/mean gradient of 95/60 mmHg respectively. The preoperative coronary angiogram demonstrated the absence of coronary lesions.

She underwent an aortic valve replacement under cardiopulmonary bypass. During the operation a tricuspid aortic valve with bluish-black leaflets could be observed. The intima of the aortic root and ascending aorta were also black pigmented (figure 2). A 21 mm Mitroflow 12A pericardial bioprosthesis (Sorin, Milan, Italy) was implanted in the supra-annular position.

The resected aortic leaflets were calcified, thickened and bluish-black pigmented being these findings more marked in the aortic than in the ventricular face. The edge of the cusps was relatively free of degenerative changes



**Figure 1** Ochronotic pigmentation of the ear cartilage and the sclera.

(figure 3). The microscopic examination revealed nodular calcification, fibrosis, hyalinization and ochronotic dark pigment deposition (figure 4). The patient needed postoperative prolonged mechanical ventilation. Three weeks later she was discharged in good condition. Regular postoperative follow-up visits demonstrated absence of structural valve deterioration until nine years later when the patient died because of a respiratory infection.

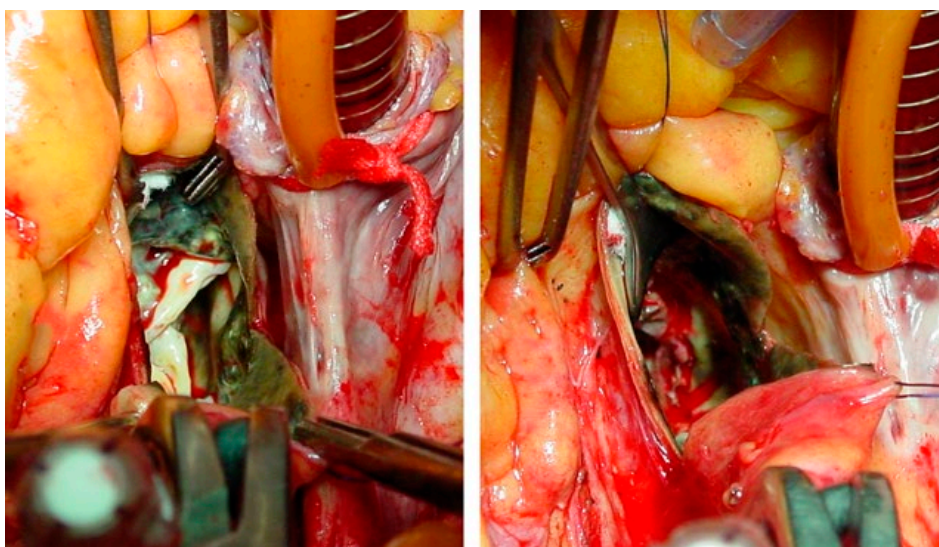
## DISCUSSION

Cardiac involvement in alkaptonuria is a rare event that not only affects the aortic valve but may also involve the mitral and pulmonary valves, endocardium, pericardium, aorta and coronary arteries.<sup>2,3,4</sup> The life expectancy of patients with alkaptonuria is not significantly reduced

although aortic valve involvement may be life-threatening and worsen the prognosis.<sup>1</sup>

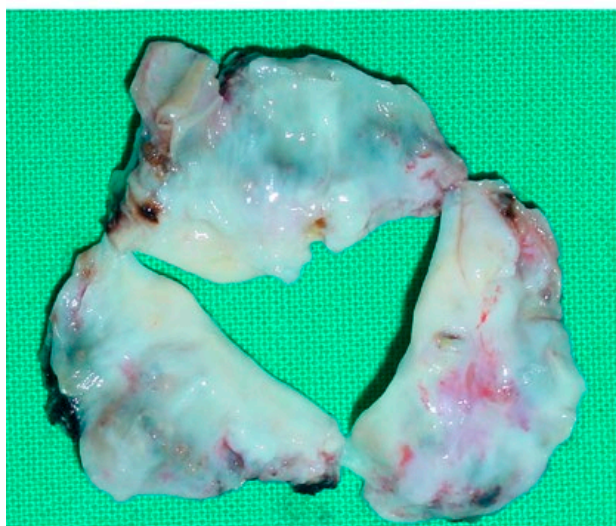
It has been suggested that the slow extracellular accumulation of ochronotic pigment in the aortic valve may stimulate an inflammatory response with progressive dystrophic calcification and fibrosis leading to valve stenosis.<sup>2,5</sup> It is important to note that pigment deposition in the aortic valve may be influenced by intravascular pressure and turbulence as we could observe in our case.<sup>4,6</sup>

Alkaptonuria is mostly asymptomatic in early life with arthropathy and heart valve symptoms appearing in the latter decades of life. The prevalence of aortic stenosis in alkaptonuria increases with age affecting around 70% of patients over of 60 years old<sup>1</sup>. In contrast, the prevalence of coronary artery disease is not increased by alkaptonuria.<sup>2,4</sup>



**Figure 2** Black ochronotic pigmentation of the aortic valve (A) and aortic intima after valve resection (B).

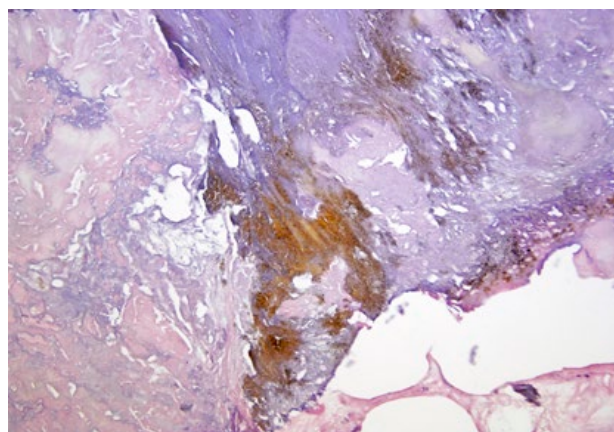




**Figure 3**

*Massive calcification of the aortic leaflets with ochronotic pigmentation. A) Aortic view. B) Ventricular view.*

The choice of the heart valve prosthesis to use in patients with alkaptonuria is under discussion. It has been suggested that bioprostheses may be exposed to the benzoquinones deposition as in native tissue, thus adversely affecting prosthesis longevity. However the recurrence of ochronosis in bioprosthetic valves has not been reported.<sup>6,7</sup>



**Figure 4**

*Histologic examination showing hyalinization, fibrosis and ochre-colored pigment (ochronosis) deposition in the aortic valve leaflets (hematoxylin and eosin x200).*

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# MORESTIN SYNDROME: BEYOND THORACIC TRAUMA

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## Abstract

*Morestin syndrome (MS) is a rare clinical manifestation consequent to an acute compression trauma to the thorax. In such an event, the sudden elevated pressure that happens to the airway and the rapid and retrograde blood flow results in capillary rupture in the head and neck vessel territory. This case reports a car accident victim that was dragged by a truck down a road with closed thoracic trauma resulting in MS. The patient presented with ecchymotic mask, neck and facial cyanosis and petechiae, ocular hemorrhage, otorrhagia, left clavicle fracture and spleen laceration that resolved with conservative measures. In this article, the authors present a specific acute syndrome due to trauma, with potential severe complications that should be recognized early and subject to a multidisciplinary and systemic approach in the emergency setting.*

## INTRODUCTION

Morestin Syndrome is typically characterized by cyanosis, cervico-facial petechiae, ocular hemorrhage, epistaxis, otorrhagia and neurological symptoms. It is due to blunt acute thoracic trauma, with extreme compression causing a sudden retrograde efflux of blood to the head and neck. The authors present a clinical case with manifestations of this rare phenomena.

## CLINICAL CASE

A 45 years old autonomous male, with no known precedents or regular medication was transported by a medical helicopter from Instituto Nacional de Emergência Médica (INEM) to a central trauma center in Lisbon, after a motor vehicle accident, where he was dragged by a truck for a few seconds, causing blunt chest trauma.

At the emergency department (ED) he was evaluated according to the *Advanced Trauma Life Support* (ATLS) protocol, with no need for invasive emergency procedures.

The patient was observed by several specialties, namely Maxillofacial Surgery and Otolaryngology that excluded trauma to their given areas, Ophthalmology that detected bilateral sub-conjunctival and pre-retinal hemorrhage on the lower temporal arcade of the left eye manifesting with diplopia, and Trauma that identified a left clavicle

fracture without neurovascular complications and no need for surgical fixation.

The patient was submitted to a computed tomography (CT) of the head, thorax, abdomen, pelvis and vertebral column that revealed only a small left side asymptomatic pneumothorax. Because he was clinically stable, without the need for emergency care, a transfer was arranged to his referral Hospital.

Upon arrival at his local hospital he still complained of light dizziness, diplopia, constant pain localized to the left clavicle, and chest discomfort, predominantly on the right anterior chest grid with no irradiation, aggravated with breathing and movements of the right upper limb.

On clinical inspection, he was conscious, calm, hemodynamically stable with no vasopressor support, breathing without effort on 2 liters of supplemental oxygen. The chest wall did not show paradoxical movement, but local pressure points, bruising and ecchymosis could be seen on the anterior right hemitorax and left acromioclavicular area. Subcutaneous emphysema was detected in the left supraclavicular and cervical region. The cardiopulmonary and abdominal observation was not altered and the limbs had no signs of neurovascular compromise. At the cervicofacial level, extensive cyanosis, multiple petechiae and ecchymosis (Fig. 1 and 2) as well as bilateral subconjunctival hemorrhage was present.

Red cell count was normal with hemoglobin of 15.5g/dL, 9500 leucocytes /L, without increased neutrophils. Rhabdomyolysis reflected in 1196 U/L of serum



**Figure 1** *Morestin mask- cyanosis and cervicofacial petechiae.*



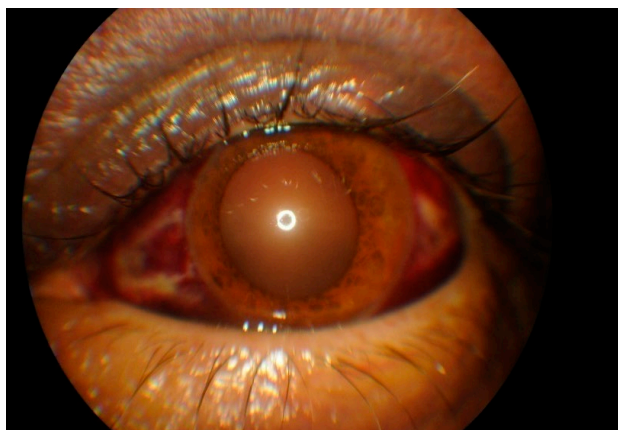
**Figure 3** *TAP CT: Grade III splenic hematoma.*

creatinase (CK) with cardiac enzymes and the remainder blood tests within normal range. The transthoracic cardiac ultrasound did not detect relevant changes.

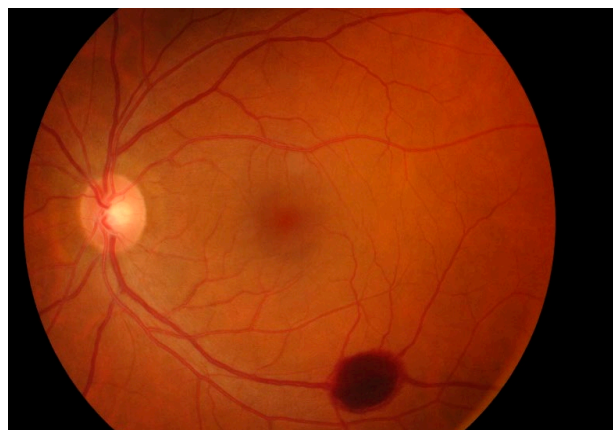
The patient had another CT that revealed reabsorption of the left pneumothorax, the already known clavicle fracture and a previously undetected grade III splenic hematoma (Fig. 3).

by Ophthalmology revealed evidence of stable bilateral subconjunctival and left conjunctiva hemorrhage (Fig. 4) and the Trauma team recommended conservative care of the clavicle fracture.

Discharge occurred on the 9<sup>th</sup> admission day clinically stable referred to the General Surgery, Trauma and Ophthalmology outpatient clinic.



**Figure 2** *Left eye subconjunctival hemorrhage.*



**Figure 4** *Pre retinal hemorrhage of the temporal inferior arcade of the left eye without alterations of the optic disc or macula.*

He was admitted to intermediate care for surveillance and from there to the infirmary under General Surgery care.

All throughout the hospital stay he had a favorable clinical, laboratory and radiological evolution, with progressive regression of the ecchymosis, serum CK leveling and gradual resolution of the spleen hematoma on the CT the 12<sup>th</sup> day after the accident. At the same time, the diplopia disappeared and reevaluation

## DISCUSSION

*Morestin Syndrome* (MS), also known as *Perthes Syndrome* or *traumatic asphyxia*, is a rare event of blunt force trauma to the chest, with only around 200 cases described in the literature.<sup>3</sup>

The most frequent causes are road traffic accidents (incidence of 1 in 18500 accidents) that make up 40% of the cases.<sup>4</sup> The remaining causes are generally



attributed to work or sport accidents.

In the MS, there is extreme and acute chest compression of a patient who, as an involuntary response to fear, takes a deep breath and closes his glottis at the moment of impact.

This causes an acute increase of intra-thoracic pressure, causing a retrograde efflux of blood from the right atrium to the superior vena cava (SVC) and to the SVC drainage territory with rupture of the head and neck venules and capillaries by the excessive pressure.

Consequently, these patients present with a typical Morestin face mask characterized by extreme cyanosis, ecchymosis and cervicofacial petechiae.<sup>1,6</sup>

Frequently, eye hemorrhage occur causing ophthalmological complaints like decreased visual acuity, diplopia or exophthalmia can be seen as well as epistaxis or otorrhagia, possibly complicated by hearing deficits.<sup>3</sup>

The reported case presented with eye hemorrhage due to inferior temporal artery lesion without complications or permanent damage.

Another mechanism existing in this syndrome is the consequent reduction of cerebral blood flow, resulting in neurological manifestations of hypoxia like dizziness, headache, confusion, syncope or even brain death.<sup>2,5</sup>

Our patient's only complaint was self-limited dizziness.

Patients frequently present with concomitant non-specific lesions from the thoracic trauma, like fractures of the rib cage or other chest bones, hemopneumothorax or other organ damage from extreme compression.

We are presenting a case with splenic laceration, a possible complication that has been described in literature.<sup>1</sup>

## CONCLUSION

MS is, therefore, a consequence of a blunt trauma of major kinetic energy, whose morbidity and mortality depends on the duration and severity of the chest compression to which the patient is exposed.<sup>1,2</sup>

These patients evaluation must follow the international recommendations of trauma care (ABCD) so as to precociously identify and treat lesions to avoid permanent damage.

This clinical case presents with manifestation of a rare syndrome that might entail serious complications or even death if not stopped and swiftly treated, while warning to the systematic and global approach to trauma patients.

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# UNUSUAL BEHAVIOUR OF A LUNG INFLAMMATORY MYOFIBROBLASTIC TUMOUR

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## Abstract

*Inflammatory myofibroblastic tumours (IMTs) are rare lesions. We report a case of a 55 year-old male, admitted with a pneumonia. Further investigation revealed a left lower lobe mass and enlarged mediastinal lymph nodes. Cytology of the bronchoalveolar lavage suggested a squamous cell carcinoma. He received four cycles of chemotherapy followed by a left lower lobectomy. Pathological analysis was compatible with IMT. Three months after surgery, a new IMT nodule located in the lingula was excised. Four months later, endobronchial involvement and the presence of liver nodules were detected. Ten months after the first surgery a CT revealed a sacrum lesion. Histology was compatible with undifferentiated sarcoma and a sarcomatous transformation was assumed.*

## INTRODUCTION

IMTs, which were first described by Brunn in 1939, represent approximately 0.02-1.2% of all lung tumours.<sup>1,2</sup> There is a lack of information about the natural history, clinical presentation and effective treatments.<sup>1</sup>

The prevalence is not sex dependent,<sup>1,2,3</sup> and may present at any age.<sup>1,2,4</sup> Preoperative diagnosis is difficult to obtain, which may delay appropriate treatment.<sup>1,4,5</sup>

## CASE REPORT

55 year-old male, with history of heavy smoking and chronic obstructive pulmonary disease (COPD), was admitted to the hospital due to a left pneumonia. A fiberoptic bronchoscopy with bronchoalveolar lavage suggested squamous cell carcinoma. The CT and PET-Scan revealed a left lower lobe mass with 92x89 mm (SUVmax 49). There was an increased uptake of FDG on stations 4R, 5,7 and 10L. EBUS of stations 4R, 4L and 7 without evidence of malignancy. The diagnosis of a stage IIIA (T3N2M0) squamous cell carcinoma was assumed.

The case was discussed in a multidisciplinary meeting and neoadjuvant therapy (four cycles of cisplatin/gemcitabine) was administered based on station 5 with suspected metastatic disease.

Regardless of a slight reduction of the lymph nodes,

the main lesion remained stable. After a negative cervical mediastinoscopy, a left lower lobectomy was performed. The histology was compatible with IMT, measuring 115x87x35 mm. Immunohistochemistry was positive for ALK and Vimentin. ALK gene rearrangements were not found. No mediastinal lymph node involvement was reported. The bronchial stump was 5 mm from the tumour but revealed a squamous metaplasia in all its length. The patient was re-staged as IIB (ypT3N0M0).

Three months after surgery, a CT-scan showed a new nodule in the lingula, which was removed. Pathology confirmed an IMT.

Four months later, a CT-scan revealed several lung and liver nodules. An occlusion of the left main bronchus, causing left lung atelectasis, required debulking of an endobronchial IMT mass. Finally, palliative radiotherapy to the left main bronchus was decided (total dose of 20Gy in 4Gy daily fractions).

Ten months after the first surgery, after the onset of back pain, a new CT-scan revealed a sacrum lesion, whose needle biopsy was suspicious for multiple myeloma.

Histological reassessment of all samples was performed. Sacrum lesion was compatible with undifferentiated sarcoma and a sarcomatous transformation was admitted.

Shortly after, he developed neurological symptoms on lower limbs and urgent spinal decompression took place.

The patient died of disease progression 18 months after the initial diagnosis.

## DISCUSSION

IMTs are considered benign or low-grade malignant tumours,<sup>1,3</sup> because of possible malignant invasion, recurrence and, exceptionally, malignant transformation.<sup>3,5,6</sup>

The exact etiology is unknown, although several reports suggest that might be related to recurrent respiratory infections or autoimmune mechanisms (such as increased IgG4).<sup>2,3,7,8</sup>

The size of the tumour (<3 cm) and free surgical margins resection are the major determinants for avoiding recurrence and increasing survival.<sup>3,5,7</sup> In our patient, the lesion was larger than 3 cm but the resection was complete. Endobronchial involvement is considered uncommon, although it is reported in up to 12% of cases.<sup>6</sup>

In most series, patients are asymptomatic and the tumour is accidentally discovered.<sup>1,3,4,5</sup> Symptoms are usually related to location and are nonspecific.<sup>2,4,5</sup>

Diagnosis before surgery is difficult. Usually a needle biopsy shows a nonspecific mixture of inflammatory cells.<sup>1,4,5</sup> In our patient, the preoperative diagnosis suggesting a squamous carcinoma may be related to the squamous metaplasia later found in the bronchial stump.

In most cases, nodules are solitary and regular,<sup>2,3</sup> being PET-Scan uptake similar to malignant lesions.<sup>1</sup> Although rare, there are some reports of distant metastasis and sarcomatous transformation.<sup>1,5,6,7,9</sup>

ALK gene rearrangements can be present in 50% of IMTs.<sup>7,8</sup> Based on that, drugs like Crizotinib may have a role.<sup>8</sup> Corticosteroids are usually not useful in adults,<sup>2,3,5</sup> except for those with increased IgG4,<sup>7</sup> but good results have been reported in children.<sup>2,3,5</sup> Chemotherapy is an option in cases of multifocal or invasive lesions or in cases of local recurrence.<sup>2,3</sup>

## CONCLUSION

Despite the past assumption of benign behaviour of IMTs, this report as well as others found in the literature, show us that this is not always true. The lack of valid therapeutic options is still an issue for those who present with disseminated disease.

## Reviewer's note:

Initial decision for induction chemotherapy lacks support after a negative EBUS!

Fernando Barata

Author's reply: We thank the reviewer for his comment. Induction chemotherapy was decided upon in a multidisciplinary meeting, based on a large (92mm) squamous cell carcinoma with a possible single station N2 disease in station 5 (stage IIIA) supported by the NCCN clinical practise guidelines.

Daniel Cabral

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# LUNG NECROSIS AFTER PARAFFIN ASPIRATION

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## Abstract

**Background:** Fire breather's lung is a rare condition that occurs after hydrocarbon aspiration. Case reports published experienced a good clinical outcome with conservative treatment. To our knowledge, there are no reported cases treated with pulmonary resection.

**Case presentation:** We report the case of a 35-year-old female trapeze artist, who suffered an accidental ingestion/aspiration of liquid paraffin. Persistent fever and elevated inflammatory markers without clinical improvement with antibiotics and bronchoscopy was seen. Computed tomography scan showing middle lobe necrosis and abscess motivated a middle lobectomy for infection control. Postoperative recovery was uneventful.

**Conclusion:** There are some cases described in the literature, normally with a favourable evolution with conservative treatment. Therefore, it is important to acknowledge that, in patients where serious complications have arisen, despite medical therapy, surgery may have an important role, and resection of the necrotic lung may prevent its potential life-threatening consequences.

## BACKGROUND

Exogenous lipid pneumonia usually occurs when oils are aspirated or inhaled.<sup>2</sup> Liquid paraffin is a tasteless hydrocarbon, poorly absorbed from the gastrointestinal tract, and innocuous when ingested. However, paraffin depresses the protective cough reflex and mucociliary transport due to its high viscosity, and consequently aspiration is a potential risk.<sup>1,4</sup> It is a cheap product, and because it has a high explosive point (90°C) it is commonly used by fire breathers,<sup>4</sup> making them a population at risk.

Aspiration pneumonitis is the most common complication of hydrocarbon ingestion (40%). Lung abscess is an extremely rare complication, only a few cases described in the literature, and most report effective treatment with antibiotics alone. Some cases evolving to pneumatocele formation.<sup>3,6</sup>

When aspiration of paraffin occurs, presentation ranges from asymptomatic patient to respiratory distress. Abnormalities seen in computed tomography (CT) scan vary from focal to bilateral, and the most common findings are alveolar consolidation and ground glass opacities, typically involving the middle and lower lobes.<sup>1,2</sup> Radiologic findings may appear 30 minutes after aspiration, although lung opacities will only be evident approximately within 24 hours.<sup>2</sup>

Clinical history, bronchoscopy with bronchoalveolar lavage – which shows fat globules on the fluid surface and the cytologic demonstration of lipid-laden macrophages – and CT scan combined, can establish the diagnosis.

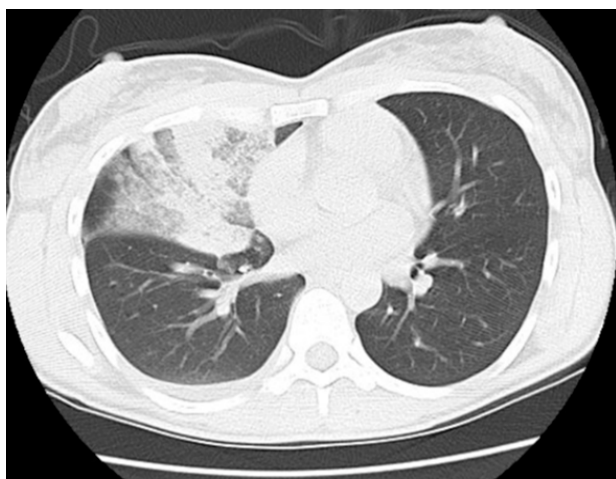
## CASE PRESENTATION

We report the case of a 35-year-old female trapeze artist, who suffered an accidental ingestion/aspiration of liquid paraffin. Patient presented with nausea, vomiting, cough and pleuritic pain, associated with elevated inflammatory markers. Chest x-ray showed heterogeneous hypotransparency on the right hemithorax (figure 1). Treatment with intravenous amoxicillin-clavulanic acid was started. Initial chest CT scan revealed middle lobe consolidation



Figure 1

Chest x-ray showing heterogeneous hypotransparency on the right hemithorax.



**Figure 2** Chest CT scan revealing middle lobe consolidation.

(figure 2). A diagnostic bronchoscopy was performed and the findings included extensive edema and erythema around the bronchus intermedius, middle and right lower lobe bronchus, with drainage of milky fluid from the middle lobe. Bronchoalveolar lavage showed some alveolar macrophages. Cultural studies were negative.

Clinical deterioration was observed on day 4, with elevation of leucocytosis (80.000 leukocytes/ $\mu$ l), C-reactive protein as high as 350 mg/L, and fever. A reevaluation CT scan showed middle lobe necrosis and abscess (figure 3). At this moment, surgery was considered, and a middle lobectomy was performed for infection control. During surgery, a clear destruction of the middle lobe (figure 4), with an important consolidation of the right lower lobe

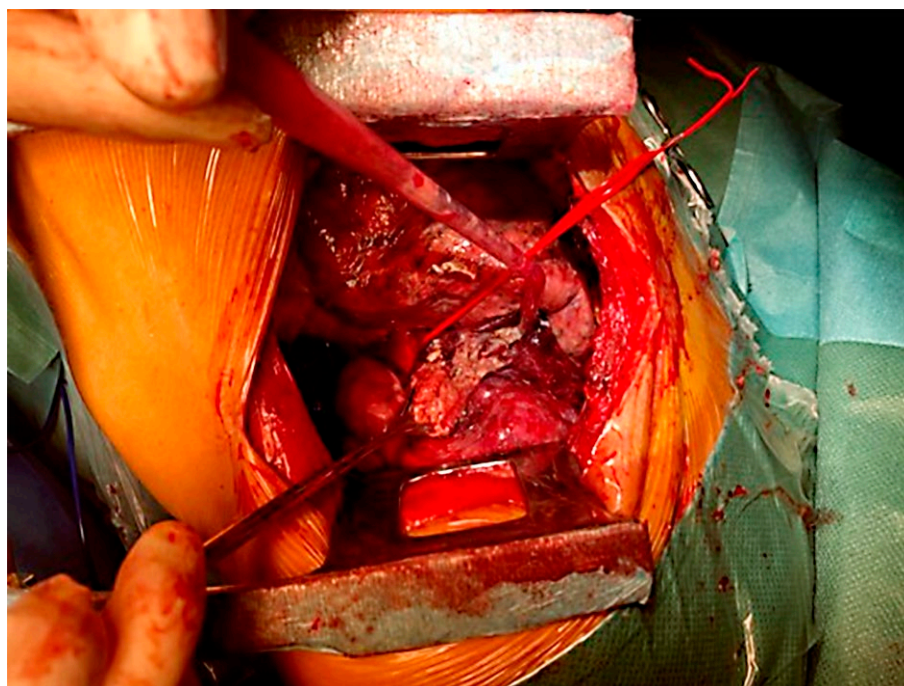


**Figure 3** Chest CT scan showing middle lobe necrosis.

was noted. The decision was to spare the lower lobe, since there was not a clear destruction. Antibiotics were adjusted to Piperacilin-Tazobactan, and respiratory rehabilitation was intensified. The patient experienced a good recovery and a progressive improvement of the lower lobe consolidation was observed. Patient was discharged on the 9<sup>th</sup> post-operative day.

#### DISCUSSION

There are few case reports in the literature of paraffin-induced exogenous lipid pneumonia in fire breathers, though a good clinical outcome with conservative treatment is described in the majority of cases, including the ones which evolved to lung abscess.<sup>3,4,5,7</sup>



**Figure 4** Intraoperative image of middle lobe destruction.



In our case, the patient has a history of paraffin ingestion associated with subsequent vomit and cough, the same symptoms described in the literature, underlying a potential aspiration. Clinical deterioration with antibiotics and supportive therapy is rare in lipoid pneumonia,<sup>2,6,7</sup> but when it happens other treatment options should be considered. Necrosis of middle lobe could potentially cause a severe infection and the standard treatment is the removal of the necrotic lung.

To the best of our knowledge, this is the first case reporting a fire breather's lung with need for lung resection due to necrosis. Therefore, we considered important to share our experience, and describe the role of Thoracic Surgery on the treatment of such severe complications.

## CONCLUSION

There are some cases of liquid paraffin aspiration described in the literature, and it is important to acknowledge the fact that, in some extremely rare cases, antibiotics will not be enough and surgical resection may be needed. Obstructive pneumonia with lung necrosis is a complication of liquid paraffin aspiration and immediate bronchoscopy should be performed. When necessary, resection of the necrotic lung may prevent its potential life-threatening consequences.

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# PENETRATING TRAUMA TO THE AXILLARY ARTERY

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## Abstract

*Axillary artery injuries due to penetrating trauma are relatively uncommon. Management of these injuries is challenging due to the complex local anatomy, rigid chest walls, and associated injuries. Open exposure with direct open vascular repair has been the mainstay of operative management. We report a clinical case of a 51-year-old man victim of penetrating trauma to the axillary artery caused by a chain-saw and repaired by open surgery with a great saphenous vein interposition graft.*

## INTRODUCTION

Vascular injuries to the upper limb occur more frequently due to penetrating than blunt trauma.<sup>1,2</sup> Among these injuries, axillary artery is the most uncommon and together with subclavian arterial injuries constitutes less than 5% of all civilian vascular traumas.<sup>3</sup>

We report a successful open surgery repair of a vascular penetrating injury to the axillary artery.

## CASE REPORT

A 51-year-old man sustained a penetrating lesion triggered by a chain-saw on the axillary fold. He received initial medical support by the extra-hospital emergency team. Thereafter, he was transferred to our facility with hemodynamically stable.

On physical examination, he presented an open wound on the axillary fold (Fig. 1) with no active bleeding, a small local, non-expanding hematoma, and signs of arm ischemia without palpable brachial, radial and ulnar pulses. The patient also showed signs of brachial plexus injury once he was not able to extend his wrist. Furthermore, he experienced impaired sensation in his upper left limb.

A computed tomography angiogram of the chest and upper limb revealed a total axillary artery transection (Fig. 2) with a thrombosed proximal and distal stump. A well-defined regional hematoma was adjacent to that segment of the artery, and no active bleeding was noted. There was an axillary vein and brachial plexus associated injuries.

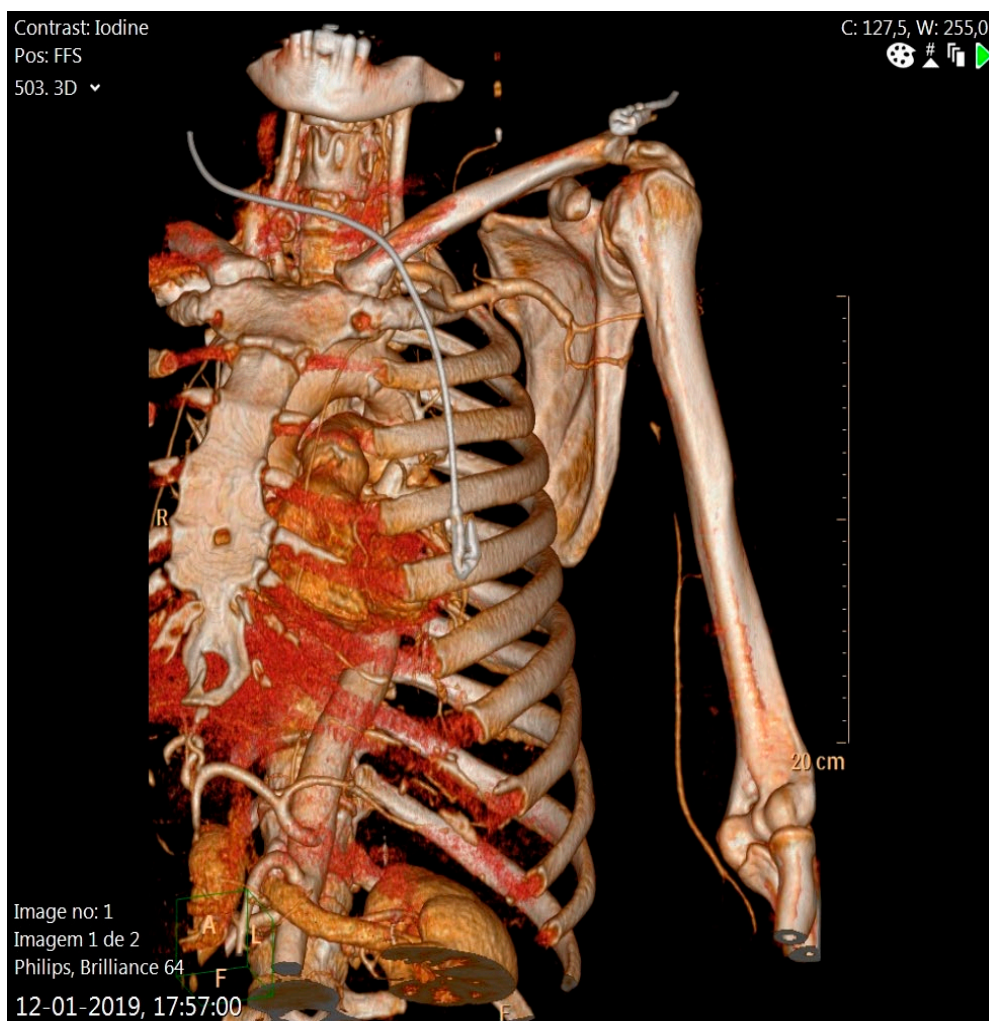
We proceeded with proximal and distal control, followed by resection of the damaged arterial segments



**Figure 1** Open wound on the axillary fold.

and conducted an axillary artery repair with reverse saphenous vein interposition grafting (Fig. 3). The axillary vein was ligated and the wound closed.

The patient was discharged three days after with a patent graft and palpable radial and cubital pulse, with

**Figure 2**

*Computed tomography angiogram of the chest and upper limb revealed a total axillary artery transection.*

no interurrences registered and indication for single anti-aggregation with acetylsalicylic acid 100mg daily.

Early exploration four weeks after the event was conducted by Plastic Surgery to establish continuity of the previous transected nerves. The graft surveillance was done at three, six and twelve months with Doppler Ultrasound that attested graft patency (Fig. 4).

The patient has now one year follow up and no interurrences registered mentioning first to third finger non disabling paresthesia

## DISCUSSION

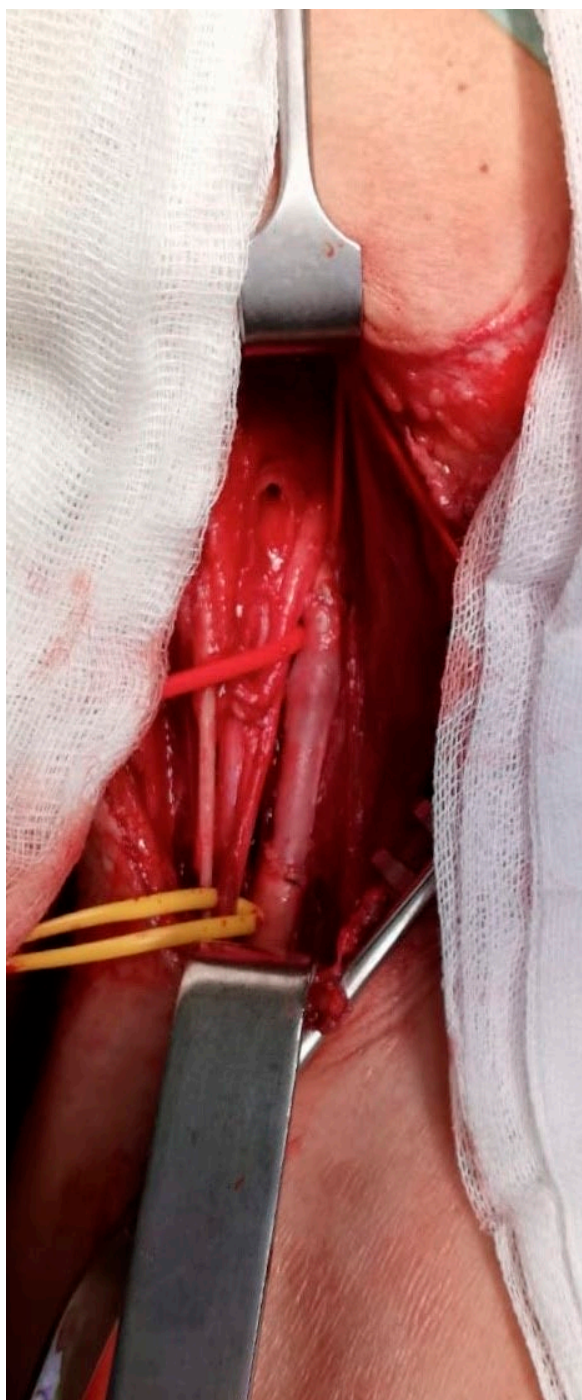
Penetrating trauma to the subclavian and proximal axillary arteries are challenging vascular injuries due to the difficulty from vessel exposure and its close proximity to important anatomic structures with mortality rates reported up to 30%.<sup>4,5</sup>

Deciding to intervene should take into consideration distal poor perfusion with lack of pulses and presence of ischemia and existence of a compressive

hematoma, especially with pulsatile bleeding.

Subsequently, the best approach between open and endovascular repair should be individualized based on the nature of the vessel injury: intimal flap, pseudoaneurysm, transection, thrombosis or avulsion. Injuries such as intimal flaps, vessel narrowing, small false aneurysms, and arteriovenous fistulae in which the artery and its runoff remain intact may be amenable to endovascular repair. In this case we had a complete arterial transection of the third part (distal to the pectoralis minor muscle) of the axillary artery with proximal and distal stump thrombosis which made open surgery the best approach.

The incidence of associated venous and brachial plexus injury varies between 35 and 70% as reported in the literature.<sup>6,7</sup> Considering venous, it is still debatable whether investing time correcting them is advantageous. Bearing in mind neurologic assessment, some reports in the literature advocate early exploration at three to six weeks to establish continuity of transected nerves and provide optimal conditions for axonal regrowth and re-innervation of distal musculature.<sup>6</sup>



**Figure 3**

*Axillary artery repair with reverse saphenous vein interposition grafting.*



**Figure 4**

*Image from Doppler ultrasound that attested graft patency.*

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# RENAL ARTERY ANEURYSM: A NEVERLAND ENTITY?

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## Abstract

Renal artery aneurysms are rare. The indication for treatment at 20mm diameter comes from studies conducted before the advent of cross-sectional imaging. We present a case of a 61years-old woman with a 23mm saccular right renal artery aneurysm under surveillance for 6 years without growing.

## INTRODUCTION

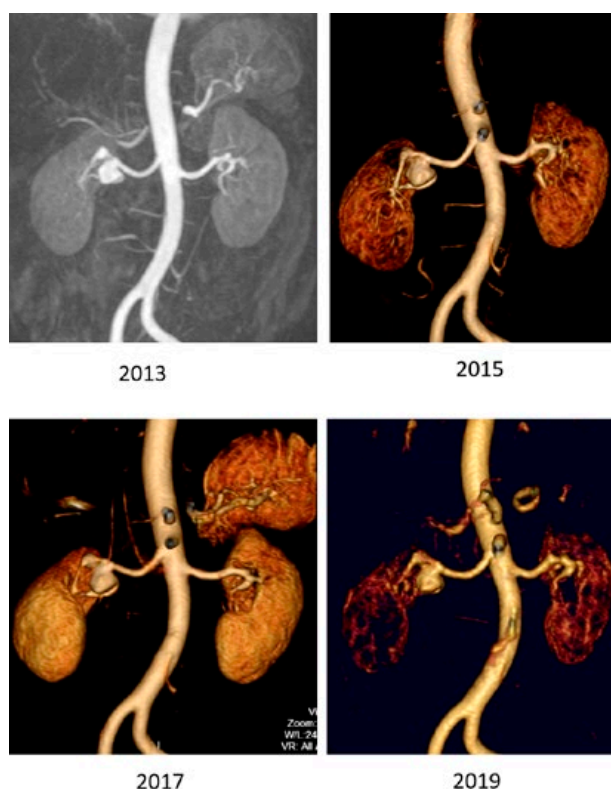
Renal artery aneurysms have an estimated incidence of 0.09%.<sup>1</sup> The currently accepted indications for treatment are symptoms, size > 20 mm, women of childbearing age. The symptoms includes rupture, difficult to control hypertension, hematuria, flank pain and abdominal pain.<sup>2</sup> In the last decade some authors proposed a revision of the diameter threshold for treatment to be above 20 mm,<sup>2-4</sup> with only one proposing a 30mm diameter as the indication for treatment.<sup>2</sup>

## CASE REPORT

A 61 years-old woman with one pregnancy, one adult son and hypertension under control with ibesartan presents with a 23 mm saccular right renal artery. She had an abdominal ultrasound that suggested renal artery alterations and was directed to vascular surgery consult. A magnetic resonance angiography was performed to characterize the aneurysm. Due to the location, only treatment with *ex-vivo* reconstruction was feasible. After discussing surveillance vs intervention, the patient opted by surveillance. After 6 years of surveillance and four magnetic resonance angiography the aneurysm remains with the same dimensions (Figure 1).

## DISCUSSION

There is growing evidence that the 20 mm threshold for treatment of renal artery aneurysms is probably exaggerated.<sup>2-4</sup> Our patient contributes to this evidence. It appears that in some patients the renal artery aneurysms behaves as a Neverland entity, refusing to grow up.



**Figure 1** Magnetic Resonance Angiography surveillance.

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# ABERRANT TRAJECTORY OF A CENTRAL VENOUS CATHETER

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During placement of a central venous catheter into the right subclavian vein it was found to be impossible to extract the guidewire. An Angio-Computed Tomography was performed, showing an aberrant guidewire path, as

the image shows. An urgent mini-sternotomy was performed to extract both catheter and guidewire under direct visualization.

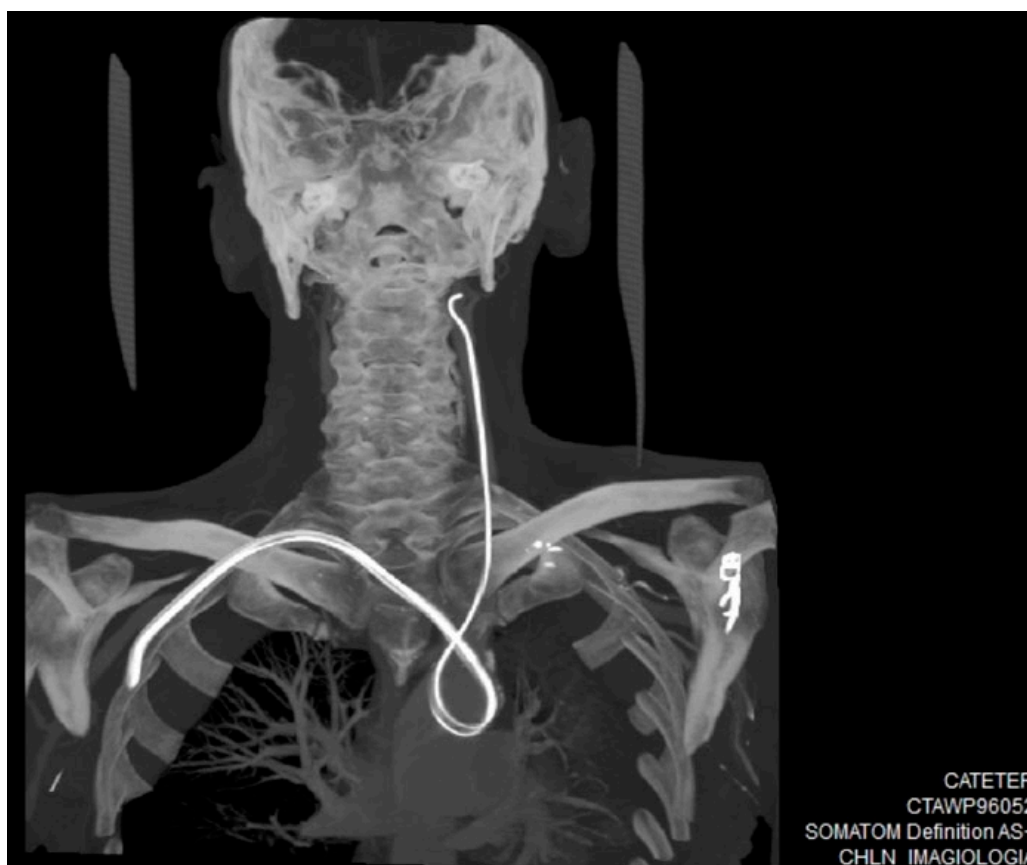


Figure 1

*Angio-CT: The guidewire pierced through the right brachiocephalic vein and brachiocephalic artery. Within the brachiocephalic artery, it exhibits a descendent trajectory towards the aortic valve, travelling through the aortic arch and ascending aorta. Next to the aortic valve, it makes a curve of 180° and rises through the left carotid artery.*



# ABERRANT PLEURAL PLAQUES

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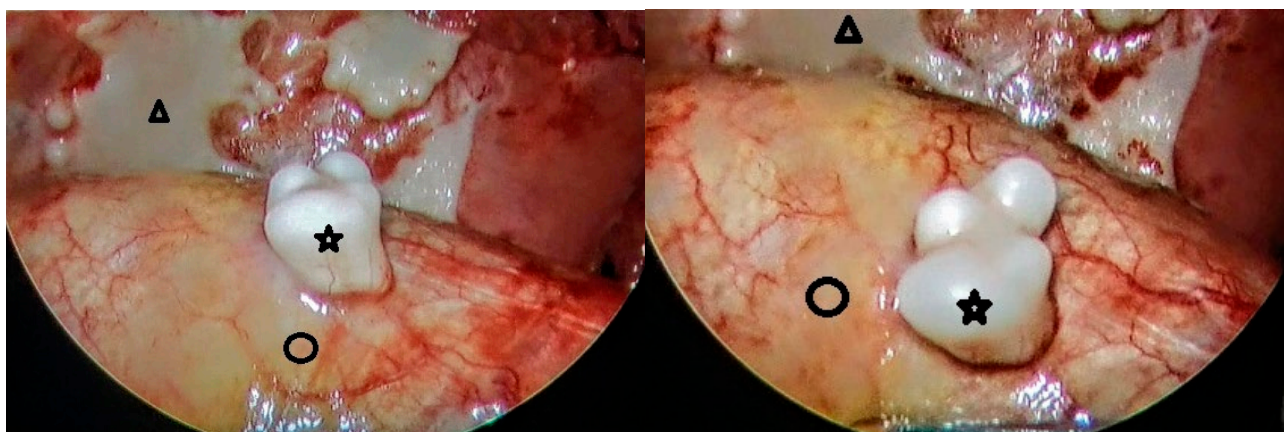
Male, 71 years old, active smoker.

Referred to our outpatient clinic due to right upper lobe nodule with 4 year follow-up, which increased in size and metabolic uptake during the last year.

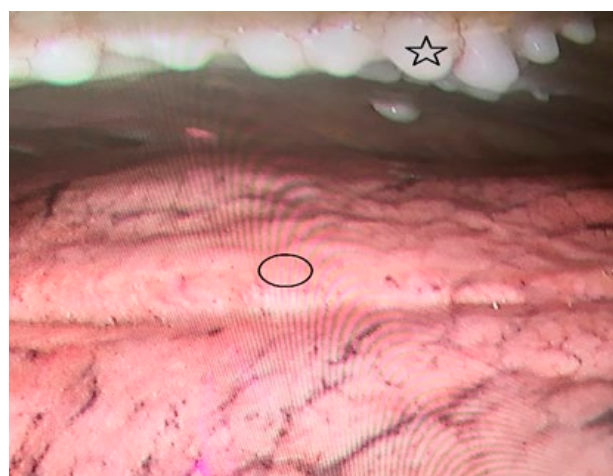
CT scan also revealed multiple pleural plaques with a diffuse pattern. The patient underwent a right upper VATS lobectomy and mediastinal lymphadenectomy after

intraoperative pathology consultation was positive for malignancy.

Intraoperative with evidence of multiple hyaline pleural plaques and aberrant neoformative lesions, mimicking teeth, on the diaphragm and parietal costal pleura, probably related to asbestos exposure.



**Figure 1** Triangle: pleural plaques; Circumference: diaphragm; Star: diaphragmatic neoformative lesion



**Figure 2** Star: parietal pleural lesions; Circumference: right lung



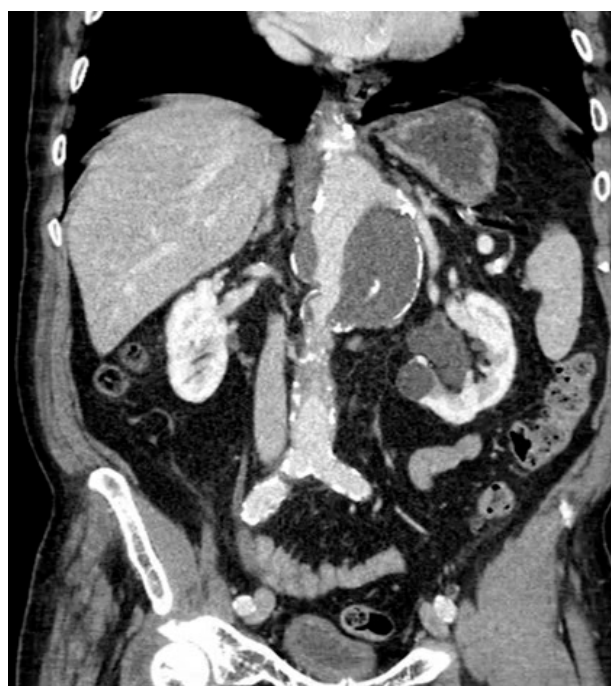
# AORTIC ANASTOMOTIC ANEURYSM AFTER INFRA-RENAL GRAFTING

Mário Moreira<sup>1</sup>, Luís Antunes<sup>1</sup>, Joana Moreira<sup>1</sup>, Gabriel Anacleto<sup>1</sup>

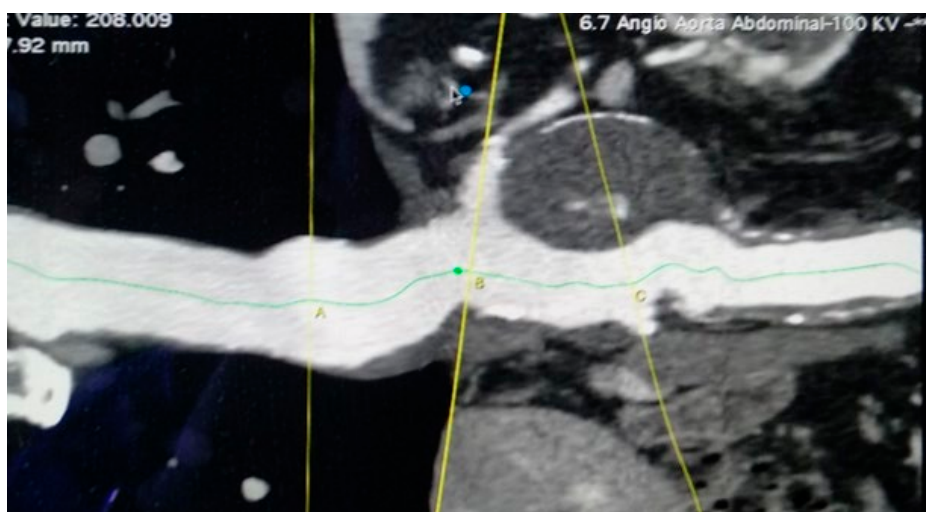
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An 87 year-old male presented with a 71mm proximal anastomotic aneurysm causing left renal artery displacement (Figures 1 and 2), 19 years after infra-renal aorto-aortic grafting for an infra-renal abdominal aortic aneurysm. Dilatation of visceral aorta was also observed. Management would be challenging but patient denied further intervention.



**Figure 1** Aortic anastomotic aneurysm.



**Figure 2** Left renal artery displacement. B line – left renal artery ostium, C line – right renal artery ostium.





# PORTOMESENTERIC VENOUS GAS AND INTESTINAL PNEUMATOSIS – RADIOLOGICAL SIGNS OF MESENTERIC ISCHEMIA

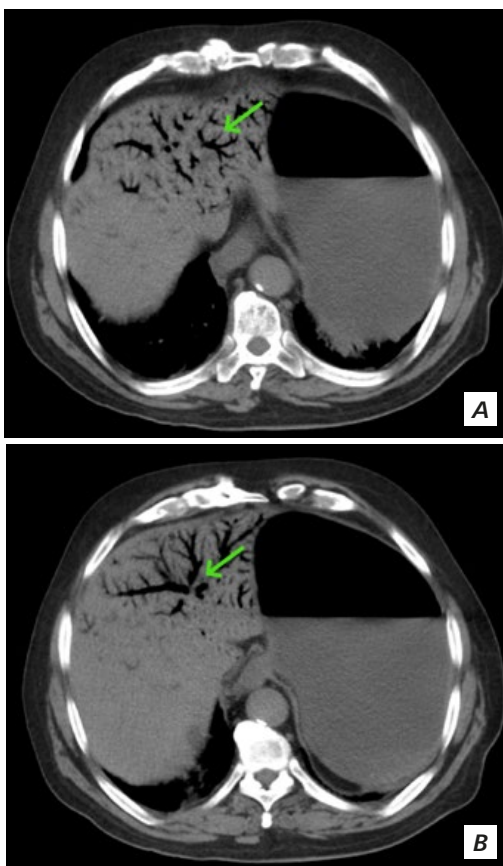
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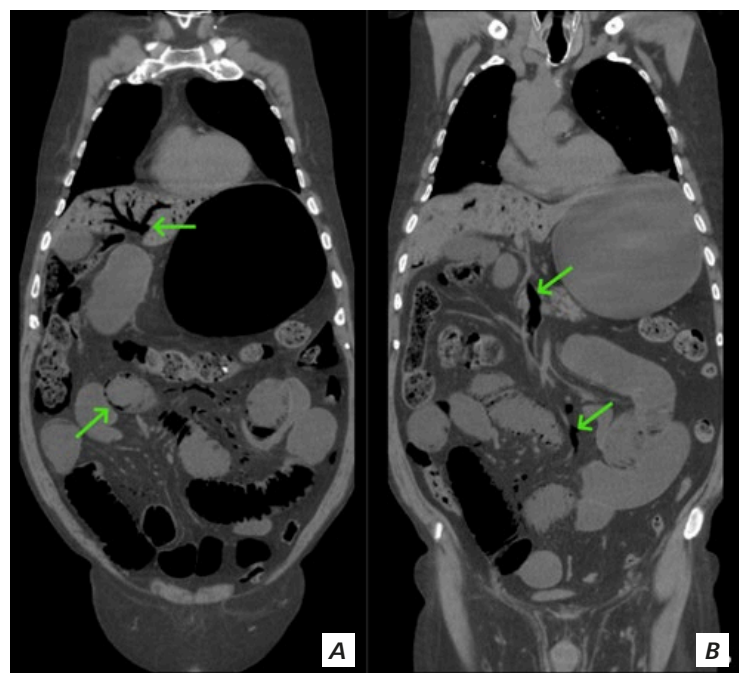
Computed tomography showing portal and mesenteric venous gas and intestinal pneumatosis, rare radiological signs that, together, favor the diagnosis of mesenteric

ischemia (70% of cases). When present, mortality is around 40-90%. Surgical exploration is mandatory with assessment of the extent of intestinal ischemia and appropriate treatment.



**Figure 1**

Computed tomography presenting portal venous gas and gastric distension.



**Figure 2**

Computed tomography presenting a) portal venous gas and intestinal pneumatosis and b) mesenteric venous gas.





