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EDITORIAL

Miguel Guerra
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Thoracic surgery residency: It's a long way to the other side of the table!

When you're a junior resident scrubbing with a senior surgeon on a given case it can be very illusory. There's music playing, the chief might be chatting about some football game last night, and whatever case it is, uniportal lobectomy, bronchoplasty, tubeless pleurectomy, whatever, can seem to happen almost effortlessly.

But, performing thoracic surgery is not at all like a train going along tracks to a predetermined destination with the chief being the engineer making minor adjustments. Rather, once you're on the surgeon's side of the table, perhaps a better analogy is carrying an injured patriot on your back through the jungle with booby traps right and left and no map, trying to navigate to base.

Training in thoracic surgery never has been idyllic and likely never will be. It is intense and rigorous. The justification for this intensity is, and always has been, the magnitude of patient illness in those who need thoracic interventions for lung cancer. This disease burden warrants nothing less than the best effort that trainees and attending staff can provide. But, this intensity translates into the opportunity to participate in many different clinical situations in a short time. It allows to absorb as much experience and mentorship as possible.

Undoubtedly, mentors are a part of the answer to this question. First and foremost, mentors come in many forms. Of course, there are mentors who have an impact, whether good or bad, during your training. The clear message is that mentors after your training are as important, if not more so, than mentors during your training. We are a product of those who came before us. A large part of this experience is passed down from professors and mentors. There are opinions, advice, technical skills, and approaches that influence us every day. Each is valuable in the moment that it is needed.

The idea is to walk away with the best from everyone, to immerse into a culture that will support one for a lifetime. There are innumerable aspects to a successful and competent surgeon: technical ability, knowledge, and judgment among many others. We all develop and then continue to evolve a style. The evolutionary pressures put on by a training program will be the most important part of the internship.

Another point to make is that learning is lifelong. I would suggest that is the most valuable thing to learn in training - learning is lifelong. Learning to be a thoracic surgeon is a dynamic process that must of necessity change with changing times. It is almost axiomatic that a new graduate in an existing practice will adapt and learn from the practice partners. The culture of learning developed in residency training must persist into practice and that this ''culture of learning'' is the most important thing that you learn in your training.

Part of the fun, and the imperative, of thoracic surgery is to embrace new technology (uniportal, robotic, etc.) and new or modified procedures, and thus to embrace learning. To do this, it is necessary to fall back on the learning pattern that was, I would hope, instilled in residency training.

Miguel Guerra | Editor-in-Chef

COMENTÁRIO EDITORIAL

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Aortic valve prosthesis type and age - no news is good news?

The choice of the most appropriate type of aortic valve in patients aged 50-70 years old is still an ongoing debate, despite being a very well-known problem that exists in the cardiothoracic and cardiology community. All of us in the field have debated with ourselves, with colleagues and with patients the best choice of prosthesis type, of anti-coagulation regime, and of expected short and long-term results with both options.

Recently, the patients´ choice has been considered of paramount importance, and rightly so. Greater access to medical information, patient generated opinions and widespread online testimonies and experiences, coupled with heightened visibility of aortic stenosis as a fatal disease, non-separable from the arrival of TAVI and of the novel anti-coagulants, have significantly added to the discussion. How, then, to decide what´s best in patients with aortic valve disease with 50-70 years old?

In this number of Revista Portuguesa de Cirurgia Cardíaca, Torácica e Vascular, Rocha et al try to shed some light into this darkened corner of knowledge in Cardiac Surgery and Cardiology. The authors have performed a retrospective study which compared short-term clinical and echocardiographic results, and long-term survival of all patients receiving an aortic valve (bioprosthesis vs. mechanical valve) in 2012 in their Department. Even though the two populations (biological vs. mechanical) were not identical, after weeding out confounders, the end results showed that short term clinical and echocardiographic results differed only in a slightly greater LV remodeling at 3 months for bioprosthesis, with other clinical and echocardiographic results (including gradients, patient-prosthesis mismatch, ICU end-points, etc.) similar. In the long-term, mechanical valves shown a statistical non-significant trend for better survival and freedom from reoperation. Unfortunately, the small overall number of patients (n=193) did not allow for definitive conclusions.

A few points should be noted, however. This study reflects surgery and overall quality of care offered 8 years ago, and significant changes have entered the field of Cardiac Surgery and Cardiology since then. Isolated aortic valve reoperations have turned into a completely routine procedure except in endocarditis cases, TAVI has become widespread, and valve-in-valve TAVI (ViV), while eschewed by many surgeons, has been accumulating evidence as a safe and effective procedure, even though most evidence comes from the ViV registries and randomized controlled trials in this regard are non-existent. But if some surgeons argue contemporary ViV results facilitate the decision to place a biological valve in younger patients, cardiologists, on the other hand, argue that if a repeat procedure is inevitable in the future, maybe we should start with the "safest" less invasive procedure, which also gives the patients the larger effective orifice area to begin with.

In fact, many interventional cardiologists argue for starting with a TAVI, then a biological prosthesis, and if this surgical valve undergoes structural valve deterioration, then a ViV.

The other solution is to place a modern mechanical valve, and avoid the growing LVOT obstruction that will inevitably develop with the staged TAVI/bioprosthesis/ViV option - a "definitive solution", since neither mechanical valves nor TAVI´s are free from endocarditis or dysfunction.

And what should we expect from modern mechanical valves? New models, like the *Onyx* valve, and the *Sorin Slimline*, which entered the market a few years ago, allow for lower INR targets, with very good hemodynamic results. These valves, while for the moment still mandating vitamin K antagonists, do change a little bit the landscape of anti-coagulation related bleeding and thrombosis.

What sense then, to make of current knowledge, and of the added data that Rocha et al´s paper brings? It is difficult to crystalize in a blanket statement a definitive answer. Isolated clinical characteristics (such as inability to appropriately take anticoagulation), are still paramount in a decision. We would all like for more definitive data on this problem. But lacking this data, perhaps the best path is really to listen to the patient. While we wait for definitive data regarding modern developments (newest mechanical valves, ViV results, contemporary reoperation results) we can keep saying to most of these patients that results are similar with both types of prosthesis, and they should choose according to their own life and ability to deal with each type of prosthesis characteristics. This paper reinforces current attitudes regarding medical choices - the patient is at the center.

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COMENTÁRIO EDITORIAL

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The arterial switch operation

"There is something fascinating about science. One gets such wholesale returns of conjecture out of such a trifling investment of fact."
Mark Twain, Life on the Mississippi, 1883

The arterial switch operation has become the treatment of choice for neonates with transposition of the great arteries (TGA). Hospital mortality is low, although single or intramural coronary arteries remain significant risk factors.[1] Once named anatomical repair by opposition with the physiological repair or atrial switch, the late results are satisfactory[2,3] but far from being anatomical as pointed by Prof. Yacoub[4] almost 30 years ago and emphasized by the authors in the discussion. We can understand these late hindrances, namely why some coronary anastomosis grow with obstruction, some patients develop neo-pulmonary trunk stenosis or ventricular dysfunction as reported.[2,3] However, why some patients will need late surgery for neo-aortic valvular incompetence due to progressive "annular" dilatation even after decades of perfect performance of the valve, is still a matter of some debate. This can be related to the impossibility of reestablish a normal spiral configuration of the outlet septum and great arteries, as pointed by the authors, the reduction in the amount of collagen in the arterial roots in hearts with TGA as compared to that of normal hearts, in addition to less extensive anchorage and embedding of both arterial roots in the myocardium[5] and/or as observed after the Norwood or Ross surgeries, the more delicate pulmonary valve is integrated into the systemic circulation and can be damaged by this high-pressure regime.

We have to congratulate the long tradition of this group in their effort to understand and publish their performance.

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ARTIGO DE REVISÃO REVIEW ARTICLE

MANAGEMENT OF THE CAROTID ARTERY STENOSIS IN ASYMPTOMATIC PATIENTS

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Abstract

Background: *An asymptomatic carotid stenosis (CS) is defined as a stable atherosclerotic luminal narrowing in patients with no history of ipsilateral cerebral or ocular ischemic events in the past six months. The bifurcation of the common carotid artery makes this area vulnerable to atherosclerosis due to the features of haemodynamic flow. The exact prevalence of asymptomatic patients with CS remains unknown and opinions on the treatment of these patients are controversial.*

Objective: *The authors aimed to review the evidence on the management of the asymptomatic CS and describe its clinical characteristics, diagnosis and treatment management.*

Methods: *A comprehensive review of the literature was carried out to collate data from relevant studies concerning patients with extracranial moderate to severe asymptomatic carotid stenosis. The data used was identified by a search using PubMed and Google Scholar with the keywords / MESH terms "carotid stenosis", in combination with the term "asymptomatic". For this study, the authors focused on publications in the past two decades, using English publications.*

Results: *A few studies have addressed the prevalence, natural course and/or prognostic impact of asymptomatic CS in patients under medical treatment or undergoing vascular surgery procedures. The prevalence of asymptomatic CS ranged from 0.3% to 4.5% in women and 0.5% to 5.7% in men - The risk of stroke/TIA in these patients was reported between 2% to 5% annually with a downward trend across time to 0.5% with current best medical therapy.*

Conclusion: *A great proportion of patients with asymptomatic CS should be submitted to conservative management with best medical therapy. However, selective surgical management should be considered if high risk features are present.*

INTRODUCTION

Our knowledge of the pathogenesis, clinical manifestations, diagnosis and best treatment of asymptomatic patients with carotid artery stenosis (CS) has evolved and changed in the last years. In this review, a detailed description of the epidemiology, pathogenesis, disease mechanisms and up-to-date diagnostic workup and management is presented.

The aim is to guide physicians through the supporting evidence and the potential efficacy of commonly prescribed regimens at preventing vascular events and pre-specified composite outcomes in patients with asymptomatic carotid stenosis.

METHODS

A comprehensive review of the literature was carried out to collate data from relevant studies in patients with extracranial moderate to severe asymptomatic stenosis.

The data used was identified by a search using PubMed and Google Scholar with the keywords / MESH terms "carotid stenosis", in combination with the term "asymptomatic". For this study, the authors focused on publications in the past two decades, using English language publications.

EPIDEMIOLOGY OF CAROTID ARTERY STENOSIS

In Europe, stroke is the second cause of mortality (1.1 million deaths/year) being the most frequent cause of death in Portugal.[1,2]

The prevalence of moderate/severe asymptomatic CS in the general population (moderate stenosis: > 50% to <69% of the lumen is narrowed; severe CS: ≥ 70%) ranged from 0.3% to 4.5% in women and 0.5% to 5.7% in men4. The annual risk of stroke for patients with severe asymptomatic carotid stenosis is approximately 2 to 5%.[5,6,7,8] It is also known that CS leads to 10% to 15% of all ischaemic strokes, so it is one of the preventable etiologic factors for stroke.[9,10,5]

PATHOLOGY AND PATHOPHYSIOLOGY OF CAROTID ARTERY STENOSIS

The presence of the carotid bifurcation makes this area vulnerable to atherosclerosis because of the features of haemodynamic flow (Figure 1).[11] The aetiology of carotid artery ischaemic stroke is mainly the result of an embolic event originating on the atherosclerotic plaque.[12]

The main structure of atherosclerotic plaques is formed by a lipid core with infiltration of inflammatory cells, coated with a fibrous capsule.[11]

Atherosclerotic plaques are present on the intima layer of arteries and are the result of a complex atheromatous process:

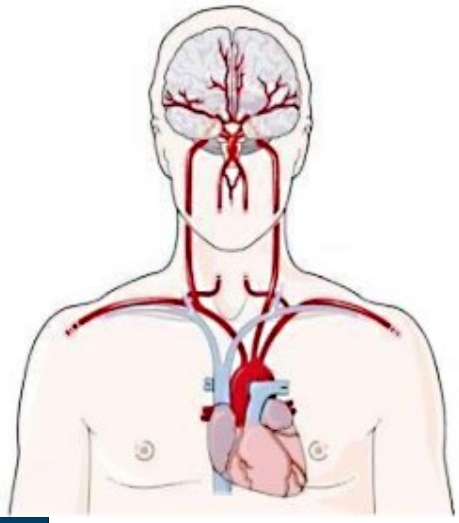

Figure 1 *Anatomy of carotid arteries. https://smart.servier.com/*

1. ↑increase in circulating LDL with vessel wall penetration.
2. Phagocytosis in the intima.
3. ↑ increase in vascularization.
4. ↑ increase in deposition of calcium and necrotic cells.
5. Fissures, ruptures and intra-plaque hemorrhages.
6. Ulceration and/or release of the plaque.
7. Deposition of platelets, clot formation, thrombosis and occlusion of the vessel (Figure 2).[13,9]

With the progression of atherosclerosis, the rupture of an atherosclerotic plaque is more likely, with thrombus formation resulting in arterial occlusion or embolism.[11] These thrombotic plaques are more often observed in patients with stroke (66.9%) *versus* TIA (36.1%) and asymptomatic patients (26.8%).[14] Initially, this occlusion can be temporary resulting in transient ischemic attack (TIA), which has similar symptoms to stroke and frequently lasts less than 24 hours.[11]

Regarding molecular pathways, initiation and progression of atherosclerosis are due to reactive oxygen

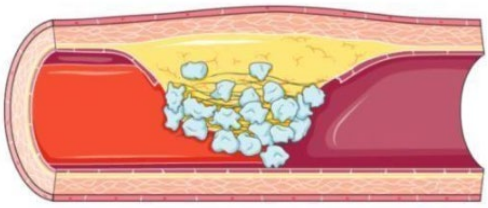

Figure 2 *Atherothrombosis. https://smart.servier.com/*

species (ROS.)[15,16,11] ROS increase the expression of cell adhesion molecules such as ICAM-1 (intercellular adhesion molecule-1), VCAM-1 (vascular cell adhesion molecule-1) and ELAMs (endothelial leukocyte adhesion molecule).[17,18] These molecules allow monocyte adhesion to endothelial cells. First, mild oxidation of low-density lipoprotein cholesterol (LDL-C) forms MM-LDL (minimally modified LDL) and then severe oxidation of MM-LDL forms oxidized LDL (OX-LDL). This increases Monocyte chemo-attractant protein-1 (MCP-1) due to stimulation of endothelial and smooth muscle cells. OX-LDL allows the differentiation of monocytes to macrophages which is promoted by MCSF (monocyte colony stimulating factor).[19] The new formed macrophages overexpress receptors for OX-LDL and produce foam cells which is the early stage of atherosclerosis.[20] Moreover, this mechanism also contributes to the instability of the atherosclerotic plaque which leads to thrombosis (Figure 3).[21]

This environment increases the expression of growth-regulating molecules PDGF (platelet-derived growth factor), bFGF (basic fibroblast growth factor), TGF-α and TGF-β and cytokines, such as IL-1 and TNF-α, which stimulate the synthesis of connective tissue and matrix. Progression of atherosclerosis is due to these mechanisms.[22]

CLINICAL PRESENTATION: UNSTABLE AND STABLE ATHEROSCLEROTIC PLAQUES

Unstable/vulnerable atherosclerotic plaques are characterized by extensive inflammation and accumulation of macrophages. Unstable plaques are more prone to rupture, leading to thrombotic and/or embolic events.[23] Unstable plaques are characterized by a thin fibrous capsule, less smooth muscle cells, more inflammatory cells and a vast lipid and necrotic core.[24] Hemodynamic stroke, in which the blood flow to the brain is temporarily suspended and then restored due to hemodynamic fluctuation, is a very rare event.

The majority of atherosclerotic plaques are stable and produce no symptoms, however, when the plaque increases considerably in size, the carotid artery lumen becomes markedly narrowed. An asymptomatic CS is

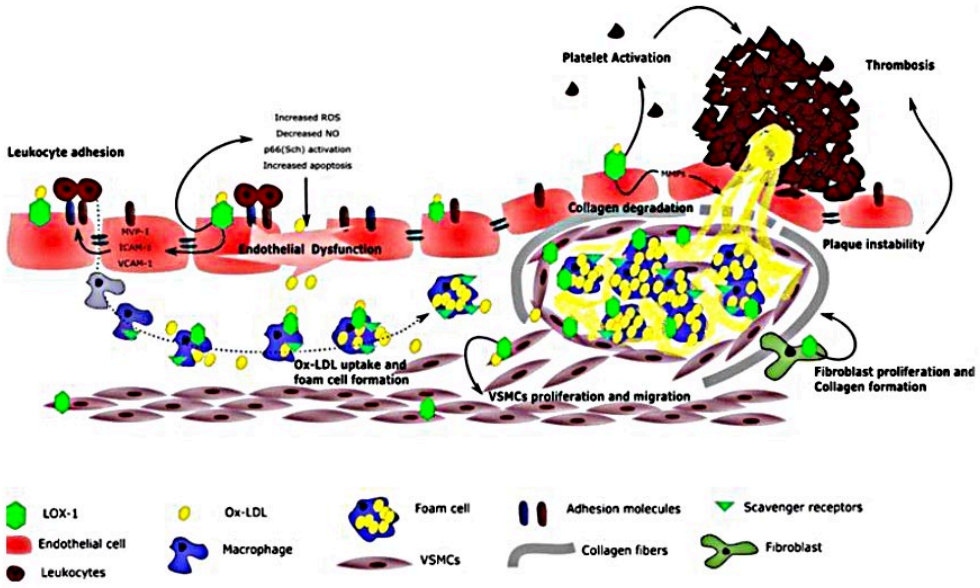

Figure 3

Molecular mechanism of atherosclerosis and posterior thrombosis.[21] Mehta AJKVKPPL. Oxidative Stress in Atherosclerosis. Genet Genomics. 2017.

present when a stable atherosclerotic plaque is detected in patients with no history in the past six months of ipsilateral cerebral or ocular ischemic events.[25]

It is known that CS is responsible for approximately 50% of TIAs.[26] The risk of having a stroke in the first month after TIAs is over 20%.[27]

RISK FACTORS

Risk factors for CS are similar to other cardiovascular diseases: dyslipidemia, hypertension, diabetes mellitus, advanced glycation end products (AGEs), obesity, cigarette smoking, lack of exercise, age, and C-reactive protein.[28,11]

Studies done by De Weerd M *et al.*, referred to cigarette smoking as the main risk factor for CS increasing the prevalence of CS in more than 50%.[29] Despite these various risk factors, the prevalence of severe CS is higher in patients with diabetes (Figure 4).[4]

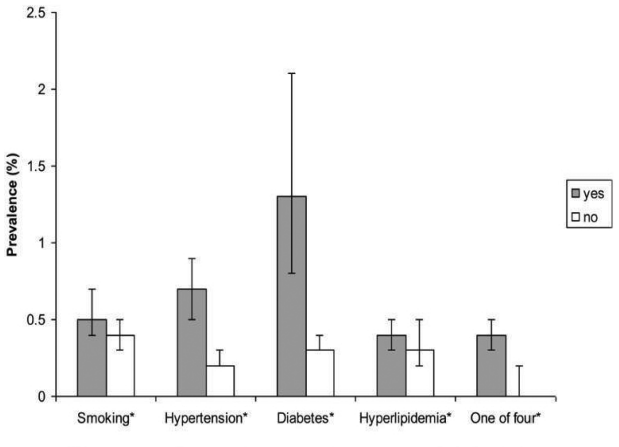

Figure 4

Prevalence of severe CAS risk factors.[4] M. de Weerd, J.P. Greving, B. Hedblad, M.W. Lorenz, E.B. Mathiesen, D.H. O'Leary, M. Rosvall, M. Sitzer, E. Buskens and MLB. Prevalence of asymptomatic carotid artery stenosis in the general population: an individual participant data meta-analysis. Stroke. 2010;41:1294-1297.

1. Dyslipidemia

Hypercholesterolemia leads to atherosclerosis due to the generation of ROS.[30] However, LDL-C is the major responsible for the development of atherosclerosis due to the effect of LDL and OX-LDL on endothelial NADPH-oxidase, leading to ROS production.[31] A meta-analysis, including 165 792 patients, of randomised trials of statins in association with other preventive measures, demonstrated a 21.1% reduction in relative risk for stroke (95% CI 6.3-33.5, p=0.009). This is possible due to reduction of LDL serum levels and the stabilization of the atherosclerotic plaque.[32] High Triglyceride levels (TG) are also a risk factor for atherosclerosis although contributing less.[33] TG can lead to formation of small dense LDL, can reduce HDL levels and increase inflammatory particles, such as ROS.[11]

2. Hypertension

Hypertension also contributes to atherosclerosis by similar mechanisms: unbalance of oxidative stress / antioxidants with resulting increase of ROS, increase of proinflammatory cytokines (IL-1β, IL-6, and TNF-α), chemokines and cell adhesion molecules (ICAM-1, sE-selectin, and sP-selectin).[34,35]

It is well known that inflammation leads to atherosclerosis and one of the best markers of this association is the C Reactive Protein (CRP) 36. Kitiyakara C *et al.* refers that increase of ROS precedes the progression of hypertension.[37]

3. Cigarette smoking

The prevalence of symptomatic CS is 4.4% in never-smokers *versus* 7.3% in former smokers *versus*

9.5% in current smokers. Furthermore, studies refer that smoking 20 pack-years has a significant correlation. Nevertheless with lower amounts of cigarette smoke, no significant association was found.[38] So, similar to other risk factors, cigarette smoking contributes to atherosclerosis by increasing expression of ROS, vascular cell adhesion molecules and proinflammatory cytokines.[39] Serum levels of Advanced Glycation End-products are also increased in cigarette smokers and their interaction with their receptor (RAGE) increases the production of ROS, activates NF-kB and vascular cell adhesion molecules and proinflammatory cytokines.[40,41]

4. Diabetes

Hyperglycemia promotes atherosclerosis due to diverse mechanisms such as oxidative stress, AGEs, and protein kinase C. Oxidative stress leads to atherosclerosis mainly due to mitochondrial mechanisms in which hyperglycemia metabolism leads to reduction of NADPH and activation of NADPH-oxidase which contributes to oxidative stress.[42,43] Finally, hyperglycemia leads to activation of diacylglycerol (DAG) which promotes the development of atherosclerosis by activating the pathway of Protein Kinase C.[44]

5. Age

The prevalence of CS under 60 years is 0.5% *versus* <5% above 80 years old. Men under 75 years old have more chance of having CS than women of the same age. Although, after 75 years of age women have more chance of having CS than men.[11] The mechanism involved is probably due to an increase of inflammatory markers that naturally increase with aging.

6. Obesity

Obesity is considered an independent risk factor for CS although being also a risk factor for diabetes, hypertension and insulin resistance and some interaction between risk factors is an issue.[45,46]

7. C-Reactive Protein

High sensitivity CRP is a proinflammatory protein that increases the production of ROS over activation of neutrophils. So, this marker is correlated with higher risk of stroke.[47] Other mechanisms include increased expression of vascular cell adhesion molecules and foam cell formation.[48]

CLASSIFICATION AND DIAGNOSIS IN CS

The majority of plaques responsible for ischemic events are moderate, however there are some high-grade plaques which increase the probability of having a stroke. Most atherosclerotic plaques are stable/asymptomatic,[49] however, Anxin Wang *et al*, concluded that in patients with metabolic syndrome, the prevalence of unstable plaques is higher than the prevalence of stable plaques.[50]

It is of the most relevance in patients with asymptomatic carotid stenosis to determine the clinical and ultrasonographic plaque predictors of progression or regression of the stenosis. In a study, 1 121 patients with asymptomatic carotid stenosis were submitted to several clinical and ultrasound assessments during 6 months and 8 years (respectively). Regression was observed in 43 patients (3.8%) and progression in 222 (19.8%). No changes were observed in 856 patients (76.4%). Independent predictors of long-term stability were: younger age, more severe degrees of stenosis, absence of white areas in the atherosclerotic plaque and patients under lipid lowering therapy.[51] Independent predictors of progression were: high serum levels of creatinine, male gender, patients not under lipid lowering therapy, less severe degrees of stenosis and larger plaque area.[51]

However, the translation to clinical practice is hampered by the low frequency of progression (only 19.8% of the patients) and the low associated stroke rate (only 30% of the 30 strokes were in the progression group).[51]

The classification of CS can be determined mainly by two methods: NASCET (*North American Symptomatic Carotid Endarterectomy Trial*) and ECST (*European Carotid Surgery Trial*). The NASCET method grades stenosis by comparison of the local luminal narrowing and the diameter of the distal internal carotid artery while ECST is based on local grade degree of stenosis.[52] Despite the existence of these two methods, the most accepted and widespread is the NASCET method, although ECST can be used as well.[52]

Despite this, the 2018 *Guidelines* of ESVS don't recommend population screening for asymptomatic patients with CS (Class III, Level C). Furthermore, *The Society for Vascular Surgery* recommends that this routine screening should only be done in patients with multiple risk factors.[53]

TREATMENT INDICATIONS FOR ASYMPTOMATIC CSS

Independently of asymptomatic or symptomatic patients with CS, the core treatment is based on control of cardiovascular risk factors. However, some of these risk factors are modifiable (CRP, diabetes, obesity, hypertension, smoking, dyslipidemia) but others are not manageable.[11]

Lifestyle changes are paramount in the delay of the progression of CS. The 2014 *Guidelines of American Heart Association* recommends: DASH diet (vegetables, fruits, fish) and/or Mediterranean diet (same but with addiction on olive oil), weight reduction (body mass index <25), regular physical exercise (at least 40 min 3/4 times a week), limited consumption of alcohol and sodium (salt restriction to 2–3 g/day of salt) and smoking cessation.[54,55,56,57,58]

Chiuve SE *et al.*, concluded that if all these lifestyle changes were adopted, the risk of stroke could be reduced by 80% among women.[59] de Lorgeril M *et. al.*, refer that with Mediterranean diet it is possible to reduce the probability of developing a stroke and/or myocardial infarction (≥60%), if secondary prevention is adopted.[60] However, if primary prevention is adopted, stroke can be reduced by 50%.[55]

The management of patients with asymptomatic CS has some debatable aspects due to the annual risk of stroke for patients with severe asymptomatic carotid stenosis being nowadays as low as 2%-5%.[5,6,7,8] Additional, evidence has shown a decrease in the risk of stroke over time and this might be due to improvements in medical therapy.[61]

For asymptomatic patients with CS < 60%, medical treatment alone is favored and for asymptomatic patients with CS > 60%, invasive treatment is considered.[62,63] To warrant that the intervention is superior to best medical treatment alone, recommendations state that the perioperative risk of stroke in asymptomatic patients with CS should be inferior to 3%.[64] Selected patients on best medical therapy, with clinical and/or imaging features that classify them as having higher probability of suffering a stroke, might benefit from surgical procedure. Moreover, the patients that in the present are being treated with best medical therapy and don't benefit from surgical procedure, should be followed with regular carotid ultrasonography.[53]

TREATMENT OF ASYMPTOMATIC PATIENTS WITH CS

1. Pharmacological agents:

These patients must be treated with intensive medical treatment which is meant to correct the risk factors mentioned previously in order to lower the probability of developing a stroke.[65]

1.1. Lipid lowering agents: The most recent *Guidelines from the ESVS* recommend high dose statin therapy for primary and secondary prevention. *Asymptomatic Carotid Surgery Trial* (ACST-1) presents results for 10-year risk of stroke/death for asymptomatic patients taking lipid lowering agents (statins) of 13,4% while in patients without taking statins, was 24.1%.[66] Atorvastatin and rosuvastatin are the two pharmacological agents with more evidence support in reducing LDL to less than 70 mg/dl and also decreasing the levels of CRP to less than 2 mg/l. These results support the use of statins as primary prevention for stroke. The major therapeutic target is to obtain, at least, 50% reduction of the initial value of LDL or reach the value of less than 1.8 mmol L−1 (70 mg dL−1).[53,67]

1.2. Antihypertensive agents: Law MR *et al.*, refers that a decrease in stroke risk is related to a decrease of systolic blood pressure.[68] Huo Y *et al.*, in 2015, found out that enalapril and folic acid (despite enalapril alone) can reduce the risk of developing a first stroke, so they concluded that enalapril is the pharmacological agent with more evidence on hard outcomes in asymptomatic patients with CS.[69] The major goal in non-diabetic patients is to reduce arterial blood pressure to 140/90 mm Hg or less while in diabetic patients is 140/80 mm Hg (*Guidelines of hypertension 2018*).[70] Besides this, if a procedure is to be undertaken, the perioperative goal is less than 180/90 mm Hg.[53]

1.3. Antiplatelet therapy: Inadequate antiplatelet therapy can lead to a greater risk of developing major bleeding events, while not decreasing stroke risk. So, the benefit versus harm has to be carefully measured in every single patient. Thus, the more recent evidence recommends monotherapy with aspirin (instead of dual therapy) as first option, while clopidogrel is reserved for patients who have contraindications to aspirin. The doses should be between 75-325 mg of aspirin (low-dose aspirin) and 75 mg of clopidogrel.[53]

2. Carotid Endarterectomy (CEA) - surgical procedure

In some patients, carotid endarterectomy may be considered. There are some clinical predictors that may help in the decision such as: age, gender, stenosis severity, progression of stenosis, plaque characteristics, presence of silent emboli and/or microemboli and cerebrovascular reserve.

2.1. Age: Earlier studies concluded that, despite the age of the patient, it was beneficial to undergo CEA because the risk of suffering a stroke in the next 5 years would be lower when compared with medical therapy. However, further investigation indicates that half of these patients with more than 75 years old, would be dead in the long term follow-up after intervention. After including the perioperative risks, it was concluded that the benefit of undergoing CEA in patients older than 75 years was lower.[66] However, in patients older than 75 years of age and with an average life expectancy beyond 5 years, CEA may be beneficial.[53]

2.2. Gender: Multiple studies were performed and concluded that the probability of suffering a stroke within 5 years is decreased by CEA in men but not in women. Women would benefit from CEA only after 10 years of follow-up. This controversial finding is explained by the inherent lower risk of suffering a stroke in women not submitted to CEA, so it is expected that the benefit needs more time in order to be apparent.[72,66]

2.3. Stenosis severity: Despite what happens in symptomatic patients, stenosis severity alone is not a predictor of future stroke in asymptomatic patients with CS.[63,73] Patients with 50-69% stenosis have a lower risk of suffering a stroke compared to patients with more than 70% stenosis (0.8% *vs.* 1.4%).74. So, to make the decision of doing CEA, stenosis severity should be conjugated with other clinical features and not considered alone.[75] Hobson R. W. *et al.*, refers that with the presence of low-grade CAS in asymptomatic patients, the best choice of treatment is intensive medical treatment.[65]

2.4. Progression of stenosis: In the ACST was found out that patients with stenosis that had developed in two grades, had four times more probability of suffering an ipsilateral neurologic event.[76]

2.5. Plaque characteristics: DUS can characterize atherosclerotic plaques by evaluating, for example, the presence of ulceration. This finding may be associated with a higher probability of developing a thromboembolic event. Furthermore, the risk is also higher if the plaque is echolucent and with more lipids than fibrotic components.[77,78] The gray-scale median (GSM) is a standardized measurement of overall plaque echogenicity/echolucency. Lower values (associated with more echolucent plaques) are associated with higher long-term incidence of cardiovascular events.[79] However, its application are prone to some subjectivity, precluding its widespread use.

2.6. Presence of silent emboli and/or microemboli: Features of the atherosclerotic plaque on computed tomography (CT) or magnetic resonance imaging (MRI) may be predictors of silent emboli. Transcranial Doppler (TCD) can be used to identify active microembolization. This could be relevant because their presence can possibly predict an ipsilateral stroke.[80,81]

2.7. Cerebrovascular reserve: A reduced cerebrovascular reserve occurs when an incomplete circle of Willis is present or when intracranial or contralateral occlusive disease is present. This situation reduces cerebral perfusion pressure and is detected by transcranial Doppler flow on cerebral vessels. According to Gupta A. *et al.*, there is a significant association with a reduced cerebrovascular reserve and stroke.

So, with the integration of these clinical features it is possible to select an high risk patient with asymptomatic CS benefitting from CEA.[83,84] According to recommendations of the *American Heart Association* (AHA), only this type of patient should be considered for CEA.

CONCLUSION

With current best medical therapy, asymptomatic patients with CS have an annual risk of ipsilateral stroke of approximately 0.5%.[85] Therefore, the main goal is to promote control of risk factors.[11]

Due to elevated mortality and morbidity associated with CS, over the years, the identification of high-risk asymptomatic patients with CS has become one of the major goals in vascular surgery. The timely identification leads to timely treatment and this will lead to a decrease in morbidity and mortality.[12]

The 2018 Guidelines of ESVS recommend that a multidisciplinary team (MDT) should be present and should be composed by neurologists and vascular surgeons. This will allow an optimal treatment in patients undergoing CEA.[53]

Selim M H *et al.*, referred that medical treatment is more cost-effective than CEA and approximately only 50% of the patients benefit from CEA.[86]

The role of carotid artery stenting (CAS) in asymptomatic patients has been a matter of controversy in the past but at the moment there are no clear indications for its use in this subset of patients with CS.[53] The management of asymptomatic patients with CS remains a challenge, but it is already known that medical and surgical treatment are developing faster and in the future stroke risk will continue to decrease.[87]

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ARTIGO DE REVISÃO REVIEW ARTICLE

WHY AND WHEN TO REQUEST FOR A PET/CT SCAN IN A LUNG CANCER PATIENT?

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Abstract

This review will focus on whole-body functional imaging applied to lung cancer disease and patient management.

Lung cancer needs to be avoided… (but if not well succeeded), suspected, screened, histologically confirmed, anatomically inventoried, prognostically staged, molecularly characterized, genetically studied and finally, therapeutically managed.

Functional imaging using 18F-fluoro-deoxy-glucose (FDG) is a non-invasive method that is widely used in oncologic disease, mainly for clinical staging and re-staging, with impact on therapy planning.

For lung cancer, the functional imaging with FDG-PET/CT is used for clinical staging and also to provide information on a pre-diagnostic phase, to categorize lung nodules according to the metabolic risk of malignancy.

Clinicians need to be aware of the different possibilities of the functional imaging information, to provide the better use of it.

This review will focus on data from the different medical fields that are considered important to informed decision making when asking for functional imaging in the daily clinical routine of a lung cancer patient.

INTRODUCTION

The purpose of this work is to review the indications for positron emission tomography with computed tomography (PET/CT), in the management of lung carcinoma, in the era of the 8th Edition of the AJCC cancer TNM staging.

The TNM staging classification applies to carcinomas of the lung including non-small cell carcinomas, small cell carcinomas and bronchopulmonary carcinoid tumours.[1] It codes the anatomic extent of the disease and creates prognostic stage groups.

The staging procedure may include a variety of non-invasive and invasive methods, and constitutes the basis for planning therapy and multicentric therapeutic clinical trials.

Whole-body PET/CT is a non-invasive anatomic and metabolic imaging modality that integrates detailed anatomic information with metabolic information.

HIGHLIGHTS OF SOME TECHNICAL ASPECT OF A PET/CT SCAN.[2]

Image acquisition:

PET/CT is a hybrid imaging technology introduced by Townsend, Nutt, and Beyer in 1998, and became commercially available in the beginning of 2001.

This imaging technique comprises the acquisition of a low radiation dose whole body computerized tomography (CT) immediately followed by the acquisition of a whole body positron emission tomography (PET).

Attenuation-corrected PET images will be reconstructed and a hybrid whole body PET/CT image will be accessible for medical interpretation.

The PET imaging component comprises a whole body in vivo distribution of a positron emission radiopharmaceutical.

Positron emission (^{18}F and ^{68}Ga) Radiopharmaceuticals:

In this work two different radiopharmaceuticals will be reviewed, presently available to perform a PET/CT scan in the clinical work-up of lung carcinomas;

^{18}F-Fluoro-deoxy-glucose (FDG) is a Fluor-18(18F) analogue of glucose largely used in oncology, mainly because of its high sensitivity to detect viable neoplastic lesions.

- At a cellular level the FDG molecule competes with glucose transporters (GLUTs) into tumour cells and also competes for phosphorylation by hexoquinase. But the FDG phosphorylated form will not progress in the glycolytic metabolic pathway, will be trapped within the cell, accumulate there and, because of

that, the radioactive signal progressively increases to be detect on PET imaging.

- The FDG uptake of a neoplastic lesion reflects a mix of biologic variables: the amount of vascularisation of that lesion, cell density, cellular rate of exogenous glucose consumption, cellular expression of GLUTs and hexokinases. On the contrary, necrosis or the amount of non-FDG uptake material like mucin, will reduce the FDG uptake/signal.
- Because of this metabolic nature, FDG is not specific for neoplastic cells and normal cell FDG uptake will also occur, according to each cell glycolytic activity rate.
- The reason for the wide use of FDG in oncology is because a large group of neoplastic cells have a very high glycolic rate that will produce high contrast uptake of neoplastic cells in between normal tissue.

FDG not only enhances most malignant tumours but can also enhance areas of active inflammation. When interpreting images, it is important to be aware that inflammatory activated cells might also show high FDG uptake and false positives could occur with granulation tissue, healing wounds, talc deposits in the pleura after pleurodesis, placement of central lines, chest tubes and gastrostomy tubes or recent percutaneous needle biopsy.

The clinical information and the anatomic data coming from CT imaging contributes to clarify the causes of these FDG uptakes, preventing imaging misinterpretation.

^{68}Ga-DOTA-somatostatin analogpeptides is a Galium-68(68Ga) positron emission-radiopharmaceutical with in vivo affinity to somatostatin (SST) cell membrane receptors (Rs).

- Somatostatin cell receptors (SSTRs) belong to the group of seven transmembrane helix proteins, able to transmit an extracellular signal into the cell.
- Five distinct subtypes of somatostatin receptors (SSTR1, SSTR2, SSTR3, SSTR4, SSTR5) have been identified, with SSTR2 showing the highest affinity for natural SST and synthetic SST analogs.
- Most neuroendocrine tumors (NETs) have high expression of SSTRs, and that opens the possibility for tumor imaging and therapy with radiolabeled SST analogs.

PET Imaging quantification

The ability to quantify physiological variables has an important role in clinical practice and is a crucial tool in multicentric oncology trials.

Particularly in PET imaging, quantifying means that the tissue or lesion's radioactive signal that is acquired will be transformed into the absolute concentration of the radiopharmaceutical in that tissue, at a specific point in time. That will be expressed by the *standard uptake value* (SUV).

In SUV calculation the most used patient variable is body weight, and not body surface area (BSA) nor lean body mass (LBM), and the most used imaging methodology is the highest activity of pixel image in the tumour region (SUV_{max}).

Another quantitative variable also used is clinical practice is SUV_{peak}. Its calculation is based on the highest activity of a spherical volume of interest (VOI) with a 1mL volume, located in tumour region position that provides the maximal activity VOI average.

A deep understanding of this imaging quantification methodology might be gained by reading two interesting references that nicely express this theme nuances over time.[3,4]

FDG-PET imaging patient preparation

Patients need to fast (except for water) for at least 6 hours.

Blood glucose level is always verified and needs to be lower than 200 mg/dL, ideally lower than 140 mg/dL.

Radiopharmaceutical administration will be intravenous, and the patient will then rest for a 60 minutes period (corresponding to the biologic FDG uptake time).

Next step will be a whole-body imaging (PET-CT) acquisition, approximately in-between 20 to 30 min.

Attenuation-corrected PET images are reconstructed and integrated PET and CT images are obtained automatically.

Diabetic patients also need to achieve a proper fast blood glucose level (« 200mg/dL, preferentially «140mg/dL), ideally just with diet control but, if necessary also with oral anti-diabetic drugs or with long-acting insulin.

Rapid-insulin should not be used before FDG intravenous administration, because it will affect FDG in-vivo distribution, increasing mass muscle uptake and reducing lesions uptake.

Dual time lung acquisition applied to solitary lung nodules

This means two image acquisitions;

- Initial whole body PET/CT scan after 60min post-FDG injection uptake time
- Second delayed segmental lung imaging, usually after 180 min-post-FDG injection uptake time.

The rational for this protocol is based on the knowledge that FDG lung lesion uptake is a dynamic and progressive process that is continuously occurring, and the plateau uptake might not be reached until a maximal period of 5h post-FDG injection.

For a lung lesion, an increase in the SUV_{max} of delayed imaging acquisition, an absolute value of SUV_{max} superior to 2,5 or if an increase of 10% or more in SUVmax occurs between the initial and delayed image, can be an indication of malignancy.

This Dual time lung imaging protocol is particularly useful for solitary lung nodule study with marginal FDG uptake of SUV_{max} 2,5.[5]

Histologic and anatomic consideration in lung cancer:[6]

Non-small cell lung cancer (NSCLC) can be further categorized into several different types of epithelial malignant tumours, namely:

- Adenocarcinoma (ADC): comprises 40% of all lung cancers, is a malignant epithelial tumour with glandular differentiation, mucin production or pneumocyte marker expression. These tumours have particular growth patterns: lepidic, acinar, papillar, micropapillary and solid.
- Other variants of ADC are: invasive mucinous, colloid, fetal, enteric, or minimally invasive carcinoma.
- ADC typically will form a peripherally located mass that exhibits both central fibrosis and pleural puckering. But other appearances might occur and an ADC could be a centrally located mass, a diffuse lobar consolidation, or may express itself as multiple lobe lesions distributed bilaterally, and even pleural thickening.
- Squamous cell carcinoma (SCC) comprises approximately 20% of all lung cancers. It is a malignant epithelial tumour with 3 subtypes: keratinizing, non-keratinizing, and basaloid SCC can also be present in various places throughout the lungs, but the most common include the central portion, along major airways forming cavities when present in larger sizes.
- Large cell carcinoma: diagnosis cannot be done in a biopsy sample, but only be achieved with tumour surgical resection. There are several different subtypes of large cell carcinoma including; large cell neuroendocrine carcinoma (LCNEC), basaloid carcinoma, lymphoepithelioma-like carcinoma, clear cell carcinoma, and large cell carcinoma with rhabdoid phenotype.
- Other less common types of NSCLC include adenosquamous, pleomorphic, spindle cell, and giant cell carcinomas, as well as pulmonary blastoma, neuroendocrine tumours, and several others.

Neuroendocrine Lung Tumours (NET): Approximately 20% of all primary lung tumors are neuroendocrine including:

- Small cell carcinoma (SCC) comprises about 13% of all lung cancer and is a very aggressive type of NET.
- Large cell NE carcinoma (LCNC) is an aggressive type of cancer, four times as frequent in men as in women, it is quite rare in general.
- Carcinoide Tumour is a well-differentiated lung NET, which includes:
  - Low-grade, Typical carcinoids with a very slowly growth rate. Advanced disease, with malignant progression is very rare.
  - Intermediate grade, Atypical carcinoids with a faster growth rate, but not nearly as fast as other major types of lung cancer.
- Since lung NETs develop in hormone-producing cells, a few patients experience paraneoplastic symptoms unrelated to the lungs, such as diarrhoea or flushing in the face.

FDG-PET/CT scan and anatomic extension of Distant Metastasis (M) staging:

Distant metastasis detection is crucial in staging since it will include the patient in stage IV.

Among 813,302 NSCLC patients eligible for final analysis diagnosed between 1998 and 2006, approximately two thirds of patients had locally advanced (27.6%) or metastatic (38.1%) disease.[7]

FDG-PET/CT scan is a highly efficient way to detect metastasis due to the fact that it is a whole body and a multiorgan evaluation, and uses a radiopharmaceutical (FDG) with high detectability of the neoplastic tissue with cellular glycolic activity.

Also, since commercial PET scanners provide spatial resolution of 4.5 to 6.0 mm , even lesions smaller than 1 cm in diameter can be detected on the basis of an increased uptake of FDG.

The ability to detect a metastatic lesion is not directly dependent on the lesion dimension, but much more related with the metabolic contrast between the metastatic lesion and the normal surrounding tissue where it is implanted.

For example, normal bone tissue presents low FDG uptake but bone metastasis usually affords a high metabolic signal, causing a high metabolic contrast with surrounding tissue. In fact, a bone metastasis could be FDG positive with a small volume well before bone density and architecture defect can be detected on anatomic CT imaging.

The same applies for a lung or a subcutaneous metastasis, where a high metabolic contrast between the metastatic lesion and the normal surrounding tissue is possible.

Pleural metastasis from lung cancer could be present with or without pleural effusion.

FDG pleural uptake is always abnormal, even with low intensity. In a lung carcinoma patient, pleural uptake is highly suspicious for metastatic pleural disease. In case that this is the only site for metastatic disease finding, a histologic diagnosis is recommended and pleural FDG uptake location should be used to guide biopsy.[8]

Hepatic and kidney metastatic lesions are usually well detected, because of the fact that these two organs show a moderate physiologic FDG uptake, and the metastatic detection is dependent on metabolic rate and lesion volume.

For brain metastasis detection, FDG sensibility is reduced (60%), because normal brain cortex has a high glycolytic rate and a physiologic high FDG uptake. Contrast-enhanced MRI has a higher sensitivity for assessing brain metastasis than PET-CT.

Besides this fact, if FDG brain imaging is included in whole body imaging, it should always be analysed with the purpose of searching for metastatic brain lesions with FDG uptake higher than normal brain cortex or searching for special cases with brain focal areas of no FDG uptake, that could be a signal of brain oedema, secondary to brain metastatic disease.

Adrenal gland metastatic disease is able to be detected by FDG uptake, even with a small volume, but for this anatomic site the specificity for metastatic detection with FDG is lower (90%) than for the other sites (96%). The reason for that is dependent on the fact that some benign adrenal adenomas (or adrenal tuberculosis) might show FDG uptake.[9]

The important message is that, an adrenal gland nodule FDG positive, needs to be conjugated with diagnostic CT information. It may then be clarified if it is a benign adenoma (hypodense and with a regular contour) or a metastatic lesion with visible capsule invasion. If diagnostic CT information cannot clarify the nodular aetiology, and if the adrenal gland is the only site of metastatic disease, than a histologic diagnosis confirmation is recommended, because a false FDG positive result could be upstaging the patient and compromising the treatment strategy.

FDG-PET/CT could identify unsuspected extra thoracic lymph node metastasis, with normal size («1cm at CT). Nodal FDG uptake higher than blood pool is criteria for suspicious nodal metastasis, and nodal FDG uptake higher than liver uptake is highly concerning for nodal metastatic disease.

Detection of a second primary malignancy could happen in particularly because FDG-PET/CT is a whole body examination, and is estimated to occur in about 3% of lung NSCLC patients. Histologic diagnosis is always necessary, and this finding will impact on that patient management.[10]

In general any potential false FDG-positive lesions should be confirmed by biopsy if it could cause an upstaging, with implication on therapy strategy.

FDG-PET/CT scan and Regional Lymph node (N) staging:

Morphologic nodal staging with CT is based on lymph node size, were a node with a short axis diameter bigger than 10 mm is suspect of metastatic lymph node.

Metabolic nodal staging with FDG has a significantly higher sensitivity and specificity than morphological nodal criteria of CT in the detection of malignant involvement of mediastinal lymph nodes.

In a meta-analysis study, the sensitivity of PET/ CT for nodal metastasis was 85% and the specificity was 95% as compared with a CT sensitivity of 61% and specificity of 79%.[11]

The clinical importance of FDG-PET is the high negative predictive value in lymph node staging, which has been estimated to be higher than 90% in several studies.

However, it is important to be aware that there are cases of FDG-PET/CT nodal false negative results for small nodes <10-15 mm diameter, due to microscopic nodal metastases occurrence, only detected by post-operative histopathology.

Also, for central primary tumours might be not possible to distinguish between the primary lesion and the adjacent hilar nodes.[12] On the contrary, false positive nodal disease may occur with granulomatous disease (tuberculosis or sarcoidosis).

In view of the diagnostic accuracy recorded with PET--CT, when there is suggestion of malignant involvement of mediastinal lymph nodes by FDG-PET/CT, complementary invasive diagnostic assessment (EBUS or other) might be necessary for histological confirmation (Figure1), in order to accurately stage the patient.[13]

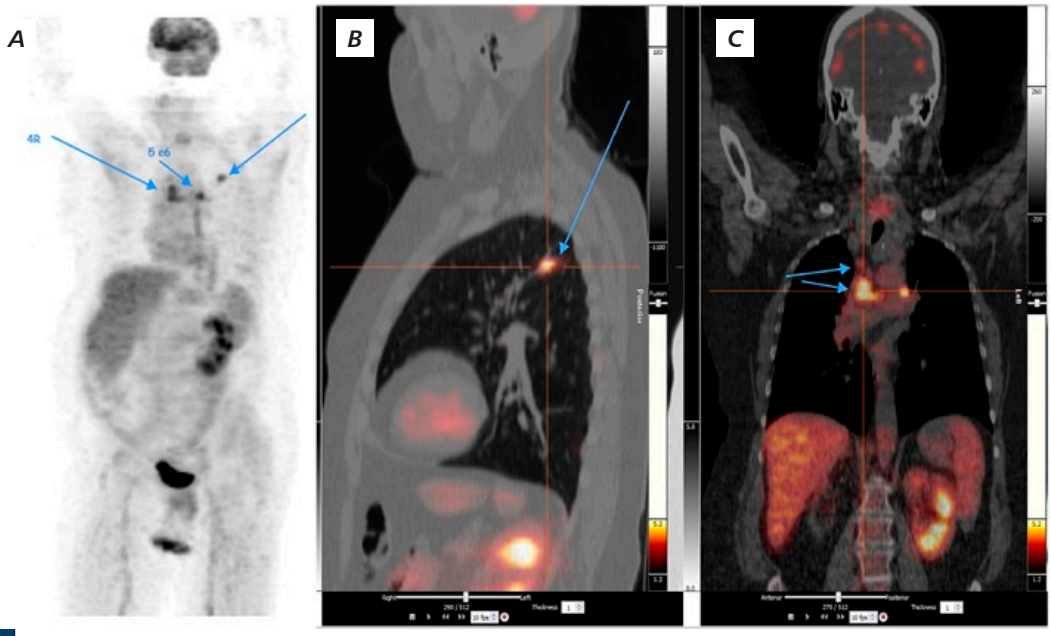

Figure 1

(A) A 68-yr-old asymptomatic male, with a CT finding of a solitary lung nodule on left superior lobe, with largest diameter of 18mm. (B) FDG-PET/CT shows positive uptake with SUVmax of 4,9. (C) At hilar region FDG uptake was not found. In the mediastinum nodal uptake was present: at sub- and para-aortic nodes (station 5-6), and at right upper paratracheal nodes (4R). No extra-thoracic FDG-uptake was present (cM0 stage). The contralateral mediastinal nodal FDG positive disease, was histologically confirmed by minimally invasive methodology, EBUS.

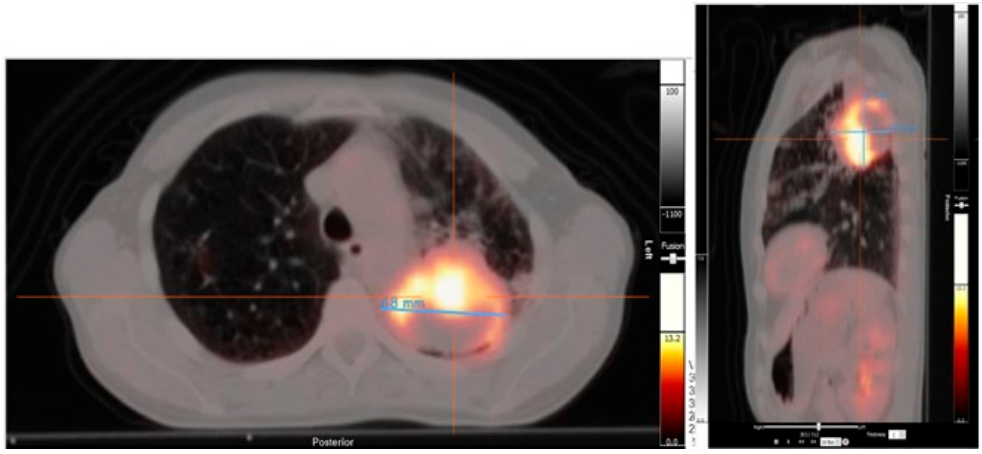

Figure 2 *59-yr-old female, with a lung mass (68mm) on the left superior lobe, with pleural contact. FDG-PET/CT imaging shows lung mass with positive uptake (SUV_{max} of 14), mainly peripheral, and a large intra-lesion necrosis. The transthoracic biopsy performed before PET/CT was non-diagnostic, because of necrotic sample.*

FDG-PET/CT SCAN AND PRIMARY TUMOR (T) STAGING

Lung carcinoma is a bronchogenic neoplasm arising from epithelial cells of the bronchial mucosa or from the cells lining the alveoli.

Although lung carcinomas may arise in any part of the lung, **Squamous cell** and **Small cell carcinomas** tend to arise from mucosa of **more central bronchi**, involving the lobar origin and the main bronchi. This more frequent central location often is the cause of obstruction and secondary atelectasis, invasion of bronchial wall and of mediastinal structures.

On the other hand, **Adenocarcinoma** tend to more often located in the **periphery of the lung**, with extension to visceral pleura, more often causing pleural invasion, pleural effusion and chest wall invasion.

Since 2011, adenocarcinoma was reclassified to reflect invasiveness and growth characteristics, into:

a) adenocarcinoma in situ,

b) minimally invasive adenocarcinoma,

c) invasive adenocarcinoma

The 8th Ed. of AJCC for lung carcinoma staging reflects this pathologic reclassification of adenocarcinomas (including the new Tis and the T1a (mi)) and also includes different T descriptors, according to new size cut-off of T category.

These two new T categories, Tis and T1a (mi), are particularly important for imaging diagnostic CT and FDG-PET/CT, because these two categories will manifest as ground-glass or partial-solid ground-glass nodules.

- Tis - carcinoma *in situ*- is a pure ground-glass lesion with a diameter «3cm, without CT imaging of solid component (and without invasive component at histopathologic evaluation).
- T1a (mi) - minimally invasive adenocarcinoma is a ground-glass lesion with a diameter «3cm, with a solid CT solid component «5mm (the invasive component at histopathology evaluation also «5mm).

It is interesting to note that, for cases of early T category (cT1b, cT1c and cT2) FDG-PET/CT scan is usually performed under the work-up of solitary lung nodule, before histology lung cancer confirmation.

For large primary lung lesions (highly suspected of cT3 and cT4), FDG-PET/CT is advised and, if possible, should be performed before lung lesion biopsy, for it will reduce the risk of unsuccessful biopsy of necrotic sample (Figure2).

Table 1 **FDG-PET/CT indication according to the 8th Ed. of TNM staging[1]:**

cTcategory	Clinical stage	FDG-PET/CT indication
Ground-glass opacities cTis		FDG-PET/CT is NOT required
cT1a (mi) cT1a (larger diameter of the solid component on CT < 1cm). Without other abnormality on chest CT.	stage IA1 cT1(mi) cN0 and cT1a cN0	FDG-PET/CT is NOT required for evaluating metastatic spread.
Candidates for treatment with curative intention.		FDG-PET/CT is indicated for evaluating metastatic spread (except for brain). FDG-PET/CT should categorize TNM uptake, with location and SUVmax quantification.

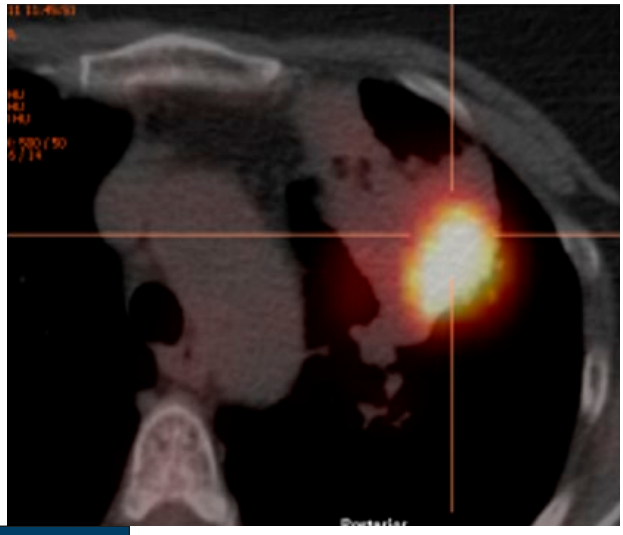

Figure 3 *Retro-obstructive atelectasis without FDG uptake in an Upper left lung FDG positive tumour.*

Also, because the whole body FDG-PET/CT imaging will detect FDG positive mediastinal nodal disease and/or unexpected distant metastasis, that information might introduce a different choice for biopsy location.

For individuals who have a solitary extra thoracic site suspicious of a metastasis, tissue confirmation of that M1 site is recommended if a fine-needle aspiration or biopsy is feasible.

Another important attribute of FDG-PET/CT is the ability to distinguish between tumour and distal atelectasis (Figure 3), secondary to tumour obstruction.

This information might have important impact on cT staging diameter and cT staging atelectasis or obstructive pneumonitis extending to the hilum and finally the tumour, but also for radiotherapy planning, this atelectasis information might significantly adjust and improve radiotherapy planning field. Changes of the therapeutic strategy due to PET/CT are especially seen in cT3 and cT4 tumours.

Another particular information of metabolic imaging is the clarification of parietal tumour invasion (figure 4), with special relevance for treatment planning of surgery and radiotherapy.

A prospective study where the accuracy of the preoperative staging of non-small cell lung cancer was evaluated comparing stand-alone CT and integrated FDG--PET/CT, the primary tumor was correctly staged in 84 patients (79%) at stand-alone CT and in 91 patients (86%) at integrated FDG PET/CT.[14]

Lymphangitic carcinomatosis, when present, can be seen on FDG-PET/CT images as a diffuse peritumoral uptake.

Work-up of solitary lung nodule /of a potencial lung cancer lesion (T):

A small note about this process at this time seems to be important since with the programmes for lung cancer screening, this investigation will be more and more frequent.

The aim of the screening procedure is to diagnose lung cancer lesions at an initial T staging level, ideally before cT2.

For indeterminate pulmonary nodules at diagnostic lung CT, and according to patient risk factor and pulmonary nodule characteristics (solid vs subsolid, dimension, unique vs multiple) a decision needs to be made between no routine follow-up required, routine CT follow-up, indication for FDG-PET/CT or tissue sampling.

The state of the art seems to be to follow the Fleischner Society's pulmonary nodule recommendations, where the ground glass lesions surveillance method is clearly indicated.[15]

FDG-PET/CT scan will contribute to the risk calculation of malignancy with the metabolic characterization of solid pulmonary nodules, following the rule (using an uptake time of 50 to 60 min):

- A nodule is positive for malignancy if SUV_{max} is higher than 2,5 » biopsy,
- If a nodule less than 1cm diameter demonstrated any FDG uptake, should be considered potentially malignant » biopsy,
- Dual point image at 1 and 3 hours uptake time) improves accuracy, because malignant lesions show increased uptake on delayed images (using a threshold of 10% SUV increase) whereas benign

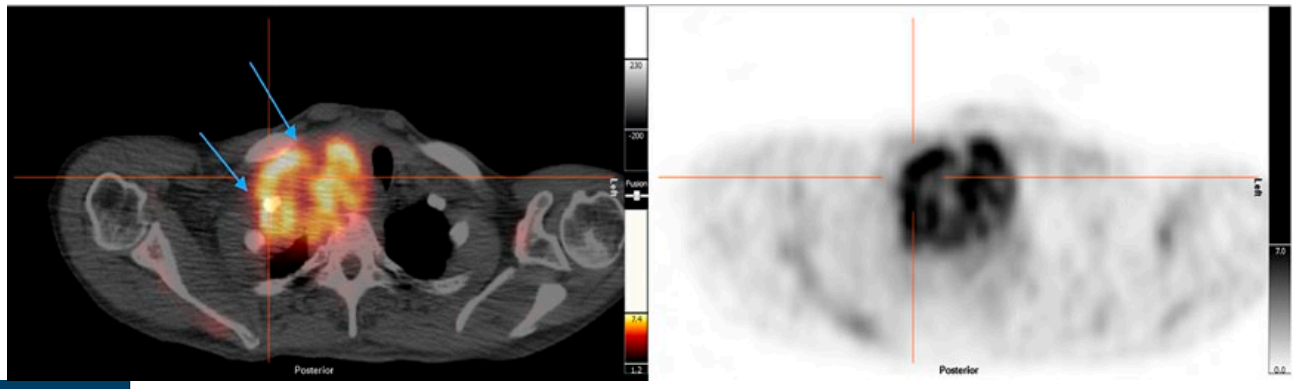

Figure 4 *Metabolic imaging of an apical right lung tumour with thoracic chest wall invasion. At functional imaging with FDG, the high tumour metabolic signal is integrated with the anatomic references.*

inflammatory lesions are stable or less active on second scan.
- Round atelectasis usually does not have FDG uptake.

Even though we should be aware that **lung nodules false positive** results might be related with benign tumours of inflammatory disease such as benign sclerosing haemangioma, leiomyoma and inflammatory pseudotumour or active granulomatous /inflammatory process (tuberculosis, fungal infection, rheumatoid nodule, sarcoid, lipoid pneumonia, talc granuloma, necrotizing pneumonia), **Lung nodules false negative** results will be present with some tumour tissue that shows no or little FDG uptake, like microscopic tumour deposits, mucoepidermoid carcinomas and biologically weak tumours (pure lepidic adenocarcinoma and carcinoid tumours).

FDG-PET/TC response criteria in solid tumours (PERCIST) vs response evaluation criteria in solid tumours (RECIST) [16,17]

Tumour progression during first-line chemotherapy occurs in approximately one-third of patients with lung cancer and this high frequency of progression emphasizes the need for monitoring treatment response with advanced imaging modalities, to adopt new treatment regimens and predict outcomes.

Currently, there is no agreement on the optimal imaging modality for post-treatment assessment in lung cancer.

Tumour measurements before and after treatment are considered appropriate criteria for evaluating T response.

The two uniform standardized response assessment criteria in solid tumours are the World Health Organization (WHO) criteria and the Response Evaluation Criteria in Solid Tumours (RECIST).

These criteria depend largely on size measurements, including bidimensional tumour measurements (the longest perpendicular diameters in the axial plane) by WHO and the one-dimensional diameter (longest tumour diameter in the axial plane) by RECIST.

Changes in cellular metabolism occur more rapidly than do changes in tumour size, and FDG PET has become a powerful tool in assessing treatment response, by providing information on the metabolic activity of tumour cells.

PET metabolic response using the PET Response Evaluation Criteria in Solid Tumours (PERCIST) has been shown to be a better predictor of histopathology response than anatomic response metrics, such as WHO criteria and RECIST 1.1

Several studies have reported significant differences in tumour SUV_{max} found on pre- and post treatment FDG--PET scans of patients who responded to therapy treatment versus the scans of patients who did not have a response.

When assessing response to therapy, the tumour standard uptake value (SUV_{max} or SUV_{peak} or SUL_{peak}) is used to measuring CHANGES in metabolic rates before and after treatment (table 2).

In this situation only an intra-individual comparison is done and that excludes the problems of variability of absolute metabolic rates errors, several times pointed as different body composition and glucose and FDG plasma clearance.

Neuroendocrine Lung Tumours (NET) metabolic particularities:[18]

Neuroendocrine tumours (NETs) were first described in 1907, and were initially named as carcinoid, because of their ability to become a malignant disease. As they arise from the enterochromaffin cells of the neuroendocrine system, more recently were named neuroendocrine tumours.

NETs may arise from a wide variety of primary organ sites, but are most often found in the gastroenteropancreatic system (57%) and in the lungs (27%).

Ki-67 index and mitotic count, adopted by 2010 WHO histological grading system plays an important role in NETs compared to other tumours, and is the primary determinant of grade in bronchial NETs (table 3).

Ki-67 is present in cells undergoing all parts of the cell division cycle (G1, S, G2 and mitosis) **but not in G0**, so the percentage of cells Ki-67 antigen positive reflects the growth fraction of a cell population.

NET lesions with avidity for FDG highlights patients with aggressive clinical behaviour, high proliferative rate and a shorter median survival, compared to those who did not (figure 5).

Table 2 **Objective therapeutic responses according to PERCIST 1.0**

PERCIST PET response criteria in solid tumours	$SUV_{peak}1$ (SUV before treatment); $SUV_{peak}2$(SUV after treatment); $\Delta SUV\% = (SUV1 - SUV2) / SUV1 \times 100\%$.
Complete Metabolic Response (CMR)	Complete resolution of 18F-FDG uptake within the measurable target lesion. Less than mean liver activity and indistinguishable from surrounding background blood-pool levels. No new 18F-FDG-avid lesions.
Partial Metabolic Pesponse (PMR)	Reduction of a minimum of 30% in the target tumor ^{18}F-FDG SUV value.
Stable Metabolic Disease (SMD)	Disease other than CMR, PMR, PMD. Equal to a differential of SUV value in between -29% and +29%.
Progressive Metabolic Disease (PMD)	30% increase in ^{18}F-FDG SUV value. Or any new 18F-FDG-avid lesion that are typical of cancer.

Table 3 **Ki-67 index and mitotic count in Lung NETs related with proliferation grade.**

Grade	Mitotic count per 2 mm²	Ki-67 index	NET lung
Gx	Grade cannot be assessed		
G1	« 2 mitotic count	« 3%	Typical carcinoid Tumour
G2	2-20 mitotic count	3-20%	Atypical Carcinoid Tumour
G3	» 20 mitotic count	»20%	NE Carcinoma

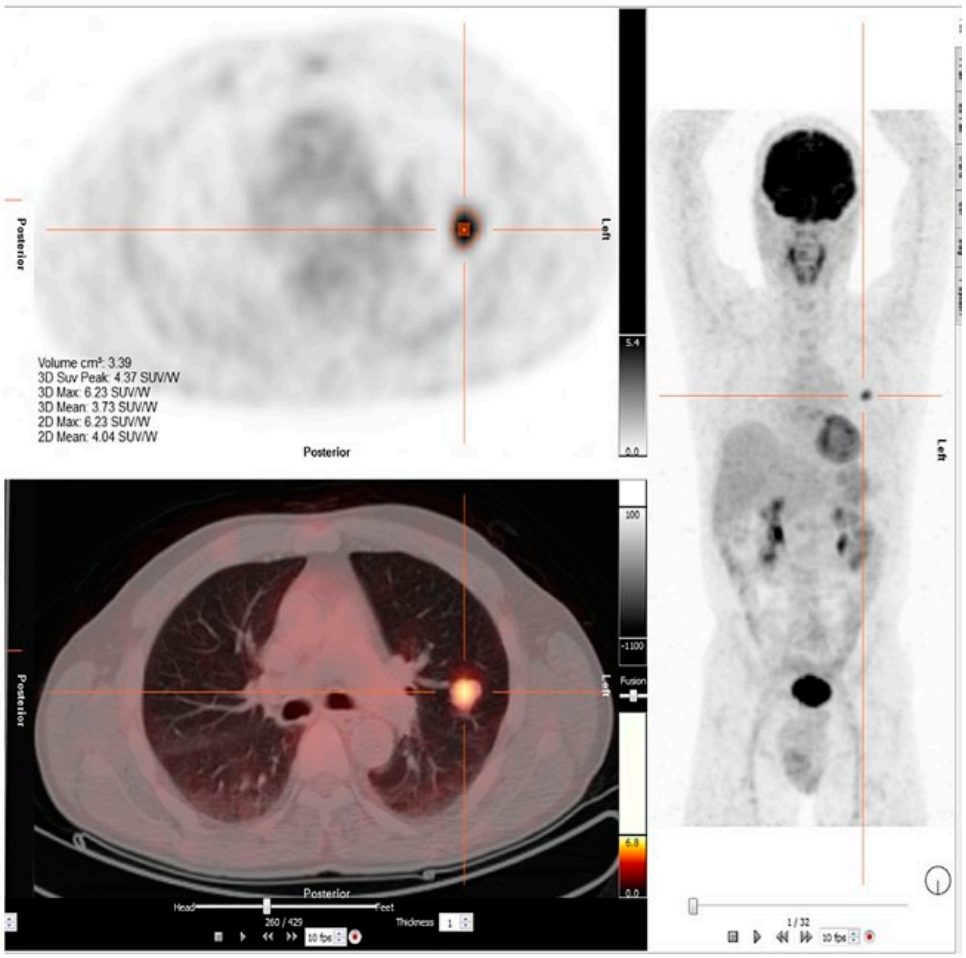

Figure 5 *A 55 year-old male, with an upper left lung lobe solid 23 mm nodule, surrounded by normal lung parenchyma. Lesion biopsy revealed a large cell neuroendocrine carcinoma, G3, Ki67>90%. FDG-PET/CT shows lung lesion FDG uptake with SUV_{max} of 6, and no other FDG uptake according to a metabolic stage of (cN0 cM0).*

Most NETs have high expression levels of transmembrane Somatostatin (SST) receptors (SSTRs), which opens the possibility for tumour imaging and therapy with radiolabeled SST peptide analogs.

Five distinct receptors subtypes (termed SSTR1-5) have been identified, with SSTR2 showing the highest affinity for natural SST and synthetic SST analogs.

A number of slightly different positron emission SST peptide tracers (Table 4) have been developed. These SST peptide tracers will allow a whole body in vivo imaging of somatostatin receptors to be performed.

These ^{68}Ga-DOTA-peptides for PET imaging will be used for diagnosis, staging and radioactive treatment of NETs, comprising the concept of theranostics (diagnostic techniques directly linked to the application of specific therapies).

Currently, there is no recommendation on which type of 68GaDOTA-peptide is preferred and logistic reasons such as availability of the precursor peptide will guide the choice in clinical practice, and the implementation of ^{68}Ga--DOTApeptide PET that may differ from country to country, mostly related with ^{68}Ge/^{68}Ga generators availability and reimbursement.

Table 4 **The affinity profiles of ^{68}Ga-DOTA-peptides differences**

^{68}Ga-labeled SST peptide analogs	Different affinities for the five SST Receptors subtypes
^{68}GA-DOTA-NOC (currently in use in Portugal)	Wide receptor binding profile, able to specifically bind to SSTR2, SSTR3, and SSTR5
^{68}GA-DOTA-TOC	High affinity for SSTR2 and SSTR5
^{68}GA-DOTA-TATE	Binds only to SSTR2, presenting 10-fold higher affinity for SSTR2 in vitro than that of the other 68Ga-DOTA-peptides

The optimal selection of therapies in a given NET patient at a given point in their clinical course remains an unanswered question. Initial anti-proliferative therapy tends to be with somatostatin analogues, with other therapies (such as peptide receptor radionuclide therapy (PRRT), tyrosine kinase inhibitors, or chemotherapy) chosen upon failure of these therapies.

The use of standardized staging criteria in NETs, as in other malignancies, has helped in categorization of patients for research purposes and to aid in prognostics. However, the use of serial anatomical imaging to determine response in NETs is complicated by the often indolent course/slow-growing nature of low-grade tumours.

Progressive disease, defined by RECIST criteria (as an increase in the sum of diameters of at least 20%or appearance of new lesions), may take years if not decades to manifest.

Even though the widespread adoption of ^{68}Ga-DOTA-peptides PET/CT has revolutionized NET imaging, CT and MRI remain the most common imaging modalities.

Functional (nuclear) imaging: ^{68}Ga-DOTA peptide - PET tracers:

The SUV_{max} of a patient's ^{68}Ga-DOTA peptide PET correlates to expression of SSTR on their NET pathology.

Consider that the well-differentiated NET lesions have more SSTRs expression, are mainly low-grade tumours and have a better prognosis, it is not surprising that avidity on ^{68}Ga-DOTA peptide PET uptake predicts improved overall survival in metastatic NET.

Although interpretation of uptake ^{68}Ga-DOTA peptide tracer changes, on serial ^{68}Ga-DOTA peptide PET scans, during treatment, is of undetermined clinical significance since

- a decrease in the SUV_{max} of a lesion could represent either response to therapy or de-differentiation of a tumour into high-grade NET (with lower expression of SST membrane receptors and a worse prognosis).
- an increasing of SUV_{max} of a lesion may either signify conversion of a signal well-differentiated tumour (with better prognosis) or alternatively

Table 5 **Biologic cellular information of dual 68Ga-DOTA-peptides/18F-FDG PET imaging**

^{18}F-FDG PET uptake in a NET lesion	• Identifies high proliferative rates • More likely present on G3 NET
^{68}Ga-DOTA-peptides uptake in a NET lesion	• Identifies expression of membrane somatostatin receptor (SSTRs) • Higher on well-differentiated, G1/2 NET

Table 6 **Dual ^{68}Ga-DOTA-peptides/^{18}F-FDG PET imaging)**

^{18}F-FDG PET NET lesion uptake	^{68}Ga-DOTA-peptides NET lesion uptake	Peptide receptor radiotherapy (PRRT) indication
Positive	Negative	PPRT contraindication. Tumour with negative or weakly positive SSTRs expression. Probable presence of de-differentiated tumour with no treatment efficacy.
Negative or weakly Positive	Positive	PRRT indicated, with ability of disease control (Kashyap et al., 2015)

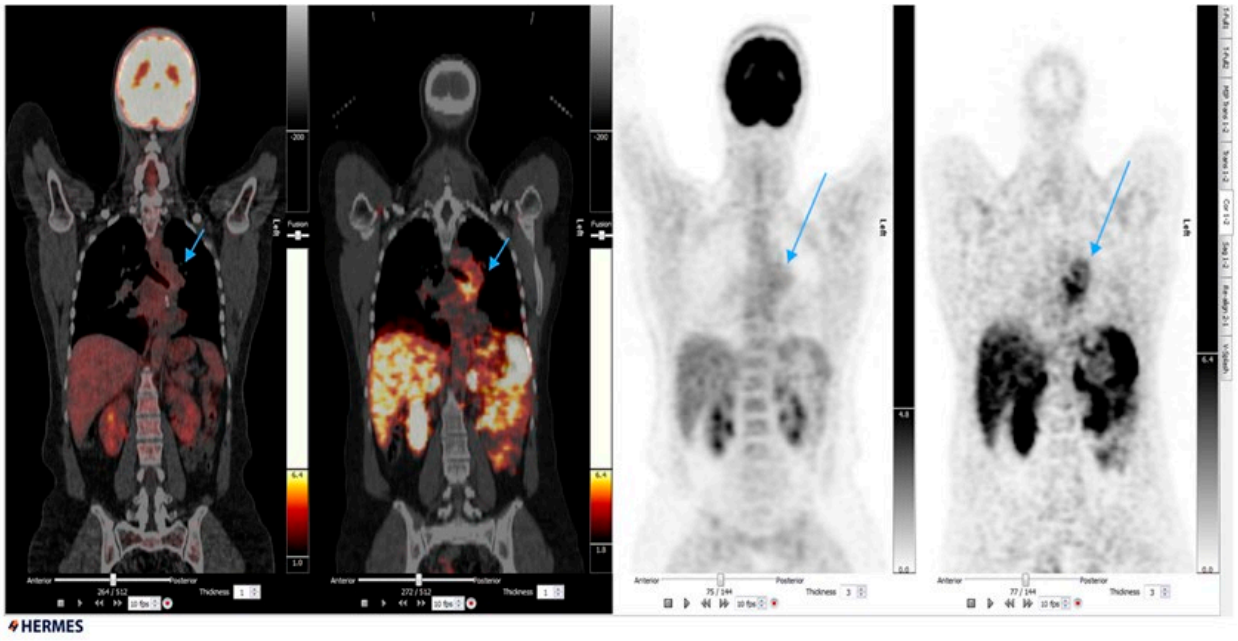

Figure 6

40 year-old female with left hilar recurrence of atypical carcinoid tumour (Ki67>5%), six years after a lobectomy for central typical carcinoid tumour. (pT2a pN0). A Dual ^{18}F-FDG PET /^{68}Ga-DOTA-peptides imaging performed at recurrence revealing a left hilar lesion DOTA-peptides positive and FDG-negative, supporting use of maintenance therapy with cold somatostatin.

tumour progression with increasing number of cells still expressing the receptors).

Dual ^{68}Ga-DOTA-peptides/^{18}F-FDG PET imaging

Dual PET imaging technique, ^{68}Ga-DOTA--peptides/^{18}F-FDG PET imaging is of potential value in NET work-up because the two scans are complementary.

In large volume lesions it is possible to find intra--lesions heterogeneous disease, , with areas of FDG avidity and others areas with ^{68}Ga-DOTA-SST peptides uptake. In this case the information might be used to indicate tissue sample collection.

The somatostatin imaging (^{68}Ga-DOTA-SST peptides uptake) is also indicated to predict peptide receptor radiotherapy (PRRT) delivery (and therapeutically efficacy) in the individual lesions/patient (figure 6).

CONCLUSION

Nowadays lung cancer is the leading cause of cancer related death.

In the near future lung cancer screening programs will bring to the daily-clinical activity a huge amount of undetermined lung nodules to deal with, promising early--diagnosis and early-stage lung cancers coming under the aim of improving overall lung cancer survival.

Emerging new lung cancer therapeutic opportunities is a new reality, that needs a more complete tumour characterization.

The tumour, the patient and the disease stage, need to be connected to the best therapy deemed fit!

Avoiding a therapy of unproven benefit is as important as missing a beneficial one.

We have more information on molecular tumour analysis and specific genetic mutations, more accurate histological discrimination, better ability of minimally invasive diagnostic and therapeutic approach, and more in vivo functional imaging ability.

How to deal with all this complexity? The answer might to be connected with the highlight knowledge of all related fields (pathology, molecular genetics, functional and anatomic imaging, minimally invasive diagnostic and therapeutic procedure, …) maintain multidisciplinary discussion, be persistence … and don't lose curiosity!

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EARLY AND MIDTERM OUTCOMES FOLLOWING AORTIC VALVE REPLACEMENT WITH MECHANICAL VERSUS BIOPROSTHETIC VALVES IN PATIENTS AGED 50 TO 70 YEARS

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Abstract

Objectives: *To compare 7-year survival and freedom from reoperation, as well as early clinical and hemodynamic outcomes, after surgical aortic valve replacement (SAVR) with mechanical or bioprosthetic valves in patients aged 50-70 years.*

Methods: *single-center retrospective cohort study including adults aged 50-70 years who underwent SAVR in 2012 with a mechanical or bioprosthetic valve. Median follow-up was 7 years. Univariable analyses were performed using Kaplan-Meier curves and Log-Rank tests for survival and freedom from reoperation analyses. Multivariable time-to-event analyses were conducted using Cox Regression.*

Results: *Of a total of 193 patients, 76 (39.4%) received mechanical valves and 117 (60.6%) received bioprosthetic valves. A trend for better survival was found for mechanical prostheses when adjusting for EuroSCORE II (HR: 0.35; 95%CI: 0.12-1.02, p=0.054), but using a backward stepwise Cox regression prosthesis type was not retained by the model as an independent predictor of survival. Moreover, mechanical prostheses showed trends for higher freedom from reoperation (100% vs. 95.5%, Log-Rank, p=0.076), higher median EuroSCORE II (2.52% vs. 1.95%, p=0.06) and early mortality (7.9% vs. 2.6%, p=0.086). However, after adjusting for EuroSCORE II, there was no significant difference in early mortality (OR: 2.3, 95%CI: 0.5-10.5, p=0.272). Regarding hemodynamic performance at follow-up echocardiogram, there were no differences other than left ventricular mass regression, which was not as pronounced in the mechanical group (-12% vs. -21%, p=0.002).*

Conclusion: *Mechanical and bioprosthetic aortic valves prostheses showed similar mid-term survival in the 50-70 age group. Further prospective and larger studies are needed to provide evidence-based recommendations on this topic.*

INTRODUCTION

The ideal type of prosthetic heart valve for Aortic Valve Replacement (AVR) in patients aged 50 to 70 years remains a matter of debate in Cardiac Surgery. In fact, the trade-off between durability and anticoagulation-related bleeding is the cornerstone of prosthesis choice and this decision requires weighing these factors on a case-by-case basis. Age, comorbidities and patient's lifestyle and preferences, among others, should be taken into account. As a rule of thumb, the perceived probability of the patient outliving a functional bioprostheses will drive the decision, and thus age is a major determinant to consider. However, there is still no agreement among leading scientific societies on the best age threshold to guide this decision.

Figure 1 represents the differences between European Society of Cardiology/European Society of Cardiothoracic Surgery Guidelines (ESC/EACTS)[1] and American Heart Association/American College of Cardiology (AHA/ACC)[2] recommendations for mechanical versus biological valves according to age. The gray zone for which both types of prostheses are appropriate is between 60 and 65 years old in ESC/EACTS Guidelines, as opposed to 50 to 70 years old in AHA/ACC guidelines. Mechanical valves were recommended as the best option for patients up to

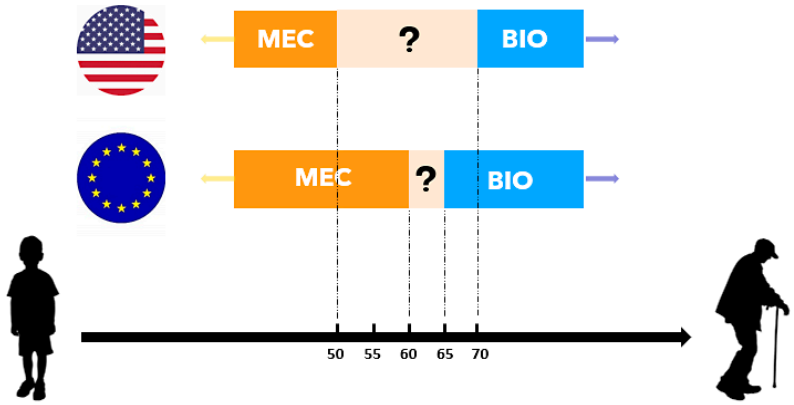

Figure 1 *Recommendations for use of a mechanical or bioprosthetic valve, according to current American (AHA/ACC) and European (ESC/EACTS) Guidelines on Management of Valvular Heart Disease.*

60 years old in the previous AHA/ACC guidelines and the evidence to support lowering the cut-off to 50 years has been questioned. On the one hand, several large, observational studies and a single recent randomized controlled trial (RCT)[3] showed similar long-term survival for the two types of prostheses in this patient population.[4-6] On the other hand, several other studies evidenced a survival benefit for mechanical prostheses in this age group[7-10], including a recent meta-analysis of propensity score-matched studies and RCT.[11]

Therefore, we aim to compare 7-year survival and freedom from reoperation, as well as early clinical and hemodynamic outcomes, after surgical aortic valve replacement (SAVR) with mechanical or bioprosthetic valves in a sample of patients aged 50-70 years.

METHODS

Study Design and Sample

We performed a single-center retrospective cohort study.

Patients aged 50 to 70 years old who underwent SAVR with a Mechanical or Freedom Solo®, Trifecta® or Perimount® bioprosthetic valves during one year (2012), at the Cardiothoracic Surgery Department of *Centro Hospitalar Universitário São João* (CHUSJ), Porto, Portugal, were consecutively included. Concomitant procedures were not excluded. Patients were grouped according to their aortic valve prosthesis – mechanical (MEC) or biological (BIO) –; the choice between MEC or BIO was an individualized, shared decision process between the patient and the surgeon.

Data Collection

Patients' data, including sociodemographic characteristics, comorbidities, echocardiography, admission status, intraoperative, and postoperative variables, were derived retrospectively from the patients' clinical records and the Department's informatics databases.

Data collected at baseline included age, sex, previous cardiac surgery, comorbidities (hypertension, diabetes, dyslipidemia, chronic pulmonary disease, atrial fibrillation (AF), coronary artery disease, cerebrovascular disease, peripheral artery disease, chronic renal disease), NYHA status, CCS status, history of smoking and obesity. From the preoperative echocardiogram, we obtained ejection fraction, mean and maximum transvalvular gradients, aortic valve pathology, and etiology. Surgical priority, procedures performed, cardiopulmonary bypass and aortic clamp times were recorded, and EuroSCORE II was calculated. Variables are defined in Table 1.

Outcomes

Survival and freedom from prosthesis-related reoperation were determined through the National Registry *Registo de Nacional de Utentes* (RNU) and consultation of informatics medical records, in May 2019. Median follow-up time was 7 years.

In the early postoperative period, we recorded reoperations and their respective reason, renal function worsening, severe thrombocytopenia, need of red blood cell transfusion, the need of inotrope support, prolonged invasive mechanical ventilation, stroke, *de novo* AF, permanent pacemaker implantation, length of intensive care unit stay, length of hospital stay and early mortality.

According to the local protocol, the postoperative transthoracic echocardiographic evaluation was performed 2 to 5 months after surgery, at a median of 3 months. Ejection fraction, mean and maximum transprosthetic gradients and patient-prosthesis mismatch (PPM) were registered.

Structural valve deterioration (SVD) was considered if any intrinsic changes in the valve occurred. A non-structural valve dysfunction (NSVD) was defined as any abnormality that did not directly involve valve components.[12]

Statistical Analysis

Statistical analyses were run on Statistical Package for the Social Sciences version 25 (SPSS) Software (IBM Corporation, Armonk, NY, USA). Categorical variables are presented as absolute and valid relative frequencies, excluding missing cases. The Chi-squared or Fisher's

Table 1 **Definition of variables and outcomes**

Variable	Definition
Chronic Pulmonary Disease	No/Yes - long term use of bronchodilators or steroids for lung disease
Coronary Artery Disease	No/Yes - >50% stenosis of 1,2 or 3 vessels
Cerebrovascular Disease	No/Yes - Stroke, transient ischemic attack, carotid surgery, carotid occlusion/>50% stenosis
Peripheral artery disease (PAD)	No/Yes – Claudication, amputation for arterial disease, previous or planned intervention on the abdominal aorta, limb arteries or carotids, abdominal aortic aneurysm, non-invasive test positive for PAD
Chronic renal disease	No/Yes, moderate - Creatinine Clearance < 85 mL/min/1.73m^2 or severe if Creatinine Clearance < 50 mL/min/1.73m^2 or Dialysis
Obesity	No/Yes – BMI ≥ 30kg/m^2
Left ventricle function	Normal-Mild: ejection fraction ≥40%; Moderate-Severe: ejection fraction <40%
Surgical Priority	Elective if admitted electively for a previously scheduled surgery; Urgent if not admitted electively and needed surgery before discharge or if required operation before the beginning of the next working day
Outcomes	**Definition**
Renal Function Worsening	Maximum post-operative creatinine > 1.5x preoperative creatinine
Need of Transfusion	No/Yes – Need of 2 or more units of Red Blood Cells
Need of Inotropic Support	No/Yes – Need of 2 or more inotropes or IABP
Prolonged Invasive Mechanical Ventilation	No/ Yes – >24 hours of mechanical ventilation
Stroke	No/Yes – Transient or Permanent Ischemic Attack
Postoperative Atrial Fibrillation	No/Yes – *de novo* Atrial Fibrillation in the postoperative period
Early Mortality	Death within 30 days after surgery or before hospital discharge
Early Reoperation	Reoperation within 30 days after surgery or before hospital discharge
Patient-Prosthesis Mismatch	Effective orifice area indexed to patient's body surface area: No / Yes, if moderate (0.85 cm^2/m^2 ≥ EOAi ≥ 0.65 cm^2/m^2) or severe (EOAi ≤ 0.65 cm^2/m^2)
Left Ventricle Mass Regression	(Pre-operative LV Mass – Post-operative LV mass) / (Pre-operative LV Mass)

exact test was used for categorical variables comparison between groups, as appropriate. Continuous variables are presented as mean (standard deviation) or median (interquartile range), according to data distribution, assessed by the Shapiro-Wilk test. The Student's t-test or the Mann-Whitney test were used for between-groups comparison of continuous variables.

Univariable survival and freedom from reoperation analyses were performed using Kaplan-Meier curves and Log-Rank tests. Multivariable time-to-event analyses were conducted using Cox Regression: 1) adjusted for EuroSCORE II, which combines many factors which could predictably cause confounding and 2) adjusting for all covariates $p<0.1$ at univariable analysis and prosthesis group using a backward stepwise Cox regression to identify potential predictor variables. Multivariable logistic regression was also used to estimate the impact of the type of prosthesis on early mortality.

Statistical models were checked for the association between covariates and dependent variables (Omnibus test, G^2) and calibration (Hosmer-Lemeshow – goodness of fit test). Discriminative power was assessed through the area under the Receiver Operating Characteristic (AUC ROC) curve (c-statistic) – considered good if >0.7. The proportional hazard assumption for Cox regression was assessed using interaction terms of time with group.

Ethics

This study was approved by the Ethics Committee and Administration Council of the CHUSJ. As this was a retrospective study, informed consent was waived. Anonymity and confidentiality were assured.

RESULTS

Study Sample

Of a total of 193 patients aged 50 to 70 years submitted to SAVR, 76 (39.4%) received mechanical valves (MEC) and 117 (60.6%) received bioprosthetic valves (BIO). Table 2 describes the main characteristics of the sample.

Table 2 **Characteristics of the sample at baseline**

	Total n=193	Bioprosthesis n= 117	Mechanical n=76	*p* value
Age, y, median (IQR)	63 (58-67)	66 (62-68)	59.5 (55-63)	<0.001
Male sex, n (%)	112 (58.0)	72 (61.5)	40 (52.6)	0.221
Obesity (BMI ≥30.00 kg/m²), n (%)	55 (28.5)	37 (31.6)	18 (23.7)	0.233
Hypertension, n (%)	140 (72.5)	91 (77.8)	49 (64.5)	0.043
Diabetes, n (%)	45 (23.3)	32 (27.4)	13 (17.1)	0.100
Dyslipidemia, n (%)	122 (64.2)	79 (68.1)	43 (58.1)	0.161
History of smoking, n (%)	51 (28.2)	34 (29.8)	17 (25.4)	0.520
Coronary artery disease, n (%)	51 (26.4)	38 (32.5)	13 (17.1)	0.018
Cerebrovascular disease, n (%)	21 (10.9)	20 (17.1)	1 (1.3)	0.001
Peripheral artery disease, n (%)	8 (4.1)	4 (3.4)	4 (5.3)	0.530
Chronic kidney disease, n (%) Moderate Severe	 61 (31.6) 14 (7.3)	 40 (34.2) 9 (7.7)	 21 (27.6) 5 (6.6)	0.653
Atrial fibrillation, n (%)	40 (20.9)	16 (13.8)	24 (32)	0.003
NYHA ≥ III, n (%)	48 (24.9)	33 (28.2)	15 (19.7)	0.184
CCS ≥ III, n (%)	14 (7.8)	9 (7.9)	5 (7.6)	0.939
Chronic Pulmonary Disease, n (%)	14 (7.3)	6 (5.1)	8 (10.5)	0.158
EuroSCORE II %, median (IQR)	2.03 (1.1 – 3.75)	1.95 (1.08 – 3.65)	2.52 (1.23 – 5.43)	0.158
Moderate to severe LV dysfunction	19 (10.0)	15 (12.8)	4 (5.5)	0.101
Reason for AV surgery, n(%)				
Aortic stenosis	123 (63.7)	88 (75.2)	35 (46.1)	0.001
Aortic regurgitation	38 (19.7)	16 (13.7)	22 (28.9)	
Stenosis and regurgitation	22 (11.4)	8 (6.8)	14 (18.4)	
Prosthetic Dysfunction	10 (5.2)	5 (4.3)	5 (6.6)	
Degenerative Aortic Disease, n (%)	91 (47.2)	75 (64.1)	16 (21.1)	<0.001
Rheumatic Aortic Disease, n (%)	28 (14.5)	8 (6.8)	20 (26.3)	<0.001
Bicuspid Aortic Valve, n (%)	35 (18.1)	20 (17.1)	15 (20.5)	0.642
Native Valve Infective Endocarditis, n (%)	7 (3.6)	6 (5.1)	1 (1.3)	0.248
Prosthetic Dysfunction, n (%)	10 (5,2)	5 (4.3)	5 (6.6)	0.519
Infective Endocarditis, n (%)	7 (3.6)	4 (3.4)	3 (3.9)	
Previous cardiac surgery, n (%)	23 (11.9)	7 (6.0)	16 (21.1)	0.002

Patients with MEC were significantly younger (60 (62-68) *vs* 66 years (55-63), p<0.001), and presented a lower prevalence of hypertension (64.5% *vs* 77.8%, p=0.043), coronary and cerebrovascular disease (17.1% *vs* 32.5%, p=0.018 and 1.3% *vs* 17.1%, p=0.001, respectively). On the other hand, they had a higher prevalence of atrial fibrillation (AF, 32% *vs* 13.8%, p=0.003), and a higher frequency of previous cardiac surgery (21.1% vs 6%, p=0.002). There

Table 3 **Surgical variables**

	Total n=193	Bioprosthesis n= 117	Mechanical n=76	*p* value
Urgent surgery, n (%)	56 (29.0)	35 (29.9)	21 (27.6)	0.733
Isolated AVR, n (%)	81 (42.0)	54 (46.2)	27 (35.5)	0.144
Multiple procedures, n (%)				
Mitral valve intervention	30 (15.5)	12 (10.3)	18 (23.7)	0.012
Tricuspid valve intervention	24 (12.4)	8 (6.8)	16 (21.1)	0.003
Multivalve	38 (19.7)	14 (12)	24 (31.6)	0.001
CABG	54 (28.0)	39 (33.3)	15 (19.7)	0.040
Ascending aorta Surgery	38 (19.7)	16 (13.7)	22 (28.9)	0.009

were no significant differences in NYHA Class, CCS class, diabetes, or chronic kidney disease. There was a trend for a higher median EuroSCORE II in the MEC group (2.52% (1.23-5.43) vs. 1.95% (1.08 – 3.65), p=0.06).

Regarding the indication for SAVR, there was a higher prevalence of Aortic Stenosis in the BIO group (75.2% *vs* 46.1%, p<0.001). The etiology of aortic valve pathology also differed – MEC patients had a higher prevalence of Rheumatic Aortic Disease (27.6% *vs* 6.8%, p<0.001), and BIO patients had a higher prevalence of Degenerative Aortic Disease (64.1% *vs* 21.1%, p<0.001). No differences regarding Bicuspid Aortic Valve or Infective Endocarditis were found.

Furthermore, intraoperatively, patients in the MEC group were more likely to undergo concomitant interventions on other valves (31.6% *vs* 12.0%, p=0.001) or the ascending aorta (28.9% *vs* 13.7%, p=0.009), but less likely to undergo simultaneous CABG (19.7% *vs* 33.3%, p=0.04) (Table 3).

Cardiopulmonary Bypass (CBP) and Aortic Cross Clamp times in the overall sample and patients undergoing isolated AVR are detailed in Figure 3. Considering isolated AVR, the groups presented similar cardiopulmonary bypass (CBP: 99 (84-112) vs 90 (80-114) minutes, p=0.339) and aortic cross-clamp times (AC: 69 (57-80) vs 65 (57-78) minutes, p=0.434).

Survival and Freedom from Reoperation

Excluding early mortality, 21 patients died during follow-up: 16 (14%) from the BIO group and 5 (7%) from the MEC group. The 7-years cumulative survival was 92.9% in the MEC group and 84.8% in the BIO group (Log-Rank test, p=0.173, Figure 2A).

Although we found a tendency for MEC to be protective of mortality after adjusting for EuroSCORE II (HR: 0.35, 95%CI: 0.12-1.02, p=0.054), adding age to the model mitigates this (HR: 0.46, 95%CI: 0.14-1.5, p=0.189) and prosthesis type was not one of the three variables identified as independent predictors of mortality in the backward method, which included prosthesis type, age, AF,

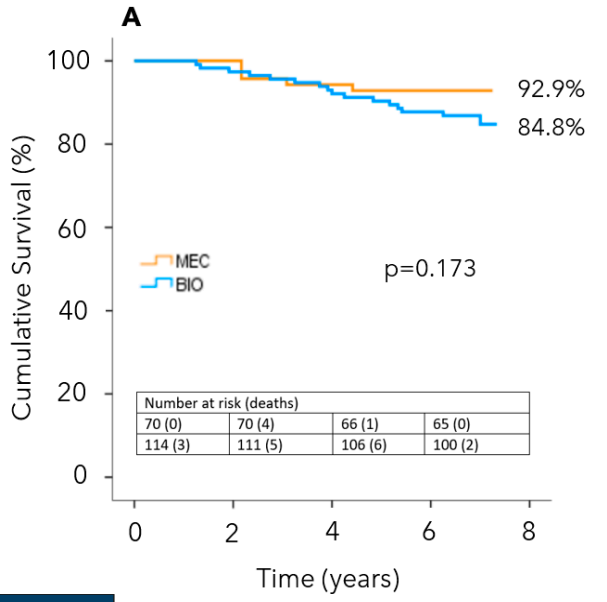

Figure 2A *Kaplan-Meier Curve for Survival (Log-rank test, p=0.173). MEC: Mechanical Prostheses. BIO: Bioprostheses.*

cerebrovascular disease, coronary artery disease, diabetes, hypertension. Atrial fibrillation (HR: 3.11, 95%CI: 1.28 – 7.55, p=0.012), diabetes (HR: 2.32, 95%CI: 0.98 – 5.53, p=0.058) and hypertension (HR: 6.88, 95%CI: 0.90 – 52.39, p=0.063) were the three variables retained by the model.

We found a trend for higher freedom from reoperation at 7 years in the MEC group (100% *vs* 95.5%, Log-Rank test, p=0.076): there were no reoperations in the MEC group, as opposed to 5 reoperations in the BIO group (Figure 2B). Four of these cases were due to Prosthetic Valve Endocarditis, and 1 due to Structural Valve Deterioration.

In-Hospital Outcomes

Table 4 summarizes in-hospital results. In the MEC group, we found a trend for a higher incidence of *de novo* postoperative atrial fibrillation (POAF, 42.6% *vs* 28.0%, p=0.079), and a higher need for inotropic support with 2

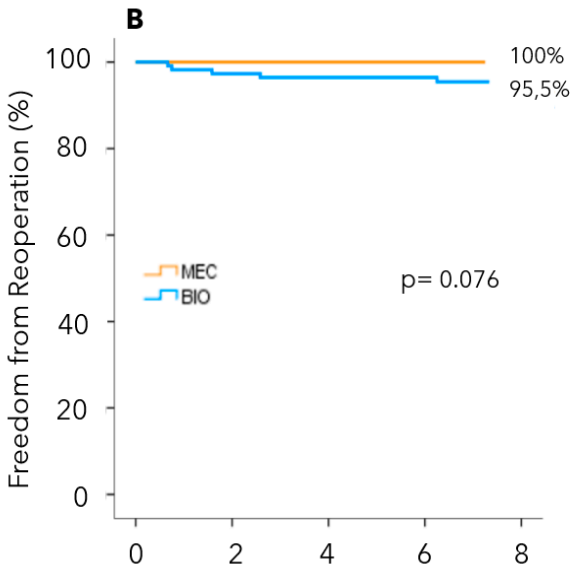

Figure 2B *Kaplan-Meier Curve for Freedom from Reoperation (Log-Rank Test=0.076). MEC: Mechanical Prostheses. BIO: Bioprostheses.*

or more inotropes (22.2% *vs* 10.9%, p=0.039). The median ICU stay was longer (6 (3-8) *vs* 3 (2-5) days, p<0.001).

There were no significant differences in renal function worsening, severe thrombocytopenia, prolonged invasive mechanical ventilation, stroke, permanent pacemaker implantation, or length of hospitalization. Reoperation in the early postoperative period was also similar between the two groups (3.9% MEC *vs* 4.3% BIO, p=0.912).

Regardless of the trend for higher early mortality in the MEC group - 7.9% *vs* 2.6%, p=0.086 -, after adjusting for the EuroSCORE II we did not find the type of prosthesis as an independent predictor of early mortality (OR MEC: 2.32, 95%CI: 0.52-10.50, p=0.272).

Hemodynamic Evaluation

Regarding hemodynamic performance assessed by echocardiography performed at 3 months (Table 4) there were no differences between MEC and BIO patients in mean transprosthetic gradient (14 *vs* 13 mmHg, p=0.115), indexed Effective Orifice Area (0.94 (0.84-1.04) *vs* 0.98 (0.86-1.11) cm^2/m^2, p=0.113) or Patient-Prosthesis Mismatch (29.2% vs 19.4%, p=0.146).

Table 4 **In-hospital outcomes and 3 months transthoracic echocardiographic outcomes**

	Total n=193	Bioprosthesis n= 117	Mechanical n=76	*p* value
In-Hospital Outcomes				
Early Mortality, n (%)	9 (4.7)	3 (2.6)	6 (7.9)	0.086
Early Reoperation n(%)	8 (4.1)	5 (4.3)	3 (3.9)	0.912
Re-exploration of thorax due to bleeding, n (%)	3 (1.6)	3 (2.6)	0 (0)	0.287
Sternal re-suturing, n (%)	2 (1.04)	1 (0.9)	1 (1.3)	0.757
Acute kidney injury, n (%)	20 (10.8)	13 (11.4)	7 (9.9)	0.742
Need of ≥ 2 RBC, n (%)	35 (20.1)	20 (19.4)	15 (21.1)	0.782
Need of ≥2 or inotropic or IABP, n (%)	28 (15.4)	12 (10.9)	16 (22.2)	0.039
Prolonged invasive mechanical ventilation, n (%)	15 (6.9)	10 (8.8)	5 (6.9)	0.656
Stroke, n (%)	5 (2.7)	4 (3.4)	1 (1.4)	0.651
Post-operative atrial fibrillation, n (%)	48 (32.7)	28 (28.0)	20 (42.6)	0.079
Permanent pacemaker implantation, n (%)	10 (5.4)	4 (3.5)	6 (8.5)	0.144
Length of ICU stay, median days (IQR)	3 (2-6)	3 (2-5)	6 (3-8)	<0.001
Length of Hospitalization, median days (IQR)	7 (6-11)	7 (6-10)	7 (6-12)	0.773
3 months Transthoracic Echocardiogram				
Left Ventricle Mass Regression, mean ± SD	-18 ± 17	-21 ± 16	-12 ± 16	0.002
EOAi, cm^2/m^2	0.96 (0.86 – 1.11)	0.98 (0.86 – 1.20)	0.94 (0.84 – 1.04)	0.113
Moderate to severe PPM, n(%)	38 (23.3)	19 (19.4)	19 (29.2)	0.146

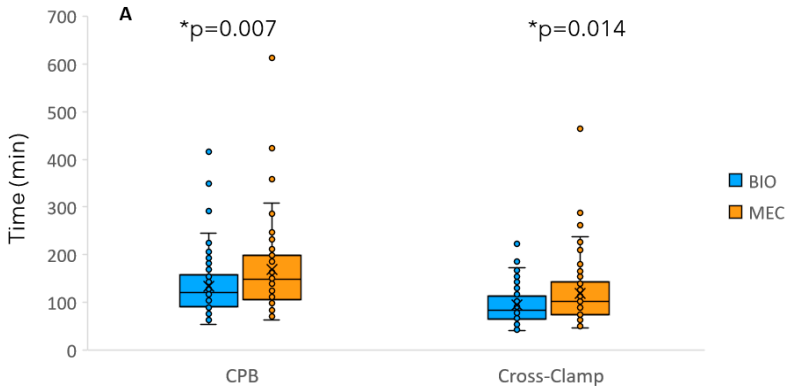

Figure 3A *Cardiopulmonary Bypass (CPB) and Aortic Cross-Clamp Time (min) in the overall sample.*

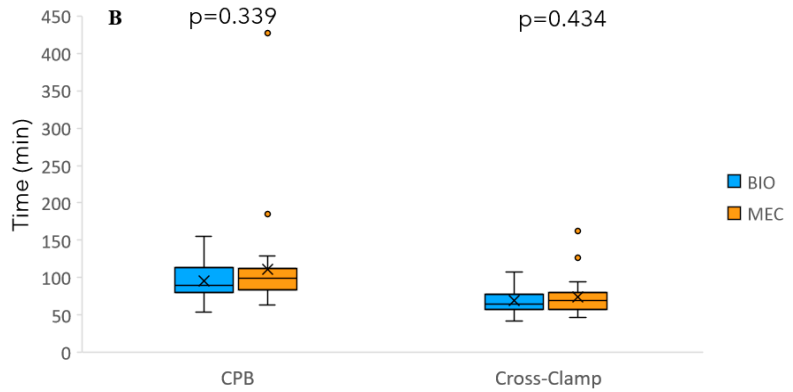

Figure 3B *Cardiopulmonary Bypass (CPB) and Aortic Cross-Clamp Time (min) for patients undergoing Isolated AVR.*

Left ventricular mass regression was more pronounced in the BIO group (-21% *vs* -12%, p=0.002) (Figure 4).

DISCUSSION

This single-center, single-year and retrospective study showed no significant differences in survival or in freedom from reoperation at 7-year follow-up, after SAVR with MEC or BIO valves, in patients aged 50 to 70 years (84.8% BIO *vs* 92.9% MEC and 95.5% BIO *vs*. 100% MEC, for cumulative survival and freedom from reoperation, respectively). However, there was a lower prevalence of postoperative complications, namely postoperative AF and need of inotropic support, and a shorter median ICU stay, as well as a trend for lower in-hospital mortality in the BIO group, which is in accordance with its lower EuroSCORE II 13 (1.95% BIO *vs* 2.52% MEC).

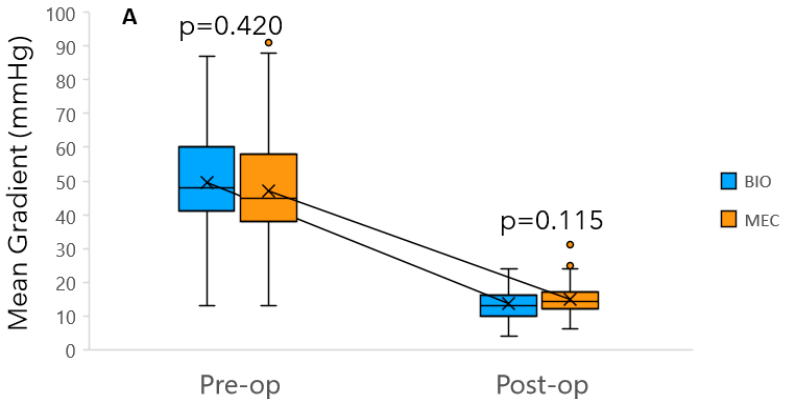

Figure 4A *Pre- and Post-operative transvalvular mean gradient (mmHg). MEC: Mechanical Prostheses. BIO: Bioprostheses.*

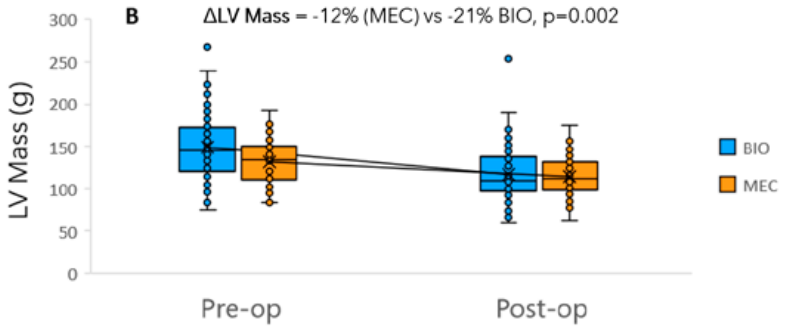

Figure 4B *Left Ventricular Pre- and Post-operative Mass. ΔLV Mass: left ventricle mass regression. MEC: Mechanical Prostheses. BIO: Bioprostheses.*

It should be noted that, by including all patients who underwent SAVR with a MEC or BIO prosthethic valve in 2012 (and not limiting our sample to primary, isolated SAVR), our study aims to provide an accurate representation of the real world setting. In fact, 59% of patients underwent multiple surgical procedures, including high risk cases such as aortic dissection and infective endocarditis.

Survival

Our study seems to support the current AHA/ACC Guidelines, according to which both types of valves are acceptable for patients aged 50-70 years, with respect to mid-term survival.

Similar conclusions have been drawn by other groups. The most recent RCT comparing mechanical and bioprosthetic valves in patients 55-70 years showed similar survival rates at 13 years (72.5% in the MEC group *vs* 69.4% in the BIO group), and type of valve was not an independent predictor of late mortality.[3] Also, in a propensity score-matched study, Chiang *et al* compared the two types of valves in patients aged 50 to 69 years undergoing primary, isolated AVR and concluded there was no significant 15-year difference in actuarial survival (62.1% in the MEC group *vs* 60.6% in the BIO group, HR: 0.97, 95% CI 0.83-1.14). Iribarne *et al* also found similar 15-year survival in both groups (60% in the MEC group *vs* 57% in the BIO group, HR: 0.87, 95% CI 0.67-1.13).[6]

However, other groups have found a survival advantage for mechanical prostheses in this age group: Glaser *et al* reported 5-, 10-, and 15-year survival of 92%, 79%, and 59% in the MEC group *vs.* 89%, 75%, and 50% in the BIO group (HR for BIO: 1.34, 95% CI: 1.09–1.66), in patients aged 50 to 69 years. A probable reason for this is the high quality of anticoagulation treatment in Sweden, which would positively influence the outcomes of the MEC group (leading to lower rates of bleeding and thromboembolic events) and distinguish it from studies performed in other countries.

It should be noted that within the 50 to 70 age group there could be subgroups whose outcomes differ and that might benefit from targeted approaches. For instance, Goldstone *et al.* compared the two types of valves in patients aged 45 to 659 and split patients into two age groups: 45-54 and 55-64, concluding that mortality at 15-years was lower in the MEC group only in the younger group (26.4% *vs* 30.6% at 15 years; p=0.03, HR:1.23, 95% CI 1.02-1.48), whereas in the older group the two types were comparable (32.1% *vs* 36.1% at 15 years, p=0.60, HR: 1.04, 95% CI 0.91-1.18).

Another point worth noting is that the benefits of MEC might only be noticeable at longer follow-up times: Kytö *et al.* compared mortality rates for the two type of valves in patients aged 50 to 70 at 1-, 5- and 10 years and found that, although there were no differences at 1- and 5- years (4.7% *vs* 4.9% and 12.7% *vs* 12%), at 10 years biological valves were associated with higher mortality – 27.6% *vs* 18.6% (HR: 1.39, 95% CI: 1.03-1.85, p=0.028).[14] Moreover, a recent meta-analysis of propensity score matched or RCT of patient ageds 50 to 70 years old, including 4648 patients, showed that mechanical valves are associated with survival benefit at 15 years (survival rate 62% *vs* 58%, MEC and BIO, respectively.[11]) These results are especially relevant for studies such as ours, as the lack of difference in survival could be due to a relatively short follow-up time, and may not hold true if we reexamine the same sample at 10 or 15-year follow-up.

Freedom from Reoperation

Unlike other studies, our results did not show a significant difference in freedom from reoperation, but a trend for higher freedom from reoperation at 7-years for the MEC group was reported (100% in the MEC group *vs* 95.5% in the BIO group, p=0.076). Both small sample size and the relatively short follow-up, which may not be sufficient for structural valve degeneration of bioprosthetic valves, could be reasons for not achieving statistical significance. Anselmi and colleagues showed that in patients under 60 years old fitted with a bioprosthetic valve, at 15 years 13.7% of patients had underwent reoperation for structural valve degeneration (SVD) and the average time for SVD was 11.9 years15 and in fact, in our study, only 1 patient was reoperated on for SVD. Other reports reinforce that the reoperation rates are consistently higher for bioprosthetic valves, especially for longer

follow-up periods: Kytö et al. presented reoperation rates of 8.5% *vs.* 1.4% at 10-years of follow-up9; Iribarne et al. showed a cumulative incidence of reoperation of 19.1% *vs* 3.0% at 15 years[6]; and a propensity score-matched study reported a cumulative incidence of reoperation of 45% *vs* 5% at 18 years.[5] Also, a recent meta-analysis by Diaz *et al* supported these findings, reporting a pooled incidence rate ratio of reoperation of 2.17 (1.67-2.86) for bioprosthetic valves, with reported mean follow-up time ranging from 6.6 to 9.8 years.[11]

However, it should be noted that reoperation does not seem to be an independent predictor of death in aortic valve replacement[16], and can be performed safely. Iribarne *et al.*, for example, showed a 30-day mortality rate of 2.4% for reoperative AVR. Chiang *et al.* interestingly, reported that the 30-day mortality rate after reoperation was lower than after a major bleeding event, 9.0% *vs* 13.2%, respectively, and the 15-year cumulative incidence of a major bleeding event occurred in 13% of MEC patients (as opposed to 6.6% in the BIO group).[4] Therefore, one should not rely solely on the assumption that, due to a higher risk of reoperation, biological valves are not the best option for a middle-aged patient.

In-Hospital Outcomes

In the unadjusted analysis, we found a trend for lower early mortality in the BIO group (2.6% *vs* 7.9%) related to the higher a priori risk of MEC group. Notwithstanding, after adjusting for EuroSCORE-II, we did not find prosthesis type to be an independent predictor of early mortality. Furthermore, there were significantly more postoperative complications (such as POAF, the need for inotropic support, or median ICU stay) in the MEC group, although this can also potentially be explained by the higher EuroSCORE-II. Several studies, including a randomized controlled trial, propensity score-matched studies, and an inverse-probability weighted study, showed no significant differences regarding these outcomes.[3-6]

Hemodynamic Performance

At follow-up echocardiogram at 3 months, both groups showed similar gradients, EOAi, and prevalence of PPM. Left ventricular mass regression, which has been suggested to be associated with improved long-term survival after AVR[17], was more pronounced in the BIO group (-21% *vs* -12%, p=0.002). However, it is not possible to ascribe these results solely to the type of prosthesis, as many factors are possibly contributing to left ventricular mass regression. For instance, patients in the BIO group were significantly older and had a higher prevalence of hypertension and coronary artery disease, as well as a higher rate of concomitant CABG. In contrast, patients in the MEC group showed a higher rate of multivalvular surgery, all of which could affect left ventricular mass regression.

Although the present study focused on age, there are other factors to consider when choosing the type of valve for a patient. For instance, a mechanical prosthesis is recommended for patients at risk of accelerated structural valve deterioration (such as patients with hyperparathyroidism). On the other hand, a bioprosthesis is recommended if there is a high bleeding risk or if good-quality anticoagulation is unlikely.[1] Moreover, patient preferences must be a crucial part of the decision.[1,2] Above all, the surgeon must aim to adequately provide all the relevant information to enable the patient to understand the compromises and make an informed decision.

In our study, aside from age, which was significantly different between the two groups, we found a higher preoperative prevalence of atrial fibrillation (AF) in patients with a mechanical prosthesis (32% *vs* 13.8%, p=0.003). This was not common in other studies.[4,8,9] The underlying reason might be that in 2012 non-vitamin K antagonist oral anticoagulant (NOACs) had not yet been widely adopted for atrial fibrillation, as only in the 2012 Focused Update of the ESC Guidelines for the management of atrial fibrillation were NOACs first recommended (and only for non-valvular AF, which was defined as AF not related to rheumatic valvular disease or prosthetic heart valves).[18] Therefore, these patients were already medicated with vitamin K antagonists, which might have tipped the balance in favor of MEC.

Although this single-year study did not address temporal changes in prosthetic valve selection at our centre, an increase in use of biological valves has been reported globally and across all age groups.[19,20] For instance, in the United States of America, the percentage of bioprosthetic valves implanted in adults rose from 37.7% in 1998-2001 to 63.6% in 2007-2011; this increased across all ages, having been most pronounced in patients aged 55 to 64 years21. There are several reasons for this trend: currently implanted bioprostheses are thought to last longer than past models, due to new anti-calcification and anti-immunogenicity strategies[22]; reoperation can be performed with low mortality rates (high-volume centers report mortality rates of 2-5% for reoperative AVR[4,6]) and there are emerging options such as Valve-in-Valve Technology (ViV, transcatheter valve implantation to replace a bioprosthetic valve), which offer safe alternatives to reoperation.[23] Thus, as bioprosthetic valves are becoming more durable and re-interventions safer, the balance between the risk of thrombotic/bleeding events versus the risk of reoperation seems to favor bioprosthetic valves in increasingly younger patients. However, it is important to keep in mind that solid evidence for widespread ViV usage and support for higher durability of recent biological valve iterations is still lacking, and that there is conflicting evidence regarding outcomes of bioprostheses in the 50 to 70 age group. Further larger and prospective studies should aim to provide evidence-based recommendations on this topic.

Limitations

It should be noted that this is a single-center study, including only a single year of SAVR, thus having a limited sample size, reducing statistical power of our results and precluding a generalization of results. Also, including all

patients aged 50 to 70 years old who underwent SAVR in 2012 reduces the comparability with other reports, many of which focus only on primary, isolated SAVR. Moreover, the type of valve for each patient was not randomized but left to the discretion of the surgeon and the patient, and we did not systematically register the motive for choice of valve type, although it would be pertinent to do so in future studies.

The retrospective nature of data precludes the inclusion of other valuable outcomes, such as bleeding events and hospitalizations during follow-up, and causes of death, which were not available, as patients' follow-up was often performed in other centers.

Despite having adjusted survival analyses for EuroSCORE II to mitigate confounding and selection bias, this score was designed towards predicting early mortality, not longer-term outcomes and only includes some of the relevant variables. Moreover, the small sample size and the small number of events limited the multivariable analysis performance. Furthermore, our median follow-up of 7 years could be insufficient to detect differences in outcomes in this sample.

CONCLUSION

In a real-world setting, in patients aged 50 to 70 years, both mechanical and bioprosthetic valves seem to be safe options, there being no relevant differences in terms of survival, at 7-year follow-up.

Ultimately, the choice of mechanical versus bioprosthetic valve replacement requires weighing the risk of bleeding and thrombotic events against the durability of the prosthesis and safety of reoperation. A shared and evidence-based decision process is key to maximize benefits for each patient. As of now, there is no single best answer. Further prospective and larger studies are needed to provide evidence-based recommendations on this topic.

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ARTIGO ORIGINAL ORIGINAL ARTICLE

AGE IS NOT JUST A NUMBER FOR A RAPID DEPLOYMENT VALVE IN OCTOGENARIANS

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Abstract

Introduction: *Aortic valve stenosis (AS) is the most common valvular pathology in the elderly and surgery (AVR) remains the gold-standard. However, transcatheter aortic valve replacement (TAVI) has become an emerging alternative to surgery. In a recent survey from the European Society of Cardiology, 9,4% stated that age was the main reason to propose for TAVI.*

Methods: *Single-center retrospective study including 353 patients (149 ≥80 years-old;204 with 60-69 years-old) submitted to AVR between 2013-2016. Primary endpoint was survival. Secondary outcomes included the rate of post--operative complications. Long-term survival was determined by Kaplan-Meier survival analysis. Continuous variables were analyzed with t-test and linear regression and categorical variables with chi-square or Fisher.*

Results: *clinical characteristics were similar between the two groups. Both had similar survival at 30 days, 12 (93,29% 60-69yo vs 91,47% ≥80yo) and 24 months (88,34% 60-69yo vs 86,11% ≥80yo). However, rapid deployment valves (RD) had better survival rates in elderly patients. Cross-clamp time was lower in ≥80yo group, with higher percentage of RD valves (20,1% vs 4.9% in 60-69yo). The rate of post-operative atrial fibrillation was higher in >80yo group (29,06% vs. 17,28%,p=0,0147). In all patients, cross-clamp time was directly related to ventilation time(p=0,025) and chest drainage(p=0,0015).*

Conclusion: *AVR after 80yo is safe. Cross-clamp time is directly correlated with ventilation time and bleeding, with a stronger correlation in patients over 80yo. RD valves reduce cross-clamp times, so their use in elderly may improve surgery outcome. Prospective studies are needed to evaluate if age may be clinical criteria for a RD.*

INTRODUCTION

Aortic valve stenosis is the most common valvular disease in industrialized countries, with an estimated prevalence of 2-7% in patients over 65 years old.[1] The prevalence of valvular disease increases with age, reaching 9.8% over 80 years old.[2] Nowadays, more octogenarians present with aortic stenosis with indication for surgery. The proportion of patients over 80 years old submitted to aortic valve surgery has been increasing in the past decades[3] due to the increasing in global average life expectancy.

Surgical aortic valve replacement (SAVR) remains the gold standard of treatment for aortic valve stenosis in low-intermediate risk patients. However, as age is an important risk factor for mortality and morbility in cardiac surgery[4], and a clear correlation between age, morbidity and mortality has been established, many surgeons hesitate to accept these patients for surgery.[4] According to The Euro Heart Survey, nearly one third of patients with symptomatic severe aortic valve stenosis and age over 80 were denied the standard of care (SAVR). One of the reasons of the refusal was "advanced age".[5]

Elderly patients often have comorbilities that stratify them in high-risk for open cardiac surgery under cardiopulmonary bypass, such as calcified aorta, poor lung function and previous cardiac surgery. However, although studies in this population are limited, SAVR can be performed with acceptable mortality and morbidity in octogenarians.[6]

Recently, transcatheter aortic valve implantation (TAVI) has emerged as an option in high-risk patients.[7] It is now recommended to be performed in high risk patients and some intermediate-risk patients after discussion in heart team. However, in a recent survey from the European Society of Cardiology, 9.4% of the physicians stated that age was the main reason to refer a patient for TAVI instead of surgery (independently from their comorbidities and surgical risk).[8] However, TAVI has also risks

and although it allows a quicker recovery, some studies state that the overall quality of life at 6 months does not differ between TAVI and AVR once operability is taken in consideration.[9]

The present study aims to access the outcome of octogenarians patients submitted to SAVR, comparing perioperative outcomes and long-term survival with a similar younger group submitted to the same procedure.

MATERIAL AND METHODS

Preoperative demographic, clinical and perioperative data were retrieved retrospectively from the clinical files from our Department. Follow-up data, including major morbidities and date of death were obtained from hospital records and from registries from the national electronic health care database. All patients were submitted to aortic valve replacement surgery between January 2013 and February 2016. All the clinical and follow-up data from patients over 80 years old (≥ 80 yo) were compared to data from patients submitted to the same procedure between 60 and 69 years old (60-69 yo). At 4-6 weeks after the surgery all patients underwent a follow-up assessment.

Statistical analysis

Normally distributed continuous variables are presented as mean and standard deviation (SD). The student t-test was used to compare means. Categorical data is reported as count and percentage, and comparisons were made using Pearson's Chi-square test or the Fisher exact test, depending on the sample analyzed. Overall survival was analyzed by the Kaplan-Meier method. Curves were compared using a log-rank test. A p-value of $<0,05$ determined statistical significance. Data was analyzed by the GraphPad Prism® software for Macintosh®, version 6.

RESULTS

From January 2013 to December 2016, 353 patients were submitted to aortic valve replacement surgery in our department (204 patients between 60 and 69 years-old and 149 patients with at least 80 years-old). Patients proposed for combined valvular surgery and/ or concomitant coronary artery bypass grafting were not included in this study.

Baseline characteristics of both groups are summarized in Table 1. In the 60-69 yo, patients had a mean

Table 1 **Demographic data: comparison between the two groups**

	60-70 years old	≥ 80 years old	*p*-value
N	204	149	
Age, years, mean ± SD	65,4 ± 2,787	82,23 ± 1,917	***<0,0001
Male sex, n (%)	123 (60,3)	61 (40,9)	**0,0003
Hypertension, n (%)	173 (84,8)	135 (90,6)	0,1066
Diabetes mellitus, n (%)	72 (35,3)	27 (18,1)	**0,0004
Dyslipidemia, n (%)	143 (70,1)	101 (67,8)	0,6462
Obesity, n (%)	48 (23,5)	13 (8,7)	**0,0003
Atrial fibrillation, n (%)	24 (11,8)	29(19,5)	0,0455
Chronic kidney disease, n (%)	9 (4,4)	14 (9,4)	0,0609
Peripheral vascular disease, n (%)	9 (4,4)	1 (0,7)	*0,0364
Cerebrovascular disease, n (%)	17 (8,3)	10 (6,7)	0,5712
Chronic lung diseas, n (%)	15 (7,4)	15 (10,1)	0,3664
Ischemic cardiopathy, n (%)	9 (4,4)	14 (9,4)	0,0609
LV dysfunction (EF < 50%), n (%)	23 (11,3)	19 (12,8)	0,5882
Hyperuricemia, n (%)	13 (6,4)	6 (4)	0,3348
Thyroid disease, n (%)	7 (3,4)	11 (7,4)	0,0956
OSAS, n (%)	16 (7,8)	4 (2,7)	*0,0384
NYHA I, n (%)	20 (9,8)	9 (6)	0,2417
NYHA II, n (%)	139 (68,1)	102 (68,5)	1,0000
NYHA III, n (%)	44 (21,6)	38 (25,5)	0,2464
NYHA IV, n (%)	1 (0,5)	0 (0)	1,0000

V: left ventricular; OSAS: obstructive sleep apnea syndrom

age of 65,4 ± 2,787 years, with the majority being male 123 (60,3%). Younger patients had a higher incidence of diabetes mellitus (p=0,0004) and obesity (p=0,0003). Hypertension was the most prevalent risk factor in both groups, followed by dyslipidemia and diabetes mellitus. In the ≥ 80 yo, patients had a mean age of 82,23 ± 1,917 years, with 40,9% of males (61 patients) [p=0,0003].

The mean predictive logistic European System for Cardiac Operative Risk Evalutation (EuroSCORE II) mortality risk was 1,168 ± 1,157 for 60-69 yo and 1,697 ± 0,75 for ≥ 80 yo (p<0,0001). There were no statistically significant differences concerning other baseline characteristics between the two groups, as described in Table 1.

Aortic stenosis was the main indication for surgery: 84,8% in the 60-69 years old group and 96,6% in the ≥ 80 years old group. In 18 (8,8%) patients in the 60-69 yo group and 4 (2,7%) in the ≥ 80 yo group the indication for surgery was aortic insufficiency, followed by endocarditis in 12 (5,9%) and 1 (0,7%) patient, respectively, and 1 (0,5%) patient with prosthesis dysfunction in the 60-69 yo group, as described in Table 2.

In 175 (85,85%) 60-69 yo patients and 128 (85,9%) ≥ 80 yo patients, surgery was performed electively. In the remaining patients, surgery was performed urgently.

None of the patients submitted to surgery in the elderly group received a mechanical prosthesis, while 57 patients (27,9%) from the younger group received one. Morrow myectomy was concomitantly performed in 20 patients 60-69 yo (9,8%) and in 20 patients (13,4%) ≥ 80 yo (p=0,3110). Surgeons opted for a rapid deployment valve in 10 (4,9%) patients in the 60-69 yo group and in 30 patients (20,1%) in the ≥ 80 yo group (p<0,0001).

The cardiopulmonary bypass time was longer in the 60-69yo group (61,29 ± 2,415) compared with the ≥ 80 yo group (55,27 ± 2,019) (p=0,071). Similarly, the cross clamp time was longer in the younger group (50,93 ± 1,892 *vs* 45,73 ± 1,591, p=0,0432).

The median ventilation time was 11,66 ± 1,898 hours in the 60-69yo group and 10,48 ±1,943 in the ≥ 80 yo group (p<0,6716). Both groups had similar chest tube drainage, intensive care unit and hospital lengths of stay (table 2).

Post-operative complications and their incidence are described in Table 3. Transfusion and hemodynamic support were the most frequent complications in both groups, although both have a higher incidence in the elderly group. Excessive post-operative hemorrhage was more frequent in the 60-69 yo group, although the incidence of re-operation due to excessive hemorrhage was similar: 8 (3,9%) 60-69 yo *vs* 6 (4%) ≥ 80 yo (p=1,00). Atrial fibrillation was more common in the elderly group (30,9% *vs* 17,1%, p=0,0031). Both groups had similar rates of acute kidney injury and stroke. Wound infection

Table 2 **Intraoperative data and clinical outcomes**

	60-70 years old	≥ 80 years old	*p*-value
N	204	149	
Aortic stenosis, n (%)	173 (84,8)	144 (96,6)	***<0,0001
Aortic insufficiency, n (%)	18 (8,8)	4 (2,7)	0,0241
Endocarditis, n (%)	12 (5,9)	1 (0,7)	**0,0094
Aortic prothesis dysfunction, n (%)	1 (0,5)	0 (0)	1,0000
Euroscore, mean ± SD	1,168 ± 1,157	1,697 ± 0,7568	****<0,0001
Biological prothesis, n (%)	147 (72,1)	149 (100)	<0,0001
Mechanical prothesis, n (%)	57 (27,9)	0 (0)	***<0,0001
Rapid depolyment valves, n (%)	10 (4,9)	30 (20,1)	****<0,0001
Morrow Miectomy, n (%)	20 (9,8)	20 (13,4)	0,3110
Elective surgery, n (%)	175 (85,8)	128 (85,9)	1,0000
Urgent surgery, n (%)	29 (14,2)	21, (14,1)	1,0000
Emergent surgery, n (%)	0 (0)	0 (0)	--
Extracorporeal time (min)	61,29 ± 2,415	55,37± 2,019	0,0710
Cross-clamp time (min)	50,93 ± 1,892	45,73 ± 1,591	*0,0432
Ventilator time (h)	11,66 ± 1,898	10,48 ± 1,943	0,6716
Chest tube 24h (cc)	624,8 ± 36,77	689,2 ± 56,65	0,3209
ICU LOS (h)	63,29 ± 4,752	76,99 ± 7,452	0,1059
Hospital LOS (days)	7,46 ± 0,89	8,303 ± 0,46	0,4507

ICU: intensive care unit; LOS: length of stay

Table 3 **Post-operative complications**

	60-70 years old	≥ 80 years old	*p*-value
N	204	149	
Blood or blood product, n (%)	99 (48,5)	92 (61,7)	*0,0173
• Blood	67 (32,8)	80 (53,7)	***0,0001
• Fibrinogen	44 (21,6)	44 (29,5)	0,1053
• Platelets	64 (31,4)	52 (34,9)	0,4936
• FFP	46(22,5)	35 (23,5)	0,8982
Excessive post-op hemorrhage , n (%)	12 (5,9)	6 (4)	0,4744
Reoperation due to tamponade, n (%)	8 (3,9)	6 (4)	1,0000
Atrial fibrillation, n (%)	35 (17,1)	46 (30,9)	**0,0031
Acute kidney failrure, n (%)	44 (21,6)	43 (28,9)	0,1338
Haemodynamic support, n (%)	83 (40,7)	66 (44,3)	0,5143
Stroke, n (%)	2 (1)	1 (0,7)	1,0000
Wound infection, n (%)	6 (3)	0 (0)	0,0414
Discharge, n (%)			
• Other hospital	23 (11,6)	15 (10,4)	0,8619
• Home	175 (88,4)	129 (86,6)	

FFP: fresh frozen plasma

was diagnosed in 6 patients from the 60-69 yo group, while none was diagnosed in the older group (p=0,414).

There were six in-hospital deaths in the 60-69 yo group and 5 in the ≥ 80 yo group. Kaplan-Meier estimates of survival at 1 and 2 years were 93,29% and 88,34% for the 60-69 yo patient, *versus* 91,47% and 86,11% for patients over 80 yo (p=0,5418) [Figure 1]. Considering only the patients over 80 yo, there are no differences in survival at 1 year between the use of conventional valves (91,32%) and rapid deployment valves (91,5%). However, at 2 years, the survival is higher in the rapid deployment group (91,48% *vs* 86,85%) (p=0,5805), although it is not statistically significant [Figure 2]. There are no demographic or peri-operative differences between these groups (data not shown).

Patients between 60 and 69 yo have significant differences in survival at 1 and 2 years when a conventional valve is used (94,61% and 90,34%) *versus* a rapid deployment valve (64% and 48%), respectively (p=0,0002) [Figure 3]. Once again, there are no demographic or peri-operative differences between these groups (data not shown).

To better understand the impact of rapid deployment valves, we correlated cross clamp time with ventilation time, chest tube drainage during the first 24 hours and ICU length of stay. A simple linear regression analysis showed a correlation between cross-clamp time and ventilation time (p=0,02491) and chest tube drainage (p=0,0015), considering all patients. No correlation was observed between cross-clamp time and ICU length of stay for all patients.

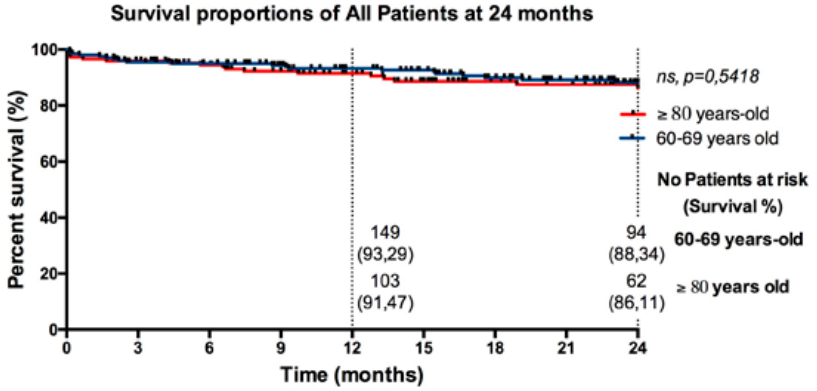

Figure 1 *Survival proportions of all patients at 24 months; ns: non-significant.*

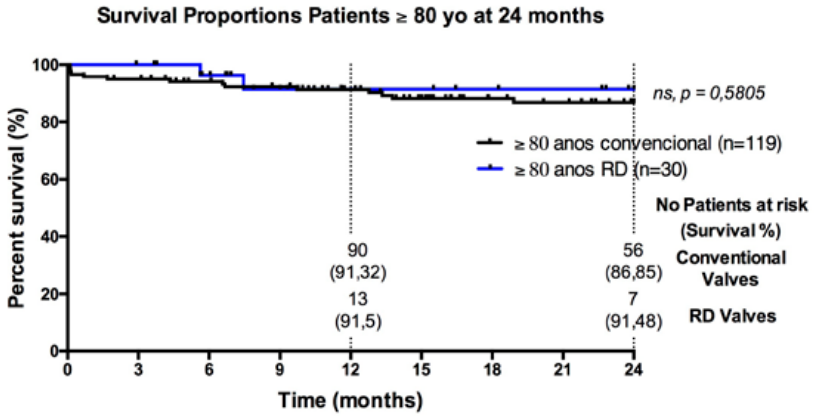

Figure 2 *Survival proportions patients over 80 year-old at 24 months, comparing conventional and rapid deployment valves; RD: rapid-deployment; ns: non-significant.*

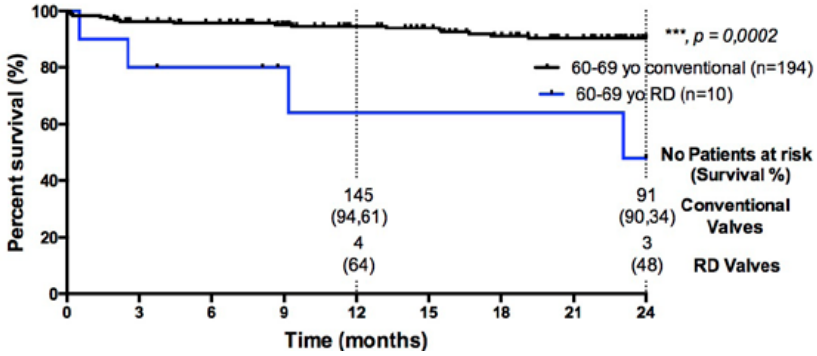

Figure 3 *Survival proportions of patients 60-69 years-old at 24 months, comparing conventional valves with rapid deployment valves; RD: rapid-deployment; ns: non-significant.*

Performing a group sub-analysis, we observed that the cross-clamp time is correlated with ventilation time (p=0,0077), chest tube drainage (p=0,0395) and ICU length of stay (p=0,0493) for patients over 80 yo. On the other hand, in patients 60-69 yo, cross clamp time was only correlated with chest tube drainage (p=0,0063) [Figure 4].

CONCLUSIONS

It is well known that elderly patients have more comorbilities and fragilities that increase the surgical risk. Particularly in cardiac surgery, the assessment of frailty is important since it is associated with the occurrence of major complications, 30-day mortality and extended postoperative length of stay. Frailty is a better predictor for mortality than morbidity.[10] However, the assessment must be individualized as it depends on the patient. Patients with the same age can have different levels of frailty. Its assessment is not yet routinely performed, but it may become useful in our pre-operative routine as the number of patients with advanced age increases.

Indeed, and as previously described, age has been assumed as a limitation for surgery. Cardiologists have been proposing low-intermediate elderly patients for TAVI instead of surgery based just on age. Even European heart association guidelines use age as a risk factor for referring for TAVI, as age over 75 years old favours TAVI as much as an EuroSCOREII higher than 4%.[11,12]

Age has always been included in risk assessment scores. EuroscoreII includes age as a continuous patient--dependent risk factor. However, EuroscoreII was launched in 2011 with a patient population median age of 64.9 years old. As mean age of patients undergoing cardiac surgery is increasing, the risk model calibration may not be as accurate as it was.[13] In fact, some studies have pointed that risk models, such as EuroscoreII, do not accurately predict mortality nowadays in elderly patients undergoing aortic valve replacement.[14]

Several studies have published data supporting that SAVR can be feasible in elderly patients, with very low mortality and complications rates.

In this study we present the results from our center in octogenarians submitted to SAVR. Patients over 80 yo had similar survival rates at 1 and 2 years to younger patients (60-69 yo), although they had a higher mean EuroscoreII (1,697 *vs* 1,168) with similar comorbilities.

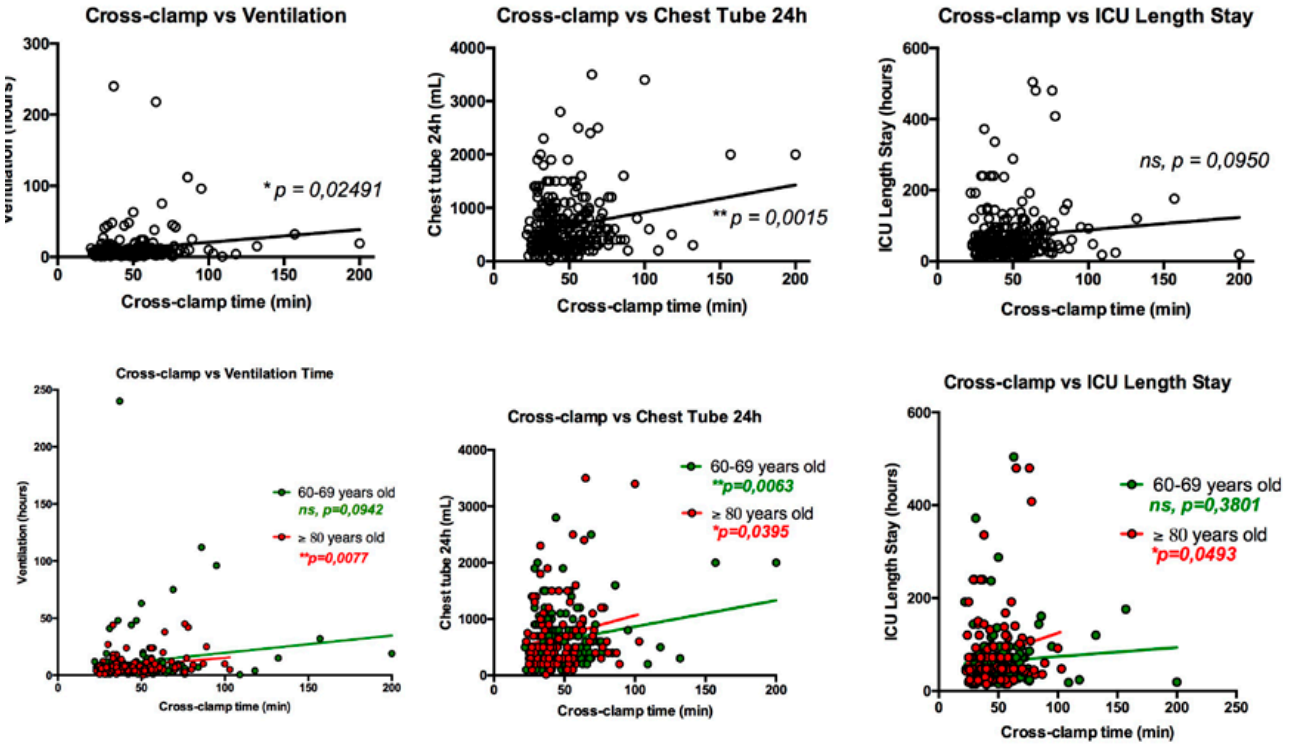

Figure 4

Cross-clamp time correlation with ventilation time, chest tube drainage and ICU length of stay for all patients; and cross-clamp time correlation with ventilation time, chest tube drainage and ICU length of stay for patients 60-69yo (green) and patients over 80yo (red); ICU: intensive care unit; ns: non-significant; yo: years-old.

Studies have shown that, considering all patients, cardiopulmonary bypass and aortic cross-clamping times are significant and independent risk factors for mortality and morbility in cardiac surgery.[15] Regarding this fact, technology in cardiac surgery has advanced in the past decades with the development of rapid deployment valves, in order to reduce morbility and mortality reducing extracorporeal circulation and cross-clamp times.

As elderly patients are more fragile, and usually have more comorbilities, shorter surgeries with reduced extracorporeal circulation and cross-clamping times are more important and may have a major impact comparing to a similar reduction in younger patients. One possible explanation for our good results in patients over 80 yo is that they had a significantly lower cross-clamp time, probably due to the higher use of rapid deployment valves in this group. Moreover, in our study, we have observed that in patients over 80 yo cross clamp time is correlated with post-operative outcomes such as ventilation time, chest tube drainage and ICU length of stay. In these patients, reducing cross clamp time with the use of a rapid deployment valve can actually reduce ventilation time and ICU length of stay and improve the outcome.

When we analyze survival of both groups comparing rapid deployment valves with conventional valves, in the older group both patients have similar survival rates at 1 and 2 years (with a better survival rate with rapid deployment valves, although it is not statistically significant). However, survival rate is significantly lower in patients with 60-69 years old when a rapid deployment valve is used. This may be explained by the use of RD valves in patients with comorbilities that are not included in EuroscoreII, such as renal transplantation or cirrhosis.

Our study has all the limitations inherent to retrospective observational studies. As a single center study our findings are related to our population, and may not be extrapolated to other populations. The limited number of patients and a small age specific group are also limitations of this study. Surgical referral and selection are other two limitations, since the cardiologists refer the majority of patients and many with advanced age are referred for TAVI without a cardiothoracic surgery appointment or heart team discussion. Moreover, follow-up was limited to 24 months and causes of death were unavailable for patients who died outside or were followed outside our institution.

Our results support the safety of aortic valve replacement surgery in the elderly, with a low rate of complications and similar outcomes to younger patients. In elderly patients, frailty assessment may be an important tool to distinguish TAVI and SAVR patients, since age itself does not support any clinical decision. More studies must be performed to evaluate if age is a clinical indication for an aortic rapid deployment valve.

Conflicts of interest

This research received no grant from any public or private institution. Authors have no conflicts of interest to disclose.

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ARTIGO ORIGINAL ORIGINAL ARTICLE

ARTERIAL SWITCH OPERATION: VARIABLES PREDICTING REOPERATION

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Abstract

Objectives: *Jatene surgery or arterial switch is performed at our institution since the late nineties. We reviewed our results to identify the main causes of reoperation and, more importantly, to determine what variables predict the need for reoperation.*

Methods: *: In this retrospective analysis were included all the 91 patients with d-TGA who underwent an arterial switch operation at our institution between 1995 and 2016.*

Results: *Mean follow-up was 10 years (range 5-25 years). Seventy-one percent of patients had simple TGA and 29% had complex TGA. The need of reoperation was 21% (n=19 patients). Right ventricle outflow tract obstruction was the main indication for reoperation (58%). The overall mortality was 9.9%. The gender (P= 0.8), diagnosis (simple or complex TGA) (P= 0,5) or the existence of palliative surgeries (P=0.9) were unable to predict the need for reoperation. The presence of anomalous coronary pattern was the only variable reaching statistical significance (P< 0.05), both in univariate and multivariate analysis.*

Conclusions: *In our series, the main indication for reoperation after arterial switch operation was right ventricle outflow tract obstruction and the only predictive variable was the presence of anomalous coronary pattern.*

INTRODUCTION

Transposition of the great arteries, defined by the presence of ventriculo-arterial discordance, accounts for 5% to 7% of all congenital heart defects, with a prevalence of 0.2 per 1,000 live births and male preponderance.[1] The diagnostic of TGA, regardless of age, constitutes an indication for surgery. Jatene surgery, performed successfully for the first time in 1975, is the treatment of choice. It is performed, at our institution, since the early nineties. Between 1995 and 2016, a total of 91 cases were performed, with 19 requiring reoperations. It is mandatory review our results and understand the indications for reoperation. Most importantly, we aimed to identify what variables better predict the need for reoperation.

MATERIAL E METHODS

In this retrospective analysis were included all patients submitted to arterial switch, between 1995 and 2016, with a total number of 91 cases. All data were analyzed using SPSS software. Categoric variables were presented as absolute values and percentages. Continue variables were presented using mean and standart-deviation or median and inter-quartile range, if they had normal distribution or not. Univariate analysis of categoric variables was done with Fisher test or qui-square. The ones reaching statistical significance, with a p-value equal or inferior to 0.05, were tested in a binary logistic regression model. Freedom from reintervention was analyzed using actuarial method.

RESULTS

Descriptive analysis of population data shows that 60% (n=53) were males. The median age at operation was 11 days. Almost all patients were assyndromic. All patients had the diagnostic of TGA, with 71% having simple TGA and 29% complex TGA, with only four patients presenting with aortic coarctation. The mean follow-up is 10 years (minimum 5 years, maximum 25 years). Eight patients (8,8%) had anomalous coronary arteries, with anomalous origin (n=7) or intramural segments (n=2). One of them had both an anomalous origin and an intramural segment.

Twenty six percent(n=24) were submitted to previous surgery or catheter interventions. The most common surgery was pulmonary artery banding (n=6). LeCompte maneuver was performed in 90 patients. After corrective surgery, 10% (n=9) required percutaneous intervention, while 21% (n=19) required reoperation, all considered late

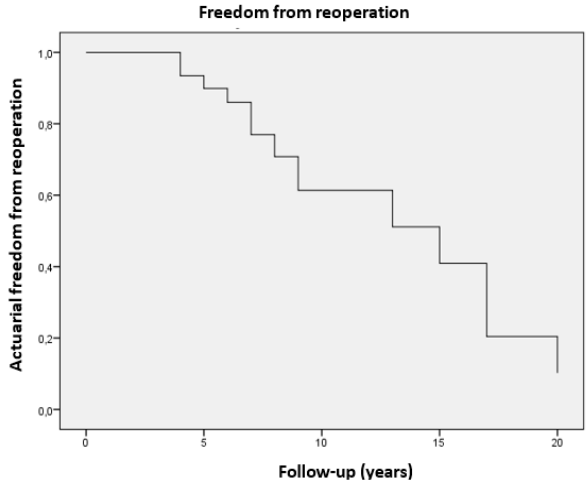

Figure 1 *Kaplan-Meier Curve for Survival (Log-rank test, p=0.173).*

reoperations. Median freedom from catheter intervention was 3,8 years. Median freedom from reoperation was 6,6 years. Figure 1 shows the actuarial curve concerning freedom from reoperation.

Cumulative mortality was 9.9% (n=9), 4 cases representing hospital mortality. Considering only the cases of hospital mortality, one case was an intra-operatory death, while the remaining three resulted from hemorrhagic complications, while on ECMO support.

DISCUSSION

Arterial switch is the treatment of choice for TGA, including TGA with intact interventricular septum or with interventricular septum defect.[2] Nowadays, this procedure has a reduced intra-operatory mortality with good long-term results. Currently, most treated patients live to adulthood, with a 20-year survival rate of nearly 90%.[1] With this improvement in surgical results, concerns are directed to coronary ischemia, neo-aortic valve disfunction and pulmonary stenosis, all possible causes of reoperation.[3] In our series and accordingly with most published results, the main cause of reoperation was right ventricle outflow obstruction, including main pulmonary artery and its branches.[1,3] Right ventricle outflow obstruction represents 58% (n=11) of all reoperations. Sixteen percent (n=3) had aortic insufficiency, 11% (n=2) had coronary lesions and 11% were reoperated because of inter-atrial communications. One patient had residual aortic coarctation (Table 1).

In published series, the incidence of pulmonary artery stenosis or its branches after arterial switch operation ranges between 10-17%.[1,4] The need of balloon angioplasty varies between 17-28% and the need of reoperation is 2-6%.[5] Pulmonary stenosis after arterial switch operation can occur at the infundibulum or at a supravalvular level, while valvular stenosis is rare. There are various mechanisms related to pulmonary stenosis, namely, the three-dimensional conformation of the great vessels associated with this disease and surgical related factors. Although Jatene surgery corrects ventriculo-arterial discordance, it does not achieve a normal spiral configuration of the great arteries. With the LeCompte maneuver the pulmonary bifurcation is mobilized anteriorly, but the great arteries remain parallel to each other and the bifurcation of the pulmonary is possibly compressed posteriorly by the aorta.[6]

The main objective of this retrospective analyze is to determine with variables better predict the need of reoperation. There was not a significant statistical difference between the median age at operation between the patient who needed reoperation and those who did not ($p = 0,1$). We tested the influence of sex, diagnosis (simple TGA versus complex TGA) and previous surgery and we were not able to find a significant statistic association ($p = 0,8$; 0,5; 0,9 respectively). The presence of anomalous coronary arteries was the only variable with a significant statistical association with reoperation ($p < 0.05$). It was, therefore, tested on multivariable analyze, achieving the same statistical significance ($p < 0.05$). Eight patients presented with anomalous coronary arteries. One of them presented with both an anomalous origin and an intramural segment. Of the remaining 7 patients, one had an intramural segment, three had type E, two had type D and one had type C anomalous coronary origin, accordingly with Yacoub's classification.[7] Considering patients with anomalous coronary arteries who underwent reoperation, only one was because of coronary ischemia. In the group of patients who underwent reoperation, the main cause was right ventricle outflow tract obstruction (n=11).

Coronary button transfer to neo-aorta (Figures 2 and 3) represents a crucial step of switch arterial surgery.[8] However, in our series, despite the association between the presence of anomalous coronary artery and reoperation, most patients were not reoperated because of coronary ischemia.

Table 1 **Causes of reoperation in patients submitted to arterial switch operation**

Cause of reoperation	Percentage	Number of patients
Right ventricle outflow tract obstruction	58%	11
Aortic insufficiency	16%	3
Coronary lesions	11%	2
Inter-atrial communications	11%	2
Residual aortic coarctation	5%	1

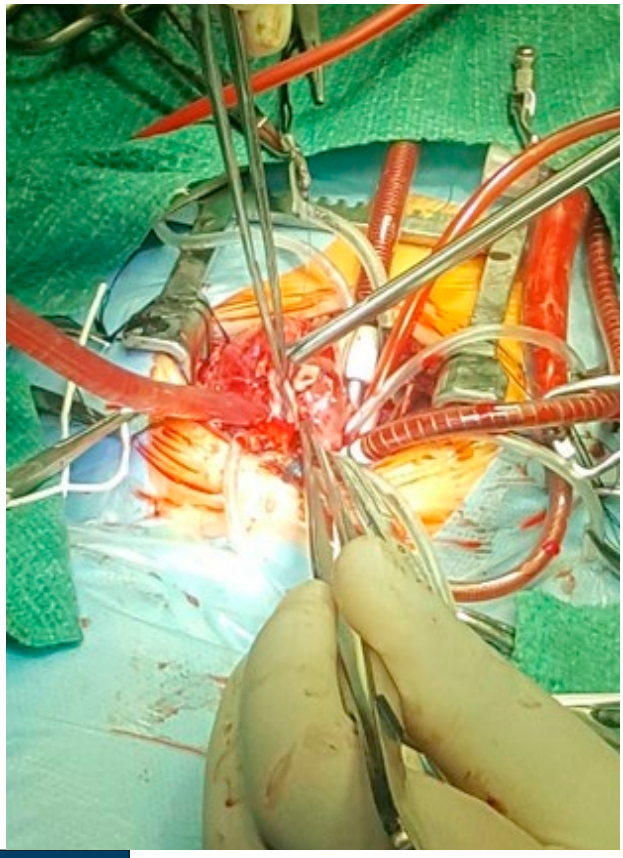

Figure 2 *Excision of the coronary buttons with the button technique.*

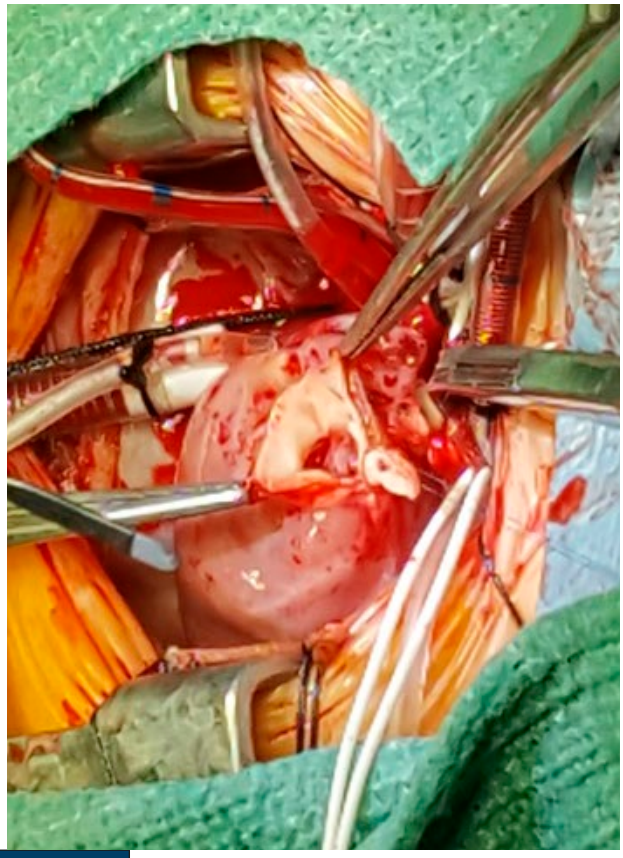

Figure 3 *Coronary button before implantation in the neo-aorta.*

On the contrary, most were reoperated because of supra-pulmonary stenosis. The presence of anomalous coronary patterns frequently requires a larger button, which might lead to sub-optimal reconstructions of the neo-pulmonary. From another perspective, the coronary anatomy depends on aortopulmonary rotation, meaning that those patterns are more frequently associated to side-by-side and antero-posterior relation of the great arteries. The limitations of our study result from the retrospective character, based in the results of a single institution.

CONCLUSION

Supra-pulmonary artery stenosis is the most frequent cause of reoperation after arterial switch operation. In our series, univariate analysis identified an association between the presence of coronary artery anomalous and reoperation, association that remained statistically significant in multivariate analysis.

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ARTIGO ORIGINAL ORIGINAL ARTICLE

SAFETY AND RISK FACTORS FOR THE MORBIDITY AND MORTALITY OF PNEUMONECTOMY: A RETROSPECTIVE 10-YEAR STUDY IN A SINGLE INSTITUTION

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Abstract

Objectives: *Pneumonectomy is a procedure with high post-operative morbidity and mortality. This study aims to assess and identify possible risk factors that can affect post-operative outcome, therefore determining the safety of pneumonectomy in specific groups.*

Methods: *A total of 63 patients submitted to pneumonectomy at our centre, from February 2008 to February 2018, were included in our retrospective study. Age, gender, side of intervention, diagnosis, pre-operative symptoms, substance abuse and comorbidities were assessed. Early and late post-operative complications, as well as death were our major outcomes. We analysed the impact of preoperative variables on major outcomes using SPSS statistics.*

Results: *We found a 9,8% surgery-related mortality and 1-year survival rate of 76,2%. The incidence of early complications in our population was of 35% while eleven patients (17,4%) developed late post-operative complications. No statistical difference was found when comparing survival time between genders or age groups. Right sided pneumonectomies seem to be associated with an higher mortality risk. No other association between risk factors and outcomes reached statistical significance in both univariate and multivariate analysis.*

Conclusions: *Pneumonectomy is a viable option regardless of age whenever the patient has a good functional and cardiopulmonary status. Gender and diagnostic group do not seem to influence adverse event risk, although right-sided pneumonectomies show an increased risk for post-operative death. Care should be taken with patients submitted to neoadjuvant therapy. All patients should be encouraged to cease smoking as early as possible before surgery, given the increased risks for post-operative complications.*

INTRODUCTION

The first pneumonectomy was performed in 1933 and was the procedure of choice during the 1950s, before surgery evolved to less invasive approaches.[1] It is often referred to as a disease itself, given the high incidence of post-operative complications, mortality and decrease in overall quality of life.[2]

Lung resection is often the best treatment modality for both malignant and several non-malignant conditions. The anatomical extension of the pulmonary pathology usually dictates the need for a pneumonectomy in detriment of less invasive techniques, as so, pneumonectomy is reserved for particular cases in which limited resections cannot be performed.[3,4]

Many risks factors have been advocated to influence the risk of post-operative complications following a pneumonectomy, although consensus still lacks within the literature. Age per se has not proved to be a risk factor, despite the higher risks inherent to the population itself, and other proclaimed risk factors remain debatable. Besides the risk for early complications, one of the most feared complications of pneumonectomy is the development of a bronchopleural fistula, which increases morbidity and severely compromises quality of life. There is still relatively little published evidence on the role of bronchial stump reinforcement in the prevention of bronchopleural fistulae.[5]

This study focuses on analysing the safety of pneumonectomy, identifying risk factors within the population

that can help determine operative suitability and predict post-operative complications, in the intent to minimize both morbidity and mortality.

MATERIALS AND METHODS

Population and data

We have retrospectively reviewed all patients submitted to pneumonectomy at the Centro Hospitalar Vila Nova de Gaia/Espinho, Portugal, from February 2008 to February 2018. A total of 63 patients were included in our study, with ages ranging from 20 to 80 years old. Patients under 18 years of age and submitted to pneumonectomy due to trauma were excluded. Patients were considered candidates for surgery whenever the underlying pathology was not addressable through minor resections (central tumours, disease invading major fissures) and whenever the benefits overcame the risks of surgery. Malignant disease with distant metastases or oesophageal infiltration were absolute contra-indications for surgery. All patients submitted to pneumonectomy were adequately studied through pre-operative imaging (either chest x-ray, chest CT, bronchoscopy and/or PET scan when needed) and lung function studies. Patients with a predicted post-operative FEV1 over 60% were considered fit for surgery.

In order to investigate risk factors for post-pneumonectomy complications, categories such as age gender, side, underlying disease, pre-operative symptoms, (such as cough, dyspnoea, haemoptysis, loss of weight) tobacco and alcohol abuse and history of respiratory and cardiovascular disease were assessed and registered. We defined an age cut-off at 70 years old, dividing our population into two comparable groups. Patients were divided in two groups in terms of underlying disease: malignancy (including all histological subtypes) and benign disease, including both infectious disease (such as tuberculosis or aspergillosis) and structural lung disease (such as bronchiectasis). In cases in which pneumonectomy was performed due to malignancy, histological type and additional therapy (both adjuvant or neoadjuvant chemotherapy and radiotherapy) were assessed.

Post-operative complications were divided into two categories: early complications, defined as those occurring during in-hospital stay (including haemorrhage, acute lung injury, surgical site infection, atrial arrhythmias) and late complications, such as empyema and bronchopleural fistula. Both early and late complications contributed to patient's post-operative morbidity. The cut off for a prolonged in-hospital stay was set at 10 days after surgery.

Total length of stay and ICU days were also documented.

Early mortality was defined as death within the in-hospital stay or during first 30 days post-discharge. Early and total mortality, as well as 1-year survival rate, were also calculated.

All data used in our study were obtained through the patient's personal medical records.

The mean follow-up time was 1458 days.

Outcome

The primary end points of analysis were morbidity, regarding early and late complications, and mortality. Age, gender, side of the procedure, diagnostic group, tobacco abuse, previous history of tuberculosis and pre-operative therapies (such as chemo and radiotherapy in cases of lung malignancy) were considered as potential risk factors. Survival curves were analysed through the Kaplan-Meier method and compared through log-rank tests. The effects of risk factors on these end points were evaluated with both univariate and multivariate analysis, through chi-square tests and logistic regression models.

Surgical technique

All procedures were performed by cardiothoracic surgeons from the Department of Cardiothoracic Surgery of the Centro Hospitalar Vila Nova de Gaia/Espinho, Porto, Portugal. Patients were submitted to either standard, extended or completion pneumonectomy, depending on the underlying pathology. Bronchial stump reinforcement with intercostal muscle flap or U sutures was performed in cases of patients submitted to neoadjuvant therapy and whenever intra-operative findings were suggestive of bronchial stump dehiscence.

RESULTS

Population and clinical setting

A total of 63 patients were submitted to pneumonectomy over the course of this study, 46 of them were male and 17 were female, with a ratio male:female of almost 3:1. Age at time of surgery ranged from 20 years old to 80, with a mean age of 59.98 and a median of 61 years of age.

Patients were divided into two categories according to age, with 16 patients within the age of 70 or older and 47 younger than 70 years of age. The majority of patients (56 patients) submitted to pneumonectomy were diagnosed with malignant disease involving the lung, either primary or secondary, as we can see in Table 1. Twenty-one patients (37.5% of those with malignant disease) received neoadjuvant therapy, while 23 were submitted to either chemo or radiotherapy after surgery. Of those receiving neoadjuvant therapy, 16 patients were aged under 70 years old while only 5 were over 70. The histological characteristics of all diagnosed malignant lung tumours are listed in Table 1. Four patients presented with structural lung disease manifesting as bronchiectasis and 3 with infectious disease (2 of them with aspergillosis and 1 with empyema). Eighteen patients were asymptomatic at presentation.

The most frequently reported symptoms were cough (24 patients) and haemoptysis (23 patients). In terms of previous medical history, a total of 66.7% of patients had a history of tobacco abuse and 12 patients (19%) had a previous diagnosis of tuberculosis during their lifetime.

Regarding laterality, 23 patients were submitted to a right pneumonectomy, while the remaining 40 were submitted to surgery on the left. Only five procedures were

Table 1 **Population demographic and clinical pre-operative data**

	(n)
Age at time of surgery (years; $\mu \pm SD$)	59.98 (±12.21)
Gender	
• Male	46
• Female	17
Diagnosis	
• Lung malignancy	56
○ Adenocarcinoma	20
○ Squamous cell carcinoma	17
○ Carcinoid	6
○ Sarcomatoid carcinoma	6
○ Bronchioloalveolar carcinoma	2
○ Small cell carcinoma	1
○ Mesothelioma	1
○ Metastasis	1
○ Unknown	2
• Bronchiectasis	3
• Aspergillosis	2
• Empyema	1
Pre-operative symptoms	
• Cough	24
• Haemoptysis	23
• Chest pain	9
• Weight loss	8
• Asymptomatic	12
Pre-operative symptoms	
• Tobacco abuse	42
• Diabetes	7
Tuberculosis	12
Side of pneumonectomy	
• Left	40
• Right	23

completion pneumonectomies. Overall, 90.5% of surgeries were standard pneumonectomies. Only one patient was submitted to an extra-pleural pneumonectomy due to mesothelioma. Of the remaining, in 3 the procedure was extended to the pleura and 2 to the pericardium.

The median length of stay was of 8 days (min.: 5 – max.: 123 days). All patients were admitted to our ICU ward on the operative day. The majority of patients were transferred to the general cardiothoracic ward in the first post-operative day, only 7 stayed in the ICU ward for over 48 hours (11.1%) due to early post-operative complications.

Outcome

We found an overall mortality of 36.5% during the study's 10-year time span. The calculated mean survival time was of 8.4 years. Meanwhile, early mortality was 9.8% (6 patients) and the 1-year survival rate was 82.5%. Survival curves are shown in Figure 1.

Median overall survival time in patients over 70 years of age was of 101.1 months, while those younger than 70 showed a median survival time of 81.9 months. No difference in survival curves was found between patients younger and older than 70 years of age (log rank: p=0.673).

Early mortality rate according to diagnostic group was of 8.9% in lung malignancy cases and of 14.3% for benign conditions.

Regarding side of the intervention, the mortality rate for right-sided interventions was of 26% and for left-sided ones, of 0%. All 6 cases of peri-operative death occurred in right-sided interventions (chi square=0.001)

No statistical difference was found when comparing survival time between genders (log rank p>0.05). Mortality among women was 5.9% and among men 10.9% (chi square = 0.549). 66.7% of early deaths occurred in patients with a history of tobacco abuse, none of which had a previous diagnosis of tuberculosis.

Mortality in patients submitted to neoadjuvant therapy was 14.3% while in those who didn't receive pre-operative chemotherapy was 7.1%. In multivariate analysis, only laterality reached statistical significance.

Regarding early complications, there was a 20.6% incidence of atrial fibrillation in the immediate post-operative period. 4.8% of cases suffered from acute post-operative haemorrhage, with a need for reintervention for haemostasis revision. Only 1.6% of patients developed a surgical site infection. Overall, the incidence of early complications in our population was 35%. Through the chi-square test, no risk factors showed direct statistically significative impact on early complications. One of the only risk factors that approached statistically significative influence on early complication rate was male sex (p=0.082). Although not reaching statistical significance through the chi square test (OR=1; 95%CI [0.085-11.70]; p=1.0), smoking seemed to increase the risk of over ten days in-hospital stays (p=0.039).

Eleven patients (17.4%) developed late post-operative complications, 8 of whom were smokers, although the association between smoking and late complications was not confirmed by statistical analysis. All patients with bronchopleural fistula were smokers and the majority of them were from the male gender and suffered from a lung malignancy (4 out of 6). Four of the patients who developed a bronchopleural fistula had been submitted to a left pneumonectomy, while the remaining two were submitted to a right pneumonectomy. Four of the patients who developed a bronchopleural fistula had been submitted to a left pneumonectomy, while the remaining two were submitted to a right pneumonectomy. Previous history of pre-operative chemotherapy did not show any influence in the development of bronchopleural fistulae. Nineteen patients were submitted to bronchial stump reinforcement, 15 through the use of an intercostal muscle flap and 4 through direct U-suture. Bronchial stump reinforcement did not show to protect from bronchopleural fistula development, instead, this complication showed to be more frequent in patients who performed bronchial stump coverage (OR=5.6; CI95%=[0.93-33.8]).

Of the 8 patients with a previous history of tuberculosis, 4 presented late complications. This outcome showed to be more frequent in younger patients, as 9

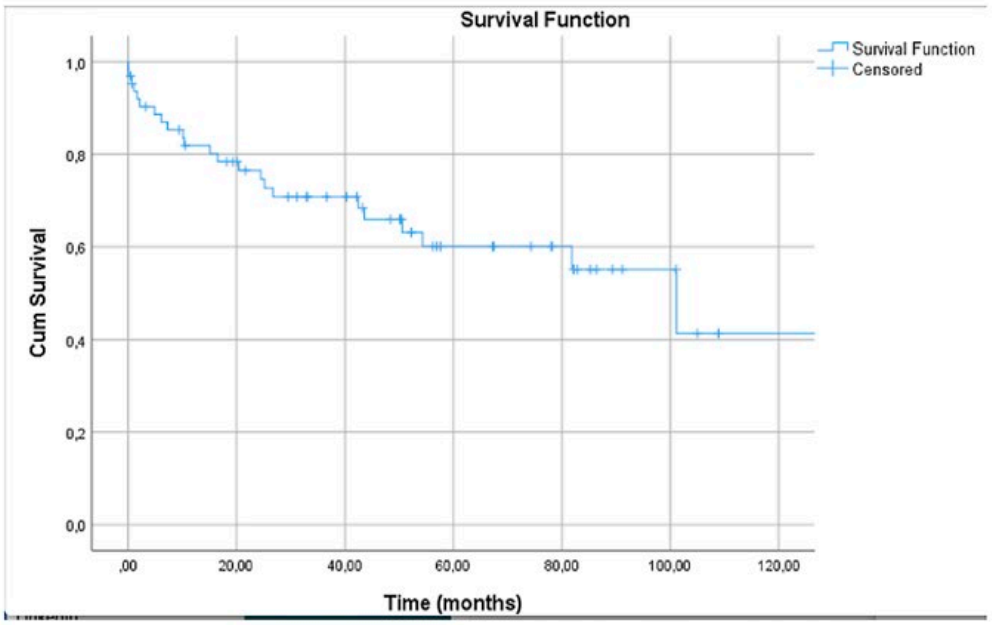

Figure 1 *Kaplan-Meier 10 year survival curve.*

out 11 were aged under 70 years old. Although neoadjuvant therapy showed to impact early complications, it failed to do so for late complications. Regarding the body side intervened, 45.5% of complications occurred in right pneumonectomies, while the remaining 54.5% occurred in left ones. The majority of patients with late complications were male (72.7%). No association was found between risk factors and the incidence of late complications in multivariate analysis. No cases of post-pneumonectomy syndrome were found during the timespan of this study.

DISCUSSION

Despite the risks and the current trend for minimally invasive procedures, there are still cases where a pneumonectomy needs to be performed. Current indications for pneumonectomy include: centrally located tumours, locally advanced tumours irresectable by lobectomy or lesser lung resections, post-infectious lung destruction, multi-drug resistant extensive tuberculosis, congenital pathologies affecting lung parenchyma and trauma incidents.[6-8] Given the extensive nature of the resection, only patients with acceptable cardiac and lung function are candidates for the procedure. Despite the advances in anaesthetic management and peri-operative care, overall morbidity and mortality related to pneumonectomy has remained stable throughout the years.[2,6]

Many risk factors have been advocated in different studies as influencing post-pneumonectomy morbidity and mortality, but, in many, no consensus was yet found. Among them, old age, male sex, cardiac failure, benign disease, neoadjuvant therapy, decreased lung function, right sided pneumonectomy, acute blood loss during surgery and tobacco abuse have been proposed to influence post-operative course.[9-14] In our study we have investigated the role of age, sex, diagnosis, laterality, history of tuberculosis or tobacco abuse and neoadjuvant chemotherapy in post-operative complications and overall mortality, in order to access which factors must be taken into account when selecting patients for surgery.

The overall mortality during the 10-year time in our study was of 36.5%, seemingly higher than most studies which report a 0-25% mortality.[10,11,15-17] This may be mostly related to the fact that studies rarely report 10-year survival rates, opting for 30-day to 5-year data presentation. Also, this overall mortality does not exclude non-pneumonectomy related causes of death. Our peri-operative mortality was 11.1%, in line with most of the current literature which proclaims overall peri-operative mortalities of 3-12%.[9,18,19] In concordance with other studies, 1-year survival rate in our study was of 76.2%, higher than that reported by Annessi et al, of about 66%.[20]

Many groups have investigated the role of age in post-pneumonectomy prognosis in an attempt to evaluate whether the procedure is safe enough to be performed in elders. It has been consistently shown that, despite the comorbidities associated with old age, pneumonectomy is safe enough to be performed in elder with adequate lung and cardiovascular function.[12,13,20-23] In our study, we have chosen to compare outcomes between 2 groups with a cut-off for age set at 70 years old, the classic definition for old age. Given the current extension in global average life expectancy, accompanied by a stable lung cancer incidence that affects mostly those in the 60-70s age group, the number of septuagenarians submitted to lung surgery has been increasing throughout the years.[11,22] Through analysis of the Kaplan-Meier survival curve, early post-operative

mortality seems to be slightly higher in older patients, but overall survival doesn't show significant differences among both groups. The Lung Cancer Group has previously shown a perioperative mortality for pneumonectomy of about 5.9%, similar to our finding of a 6.5% perioperative mortality in patients aged over 70.[24] Age also did not show impact in the incidence of post-operative complications in our study, either early or late ones. Although one might predict higher morbidity in older patients, given their frequent comorbidities, studies are consistent in considering that pneumonectomy should be attempted in cases in which the patient is considered fitt for surgery, especially in cases of lung cancer, regardless of age.[12,13,23]

While in the past, tuberculosis was one of the major indications for pneumonectomy,[10] currently, with the development of multi-drug treatment for tuberculosis, patients with lung malignancy represent the main objects of pneumonectomy. In our study, although the majority of patients suffered from a lung neoplastic disorder, precluding us from a faithful analysis, those with benign diseases seemed to experience an increased risk for early death. "Benign" diseases, in this study, included both structural and infectious diseases, probably affecting both lungs. An unhealthy contralateral lung renders it more difficult for patients to recover after pneumonectomy. Other studies have corroborated this finding, showing a worse prognosis in patients with benign disease submitted to pneumonectomy, especially in terms of early peri-operative risk.[7] The reported higher surgical and peri-operative risk in benign diseases seems to be related to the amount of scar tissue and adhesions around major vascular structures that can difficult surgical dissection and increase the risk for bleeding.[10] Regardless, pneumonectomy is safe in cases of lung cancer, with an estimate mean survival time of 8.4 years, compared with the disappointing results of palliative non-surgical therapies alone, with reported mean survivals of 10-12 months in the study of Bolukbas et al, along with the predicted 5-year survival rate of only 10% in those with Stage I lung cancer reported by Van Meerbeeck *et al.*[12,13,22] Although tuberculosis was not the major indication for pneumonectomy in our patients, 19% had a previous history of Mycobacterium tuberculosis infection, which did not prove to influence neither post-operative morbidity nor mortality.

Right-sided pneumonectomies seem to be inherently associated with higher post-operative risks in other studies, attributable to the increased tension in the right ventricle resulting from delivering the whole cardiac output to the smaller left lung.[13,25] Accordingly, we have found in our study that all post-operative deaths occurred in right sided pneumonectomies. Regarding complications in the remaining patients, only the development of Acute Respiratory Distress Syndrome (ARDS) occurred predominantly in right sided pneumonectomies, probably due to acute stress to an unprepared right ventricle ($p<0.05$).

In the report from Shapiro using the STS Database[9], male sex showed to impact the risk of post-operative events. In our study, we have also found both a higher mortality rate and a higher incidence of early complications, such as haemorrhage and surgical site infection. The reason for that remains to be understood, although the higher number of male patients in our study may be a confounding factor in the extraction of conclusions.

There was a high prevalence of smokers in our population, with an overall mortality of 35.7%. Smoking showed to increase the incidence of early post-operative complications and was associated with longer in-hospital length of stay, findings in strict correlation with one another, since complications inherently augment the mean in-hospital time.

In those with a lung malignancy, neoadjuvant chemotherapy has been reported to increase the risk of both morbidity and mortality after surgery.[20] In our study neoadjuvant therapy did not prove to influence early post-operative mortality but did influence 10-year mortality rate in multivariate analysis, probably due to long-term systemic effects of chemotherapy treatments.[25]

Early complications occurred in 35% of patients. The most frequent early complication was atrial fibrillation, which occurred in 20.6% of patients, an incidence concordant with the 11-28% frequency interval reported by Foroulis *et al.*[30] Although atrial fibrillation is even more common in pneumonectomies involving pericardial dissection, due to atrial irritation,[20] this did not seem to occur in our study, probably showing that our results underestimate the real incidence of arrhythmic events.

Bronchopleural fistula development is one of the most feared complications of pneumonectomy. In our study, we found a frequency of 9.5% of late bronchopleural fistulas, causing overwhelming morbidity in patients. All patients had a history of tobacco abuse which probably contributed to fistula development. Most studies have proposed right pneumonectomies as a risk factor for fistula development,[10,14] although, our findings did not corroborate this statement. Nineteen patients were submitted to bronchial stump reinforcement either with intercostal muscle or U-sutures, although, this did not seem to influence the incidence of bronchopleural fistula.

One of the biggest limitations in our study is the short sample size and the high heterogeneity of our population. Although, we found this study to be relevant, since pneumonectomies are high risk procedures and risk factors are still contradictory and not well defined. We believe this surgery must be attempted whenever it is believed to be the treatment approach offering the longest survival expectancy with acceptable morbidity for each patient, as so, patients must be thoroughly studied, and indications should be individually defined. More studies evaluating the impact of cardiopulmonary status variables on outcome are in need.

CONCLUSIONS

Pneumonectomy is a safe and viable option for cases in which lung tumours are not accessible through less invasive resections and the patient is considered fit for surgery.

The procedure is safe in elders. Gender and diagnostic group do not seem to influence adverse event's risk after

a pneumonectomy, although benign disease might increase post-surgical adverse outcome risk. Right sided pneumonectomies may be associated with higher mortality rates. Tobacco seems to increase the risk of both early and late complications. Smoking cessation should be encouraged in all cases. Patients considered candidates for pneumonectomy should be carefully selected, accounting for their previous medical history and cardiopulmonary risk factors.

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RUPTURED SINUS OF VALSALVA INTO THE RIGHT VENTRICLE: A NEW MANAGEMENT STRATEGY

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Abstract

We present 2 cases presented to the emergency department with shortness of breath (SOB). Their preoperative echocardiographies showed ruptured right sinus of Valsalva (RSOV) into the right ventricle (RV). Ventricular septal defect (VSD) was diagnosed only intraoperatively.

CASE 1

A 23 years-old Pakistani male patient with history of cardiac murmur, presented to the emergency department (ED) with palpitation and progressive SOB for few weeks. His vital signs were normal, continuous murmur was heard over the left sternal border with clear chest. Blood investigations showed high pro-BNP. There were cardiomegaly and prominent broncho-vascular markings by chest x-ray. Pre-operative 2D transthoracic

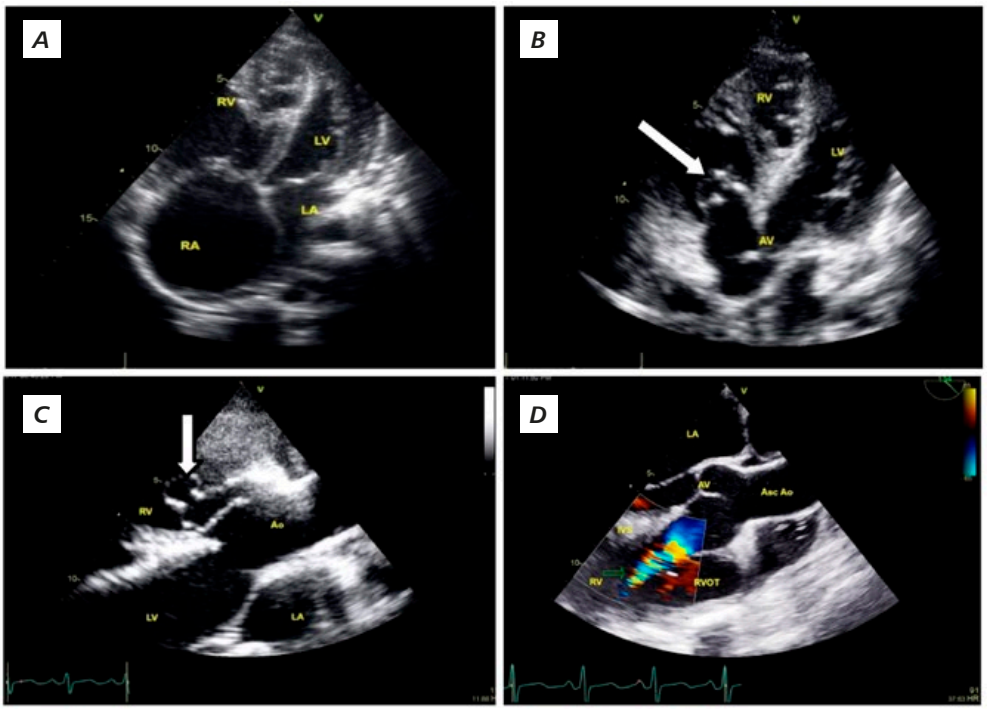

Figure 1

***(A)** Apical 4 chamber TTE view; marked RV and atrium enlargement. **(B)** Apical 5 chamber TTE view, the arrow is pointing at the RSOV **(C)** Parasternal long axis view (PLAX). **(D)** Colour Doppler flow across the ruptured sinus. RA: right atrium, LV: left ventricle, LA: left atrium, AV: aortic valve, AO: aorta.*

echocardiography (TTE) showed dilated sinus of Valsalva; 4.2cm in diameter with ruptured right coronary sinus into the right ventricle outflow tract (RVOT), no VSD could be detected. Ejection fraction (EF) was 57%, severe tricuspid regurgitation and severe pulmonary hypertension; 104mmHg.

Intra-operative findings were the same. Additionally, there was a sub-aortic VSD. He underwent repair of the RSOV and the VSD using a tailored synthetic hemashield Dacron patch and repair of the tricuspid valve. The postoperative course was uneventful.

CASE 2

A 35 years-old previously healthy Indian male patient, presented to ED with SOB for two days, gradual onset and progressive course. Chest showed continuous murmur over the left sternal border, decrease air entry on lungs bases with crepitation. Blood investigations showed markedly elevated pro-BNP. Chest X ray showed increased broncho-vascular marking with bilateral mild pleural effusion. Preoperative TTE and

TEE showed ruptured aneurysm of right coronary sinus of valsalva into the RVOT, no VSD could be detected, EF was 55%.

A small sub-aortic VSD was discovered intra-operatively in addition to the RSOV. The VSD was repaired using pledgetted proline stitch after repairing the Valsalva defect using a double tailored hemashield Dacron patch. The patient had the same postoperative course as the 1st patient.

the non-coronary sinus (23%), and rarely in the left coronary sinus.[2]

It is frequently associated with VSD (30-60%), bicuspid aortic valve (15-20%) and aortic regurgitation (44-50%).

Rupture of the aneurysmal sac may occur spontaneously or be precipitated by exertion, blunt trauma, or cardiac catheterization. Rupture into RV is most common (60% to 90%), right atrium (10%) and left atrium (2% to 3%).

Aneurysm of the sinus of Valsalva in Asian patients compared with Western series is characterized by a higher incidence, more originating from the right coronary sinus (85.8% *vs* 67.9%), more rupture into the RV (72.5% *vs* 60%), a higher incidence of association with VSD (52.4% *vs* 37.5%), and lower incidence of association with bicuspid aortic valve (0.6% *vs* 7.8%), both Asian and Western patient series have similar incidence of combination with aortic regurgitation (33.6% *vs* 32.7%).[3]

TTE identifies sinus of valsalva aneurysm in most cases. TEE may be necessary in as many as 25% of cases. The ruptured aneurysm by echocardiography frequently has a "wind-sock" appearance; that is an elongated tubular structure expanding and collapsing with the cardiac cycle. Some cases of RSOV aneurysm reported missed VSD. 3D echocardiography is usually useful in precise anatomical delineation of RSOV particularly if it's associated with VSD.[4] In the presence of coexistent VSD, the large shunt of RSOV overlaps VSD flow which may be difficult to recognize on 2D echo. Magnetic resonance imaging (MRI) allows an exact presentation of the anatomy, including areas that are difficult to assess, so it may be considered in stable patients.

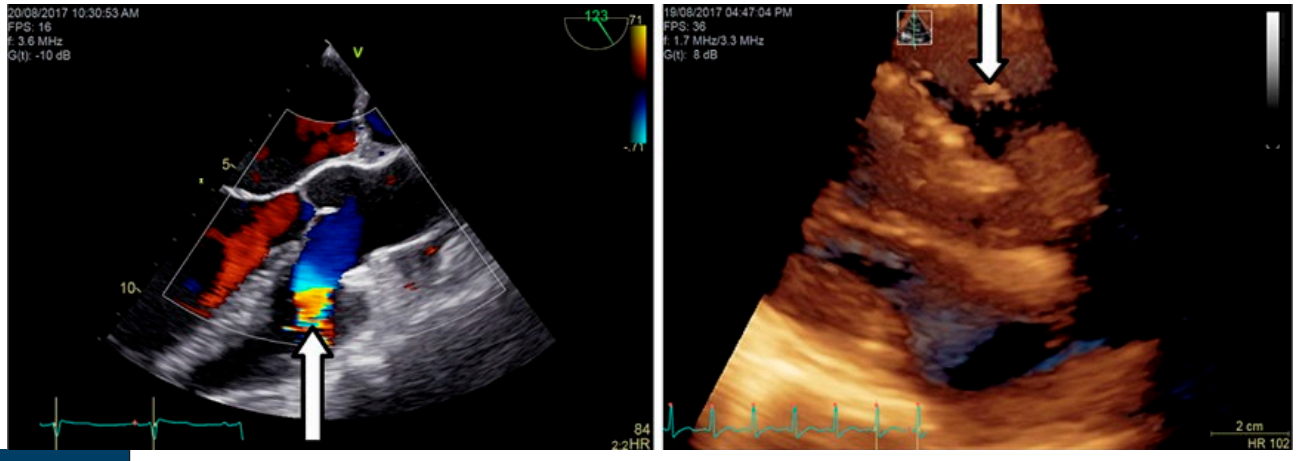

Figure 2 *A) Midesophageal lateral axis view at 120 degrees with color. B) 3D TTE PLAX showing the ruptured sinus.*

DISCUSSION

Incidence of Sinus of Valsalva aneurysms is 0.1% to 3.5% of all congenital heart defects,[1] male preponderance (4:1), high in Asian populations. The aneurysm is found most commonly in the right coronary sinus (77%),

In our cases we believe that VSD's were missed preoperatively because either the large aneurysmal sacs were covering the VSD or because of the overlap of the two shunts. In addition, in the first case right ventricular pressure was high approaching systemic pressure which probably reduced the shunt across the VSD.

Early and aggressive intervention is recommended to prevent endocarditis or enlargement of the ruptured aneurysm; the long-term results are excellent after surgical repair,[5] with actuarial survival rate is 95% at 20 years. If left untreated, patients die of heart failure or endocarditis within 1 year after the onset of symptoms.

CONCLUSION

RSOV aneurysm need vigilant preoperative assessment for coexisting cardiac defects, including TEE, with 3D reconstruction if available. MRI is an option if the patient is stable and can tolerate it. Surgical repair is still the modality of choice in many cases.

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A PATIENT IN THE INCUBATION PERIOD OF SARS-COV-2 SUBMITTED TO OPEN-HEART SURGERY

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INTRODUCTION

On the 11th March 2020, WHO announced the Covid-19 outbreak a pandemic. The Centro Hospitalar Universitário S. João (CHUSJ) was the main referring Hospital for the disease in the Northern Region of Portugal, which implied critical resources allocation for the foreseen increased number of admissions. The Department of Cardiothoracic Surgery cancelled all elective surgeries by the 13th of March, while maintaining an adequate level of response for emergent, urgent and high priority cases.

CASE REPORT

In this context, a 76-year-old male with a past medical history of myocardial infarction, EVAR implantation, peripheral artery disease, COPD and metabolic syndrome, presented in the Emergency Department with chest pain lasting for more than 12 hours. A posterior wall NSTEMI was diagnosed after elevated hsTnI and EKG changes. The echocardiogram displayed moderate left ventricle dysfunction, with hypokinesia of anterior and lateral walls plus akinesia of the posterior wall. He was admitted to the Coronary Care Unit, a coronary angiogram performed 5 days later and after Heart Team revision, recommended for surgical revascularization. Although initial episodes of fever and mildly elevated CRP, absence of respiratory symptoms, downward trend of the CRP and a normal CT scan allowed scheduling of cardiac surgery.

The patient was submitted to bilateral internal thoracic artery grafting to the left anterior descending and obtuse marginal branch arteries, under cardiopulmonary bypass and cardioplegic heart arrest. After a straightforward operation, the patient was transferred to the ICU in stable condition.

Initial post-operative blood work and chest X-ray revealed unremarkable, but a new episode of fever raised the suspicion of SARS-2 infection. Despite all clinical evidence being in contradiction of SARS-CoV-2 infection, a sample was obtained and tested positive. According to the Hospital policy, the patient was transferred to a dedicated COVID-19 intensive care unit.

In the next 48 hours, respiratory failure followed, the diagnosis of viral pneumonia established with a super-infection with Klebsiella ornithinolytica imposed. At this point, antibiotic therapy with pyperacilin-tazobactam and vancomycin adjusted for renal impairment were initiated. No immunomodulator was prescribed.

Weaning with success after protective mechanical ventilation was achievable on the 16th day after admission. The patient proceeded on good convalescence despite the identification of *de novo* severe left ventricular disfunction on echocardiogram. However, no vasopressor support was required and no need for dialysis, notwithstanding a slight rise in serum creatinine, maximal value was 2,0mg/dL.

On the 22nd post-operative day, was transferred to the ward to resume respiratory and motor physiotherapy. During the final period of hospitalization, he remained apyretic, without respiratory symptoms and the CT-scan showed resolution of pneumonic infiltrates. After resuming activity, he was free of angina. Before discharge, echocardiogram displayed a preserved left ventricle ejection fraction only with abnormal motion of apical interventricular septum.

The patient tested negative in RT-PCR SARS-CoV-2 test for the first time 38 days after the diagnosis, and subsequently for three more times before being discharged home in excellent condition, 53 days after surgery.

DISCUSSION

To our knowledge, this is the first report in Portugal, of a cardiac surgery in a patient with Covid-19. Covid-19 virus adversely affects both cardiovascular and respiratory systems, hence cardiac patients have a worst prognosis.[1] In particular, patients with coronary artery disease have an increased risk of severe Covid-19 infection, as they usually present with old age, hypertension, diabetes, obesity and cardiac and pulmonary disease. Furthermore, viremia may

originate acute cardiac injury,[2] potentially impairing cardiac muscle recovery after successful revascularization. During Covid-19 pandemic, there is a shortage of intensive care beds and SARS-CoV-2 pneumonia is faster and more violent in post-operative patients, with a reported mortality rate up to 20.5%.[3,4] However, these same patients usually portray severe clinical conditions, delayed surgery will unfavorably impact on survival and quality of life. Hospital resources must be allocated for the demanding increase in health care of critical patients with Covid-19 infection, while maintaining an adequate response to other life-threatening diseases as coronary or valvular heart diseases. During the mitigation phase of disease, rigorous criteria are essential to assure disease free circuits for these serious conditions and surgery should only be indicated for high priority cases. Written protocols should assist the Heart Team with difficult decisions and surgery should be postponed in elective cases.

Protection of both health care professionals and in-Hospital patients is of outmost importance. To prevent cross-infection, it is a current policy in our Department to test all patients and retest them every 5 days, because it is near median incubation period.[5] Infected patients should be treated in dedicated SARS-CoV-2 units where experience of caring teams is maximized, while minimizing cross-infections.[6] In the case of preoperative diagnosis of infection, medical treatment should be enhanced, and the surgery should be postponed until the patient recovers from the infection. If an infected patient needs emergent surgery, then patient and family must understand the high risk of the procedure and high probability of cardiorespiratory complications.

Further studies are needed to improve healthcare of cardiovascular patients in these difficult times.

Acknowledgments

We recognise the expertise and dedication of Health Professionals of the Department of Intensive Medicine of CHUSJ in the care of this patient.

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TRICUSPID PROSTHESIS MALFUNCTION UNMASKED BY EXERCISE STRESS ECHOCARDIOGRAPHY

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Abstract

Exercise echocardiography is used mainly in the study of patients with coronary artery disease, however the technique is increasingly used in the study of other pathologies.

We present the first case of use of exercise stress echocardiography for clinical decision in one patient with biological prostheses in tricuspid position.

The clinical exam, the echocardiogram, the cardiac MRI, the NT proBNP were normal and the patient has been considered to have no indication for surgery.

The patient was only presented and accepted for surgery after the results of exercise stress echocardiography.

CASE REPORT

We describe the case of a 52 years-old Caucasian male, member of the Portuguese army that at 30 years age, has a motorcycle accident with chest trauma with a long stay in Hospital. He also is athlete with at least six-hour weekly training schedule that competes in marathon and half marathon frequently. Since four years ago he refers to be unable to increase speed when running after the first four kilometers of competitions. He went medical evaluation and severe tricuspid regurgitation and right ventricular and atrial dilation was noted. After complete study, he has been submitted to cardiac surgery and a biologic prosthesis (St Jude Medical Epic 29) was given in tricuspid position.

After recovery right ventricle became normal with normal ventricular function and the echocardiogram reveals tricuspid mean gradient of 5 mmHg, however the patient is unable to walk more than 200 meters without extreme fatigue.

An echocardiogram and an MRI were done and were considered normal. Blood levels of NT- proBNP were also normal.

Physical examination revealed normal cardiac auscultation and normal radial, carotid and femoral pulses. The rest echocardiogram, done in orthostatic position, reveals a tricuspid mean gradient of 6 mmHg. (Figure 1) The patient was referred then to Hospital da Cruz Vermelha for Treadmill exercise echocardiography that was performed following the modified Bruce protocol (6 minutes)

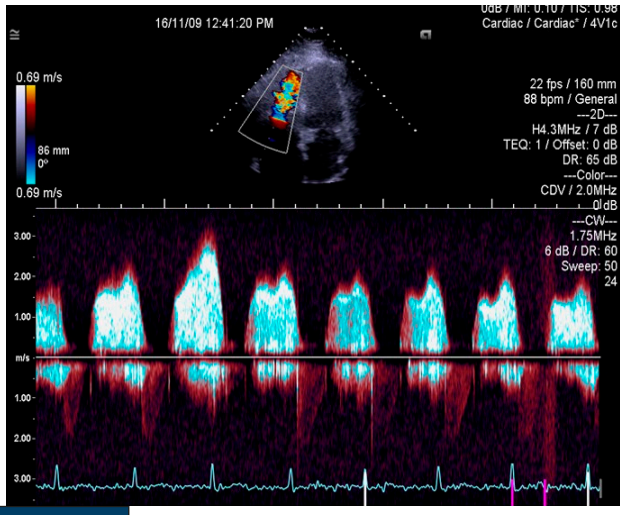

Figure 1 *In this figure we can see the tricuspid mean gradient (6 mmHg) evaluated in orthostatic position in the treadmill before start exercise.*

and an huge increase in mean gradient was seen (Figure 2) A mean gradient of 22 mmHg was attained (Increase of 16 mmHg). We suggest that substitution of tricuspid prosthesis should be considered. Some months later tricuspid prosthesis was substituted – a huge amount of pannus was seen - and exercise stress echocardiogram was done with increase of tricuspid mean gradient from 4 mmHg to 10 mmHg and a duration of 14 minutes (modified Bruce Protocol). The patient feels normal again.

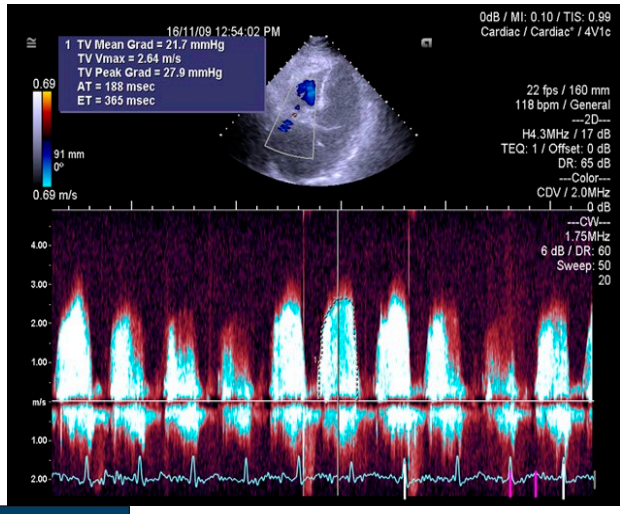

Figure 2

In this figure we can see the tricuspid mean gradient (22 mmHg) evaluated at peak exercise before stop exercise. (variation of 16 mmHg in tricuspid prosthesis mean gradient and huge variation of mean gradient associated with respiratory movements.)

DISCUSSION

A significant part of the patients with aortic valve disease and mitral valve disease that are submitted to surgery are given a prosthesis.[1,2] Most prosthetic valves are inherently stenotic,[3,4] being the effective orifice area some times too small in relation to body surface, a phenomenon classified as valve prosthesis-patient mismatch.[5] In clinical practice, it is common that normally and abnormally prostheses can produce similar gradients at rest and exercise stress echocardiography may be valuable in confirming or excluding the presence of prosthetic valve dysfunction or mismatch. This is particularly true when we have disagreement between symptoms and the hemodynamic profile evaluated by Doppler echocardiography at rest.[5-8] According to Picano[3,4] a disproportionate increase in trans-valvular mean gradient (greater than 20 mmHg for aortic prosthesis or greater than 10 mmHg for mitral prosthesis) generally indicates severe prosthesis dysfunction or mismatch. To the best of our knowledge this is the first case of tricuspid prosthesis mismatch demonstrated with exercise stress echocardiography. The most recent recommendations (3) make no reference to tricuspid prosthesis patient mismatch however using the criteria used for mitral prosthesis evaluation with stress echo encourages us to assume that this is the case of our patient.

We use exercise stress echocardiography in patients with prosthesis whenever there exists discrepancy[9,10] between the gradients evaluated in the echocardiogram and the presence of the symptoms. Evidence based cut-off gradients are needed for clinical decision. Until there we associate the exercise Doppler parameters with the clinical and the exercise test data for decision.

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COMPLEX MEDIASTINAL TUMOUR IN PREGNANCY: CASE REPORT

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Abstract

A 19 years-old woman, on her 17th week of pregnancy presented to the emergency department with thoracic pain and vomiting. An empyema was diagnosed and she was transferred to a tertiary hospital for treatment. After drainage of the empyema a mediastinal mass was detected and a thoracic MRI revealed a multicystic lesion of the anterior mediastinum, causing cardiac and left lung compression, suggestive of a complicated teratoma. After a multidisciplinary discussion involving pulmonology, radiology, obstetrics and thoracic surgery, she was operated successfully by clamshell incision. A mature complicated teratoma was resected and a left pleurectomy/decortication performed. She was discharged on day 17 with no obstetrical or respiratory symptoms.

CASE REPORT

A 19 years-old female, with a normally progressing 17 weeks gestation, presented to the Obstetrics emergency room, complaining of nausea and vomiting and pain in the left lower chest. She referred a persistent cough for at least 2 weeks and nausea and vomiting for the last month, with great difficulty in ingestion and a subsequent weight loss of 4 Kg. She also mentioned low grade fever since de day before. This was her third visit to the Emergency ward where she had been medicated and discharged without a specific diagnosis apart from nausea and vomiting of pregnancy. At physical examination, the patient showed dyspnea, a mild tachycardia and abolished breathing sounds on the left hemithorax. The obstetrical ultrasound revealed a fetus with good vitality

A white left lung was present on the chest X-ray and exploratory thoracocentesis showed gross macroscopic purulent material. Thus, the patient was transferred to the pneumology department of a tertiary Hospital with the diagnosis of left pleural empyema. Upon arrival, a chest drain was inserted in the left pleura with drainage of 2000cc of purulent material, and a mediastinal mass became apparent on the x-ray (Fig 1).

The chest MRI revealed an anterior mediastinal mass, of 7,9X9,3 cm, with solid and cystic components, the latter extending to the contralateral mediastinum with a maximum radius of 8,7X12,3 cm, and a posterior left pleural cavity extension. Compression was exerted on the heart and on the left lung hilum, pushing the mediastinum towards the right and causing atelectasis of the left lung. There were no signs of vital or vascular structures invasion (Fig 2).

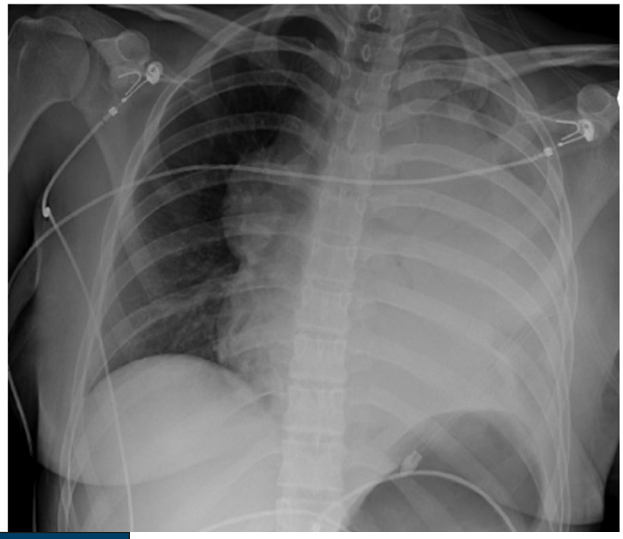

Figure 1 *Chest x-ray after drainage.*

The diagnosis of mature teratoma was considered for the main mass but the cystic pouch on the right anterior mediastinum remained a mystery and the diagnosis of immature or complicated teratoma was the second best hypothesis.

After obstetric and thoracic surgery consultation, primary surgery was advised as soon as possible. The patient was then transferred to the thoracic surgery

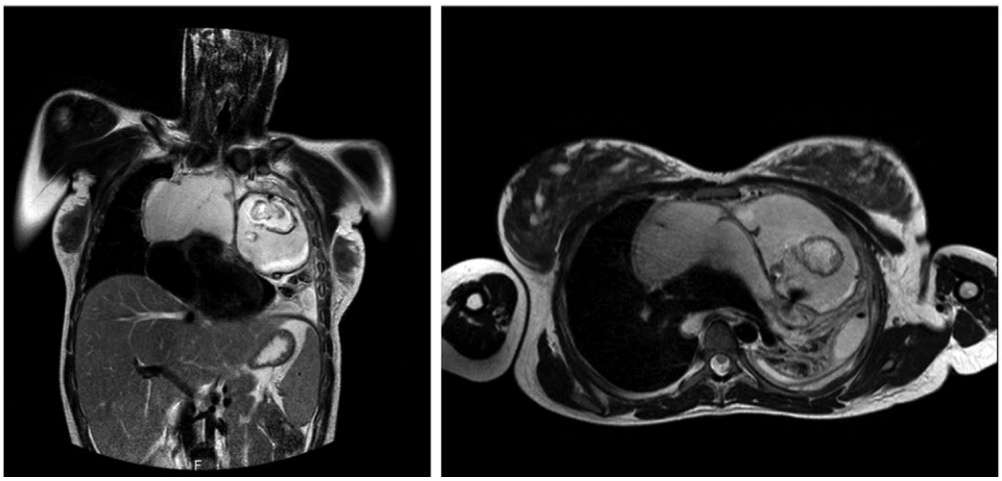

Figure 2 *MRI revealing an anterior mediastinal mass with cystic and solid and left empyema.*

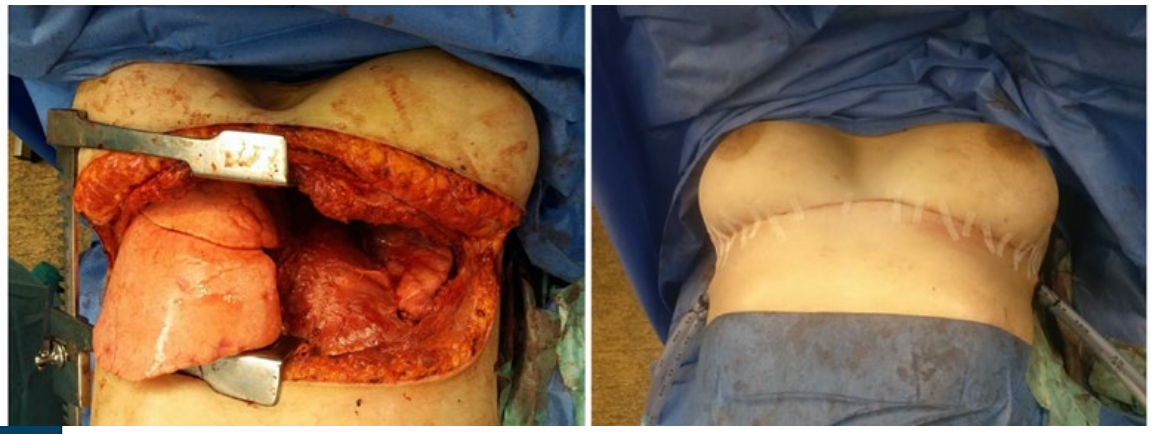

Figure 3 *Clamshell incision.*

department and underwent surgery at the 19th week of gestation. A clamshell incision offered maximal exposure of the mediastinum and of both pleural cavities avoiding compression on the abdomen (Fig 3).

Several cystic masses were found on the anterior mediastinum, with a solid component containing hairs and fat on the left side. The macroscopically mature teratoma (Fig 4) was surrounded by a large quantity of purulent material that filled all the pouches in the anterior right mediastinum and left pleural cavity.

The mass was completely resected within its capsule and all the pus filled cavities were cleared and dissected. A left pleurectomy and decortication were required to reexpand the left lung. Preservation of both phrenic nerves was accomplished. During surgery, the mother was hemodynamically stable, having received 4 units of red blood cells and 2 units of plasma.

The patient was transferred to the ICU where she remained for 4 days and weaned from the ventilator 12 hours after surgery. An ultrasound performed on the first post-operative day revealed a fetus with good vitality. A transient cholestatic complication with bilirubin 2,61 mg/dL, with normal abdominal ultrasound was detected in the first post-operative day. The left lung showed good expansion on the X-rays and the drains were sequentially removed as they stopped draining and bubbling. Penicillin,

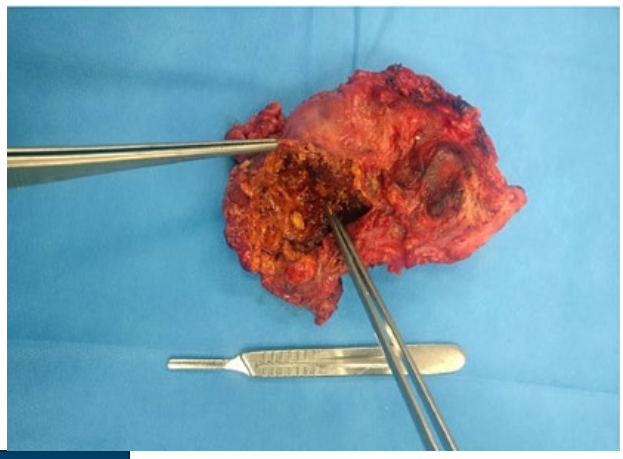

Figure 4 *Mature teratoma.*

according to sensibility tests of a Streptococcus anginosus isolated in the pleural fluid, was maintained for 21 days. Before discharge on day 17, she was observed by the high risk obstetric team and an ultrasound was performed confirming a 21 weeks female fetus with no malformations, normal amniotic fluid and good vitality.

DISCUSSION

Large mediastinal masses always pose a difficult challenge in the decision algorithm for diagnosis and therapy but in the mainstream if it is considered non-invasive, it is resectable and therefore should be primarily approached for complete resection.[1] Although the description of teratoma growth during pregnancy and puberty supported by the presence estrogen and progestrone receptors on these tumours,[2,3] can be found in the literature, a study by Caspi *et al.* reviewing 56 mature ovarian teratomas during pregnancy revealed no change in tumour volume during pregnancy, so the hypothesis of tumour growth associated with pregnancy hormones does not seem to apply to mature teratomas.[4]

Another hypothesis is that the teratoma itself may have ruptured and infected causing the empyema. Cases of mediastinal mature teratoma rupture have been reported into adjacent organs causing a myriad of symptons from cutaneous fistulas to pericardial tamponade.[5,6]

Streptococcus anginosus group comprises the microbiota of the normal gastrointestinal tract and pharynx. When it becomes pathogenic, it usually causes abscess formation and endocarditis, requiring drainage and antibiotherapy with β-lactam antibiotics.[7]

The second trimester is considered the safest one for surgical intervention. The teratogenic risk of anesthetic or antibiotic medication is low and the size of the pregnant uterus does not pose a problem yet. Imaging by MRI can be safely performed during pregnancy and played a fundamental role in the diagnosis of this condition providing precious information on the resectability of the mediastinal mass.

CONCLUSION

Pregnancy is a sensitive period in which a woman is physiologically immunosuppressed, putting the expectant mother at risk for infectious agents. This case had a good outcome, both for the mother and the fetus, as a result of a multidisciplinary approach that lead to a diagnosis and treatment of a complicated ruptured mediastinal teratoma.

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EMBOLIZATION OF IMPLANON DEVICES – LUNG SPARING VIDEOASSISTED THORACIC SURGERY

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Abstract

A 31-year-old-woman with an etonogestrel implant on her left upper arm presented with unfavorable change in her menstrual bleeding pattern and requested for its removal. The non-palpable device was perceptible in the left hemithorax by radiography. Thoracic computed-tomography showed migration to a sublobar branch of the left lower pulmonary artery. Despite the absence of thoracic symptoms and the lack of management guidelines, the device was removed by a lung sparing approach with videoassisted thoracic surgery, due to the unknown long-term effect of the embolized implant.

Keywords: *contraceptive implant; implanon; lung embolization.*

INTRODUCTION

Subdermal contraceptive implants are an effective option of family planning. Implanon NXT® is a single-rod long acting subdermal hormonal contraceptive implant (68 mg of etonogestrel, 4 cm in length, 2 mm in diameter).[1,2] Migration and embolization have been described previously, and surgical retrieval is advised.[1,2] Radiography can be of diagnostic use since the device has a radiopaque component.[3] We report a case of a subdermal contraceptive device removal from a segmental pulmonary artery by videoassisted thoracic surgery (VATS) without lung resection.

CASE REPORT

A 31-year-old-woman requested the removal of her Implanon NXT® inserted on the left arm 2 years before, because of changing pattern in menstrual bleeding. Device couldn't be palpated on insertion site. Chest radiography showed a linear opaque structure on the left hemithorax. (Figure 1, panel A) Thoracic computed-tomography demonstrated a linear radiopaque object compatible with migration of the device to a segmental branch of the left pulmonary artery (Figure 1, panel B). Despite being asymptomatic, and the lack of evidenced-based studies, implant was removed by a minimally invasive approach.

VATS was performed by a left 2 port-technique with the working port in the 4th intercostal space (2,5 cm) between the midaxillary and anterior axillary lines, and an inferior 1 cm port in the midaxillary line. On inspection there were no adhesions. Device was palpated in the lumen of the posterior basal segmental artery of the left lower lobe. (Figure 2, panel A) Once artery was thrombosed, dissection of lung parenchyma was done with an energy device,the implant was located inside the thrombosed segmental artery and carefully removed. There was no bleeding. (Figure 2, panels B-C) Cautery and biologic glue were used to seal the exposed lung. (Figure 2, panel D) Patient was discharged on day 3 with an uneventful post-operative course.

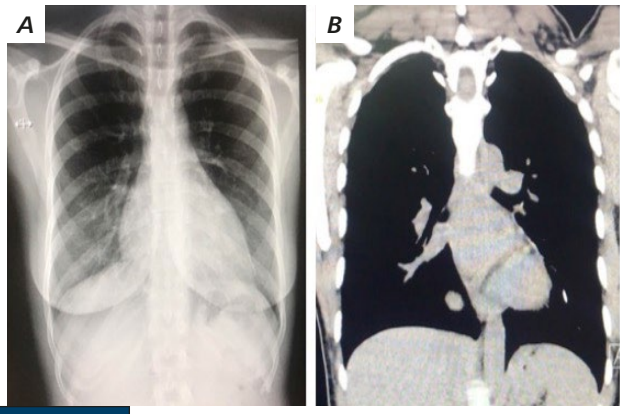

Figure 1 *(A) - Chest X-Ray: radiopaque structure on the left hemithorax. (B) - Chest computed-tomography: radiopaque structure in a segmental branch of the left pulmonar artery.*

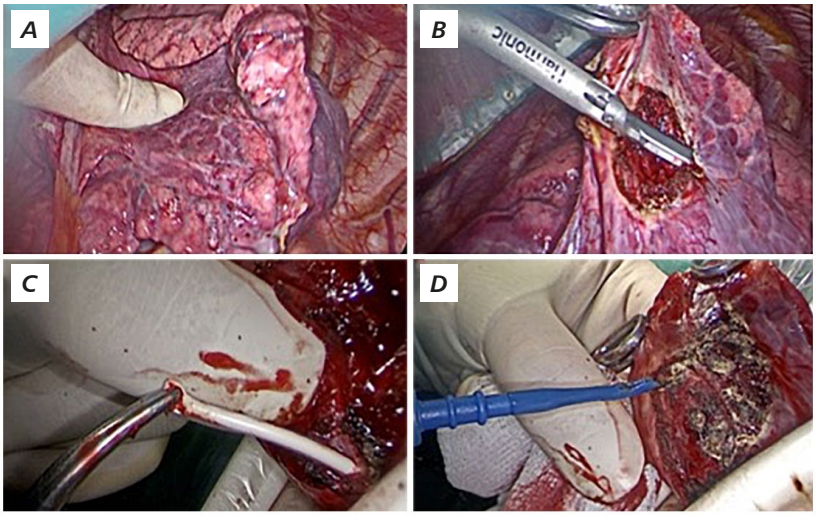

Figure 2 *Video assisted thoracic surgery by 2-port technique.* ***(A)*** *Identification of the device.* ***(B,C)*** *Dissection of lung parenchyma through the implant and removal of the device.* ***(D)*** *- Lung parenchyma being sealed with energy device.*

DISCUSSION

Implanon NXT® is a subdermal device inserted in the inner side of the non-dominant upper arm. Besides regular metrorrhagia, migration has also been reported.[2-5] Embolization of the implant to the pulmonary vasculature is a rare entity, usually asymptomatic, but dyspnea and chest pain have been reported.[2] To our knowledge, there are approximately 20 reported cases on literature of migration to pulmonary vasculature.[6] Those cases were managed conservatively, endovascularly or by surgery.[1,2,5,6] When surgery was performed there are reports of sublobar resections by VATS and thoracotomy.[1,2,5] Thomas *et al.* also described a thoracoscopic retrieval by arteriotomy.[4] Besides the published cases, Kang *et al.* outlined 9 cases of migration to the pulmonary artery submitted to the FDA Adverse Event Reporting System (FAERS) database.[3]

Migration of subdermal contraceptives should be checked up regularly with close supervision of first-time medical caretakers.[2,3] Once it becomes a non-palpable device, a diagnostic work-up should take place either by X-Ray, ultrasound or CT scan, to confirm location.[1-3,7] A non-palpable implant can be due to deep implantation, migration or embolism, which are uncommon events cause by wrong implantation technique (insertion into the biceps muscle), substantial weight loss or strenuous activity.[1-4] Embolization can also happen because of an inadvertent implantation or erosion into the basilic vein (with all the intravascular journey to the pulmonary artery).[2-4,7] In the presented case there were no reported complications regarding the insertion of the device.

The majority of intravascular foreign bodies does not produce symptoms immediately. There are no management guidelines, and long term consequences of leaving a contraceptive device in the pulmonary vasculature are unknown. Surgical retrieval should be considered given the known risk of infection, thromboembolism, retrograde migration or undesirable infertility.[1,4]

CONCLUSION

Removing a device from a segmental branch of the pulmonary artery is challenging and potentially risky. On the few reported cases treated surgically, lung resection wasconsistently performed, except for one single case.[1,2,5,7] This case shows that it is possible, in selected cases, to perform the retrieval of hormonal devices from pulmonary vasculature by minimally invasive surgery without lung resection.

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GIANT PLEURAL TUMOR AND SEVERE HYPOGLYCEMIA: DOEGE-POTTER SYNDROME IN A PREVIOUSLY HEALTHY FEMALE

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Abstract

Introduction: *Doege–Potter's syndrome is a rare paraneoplastic syndrome, consisting in hypoglycemia and solitary fibrous tumor of the pleura. These tumors represent <5% of all pleural tumours and can only be cured by surgery. In this article, we report a case of a patient presenting with severe hypoglycemia, as the only symptom, and a mass occupying the entire left hemithorax.*

Case presentation: *A54 year old female with severe hypoglycemia, a chest radiography with almost total opacification of the left hemithorax and a computed tomography scan with a mass in the left hemithorax. Surgery was performed and a mass with 30cm × 18cm × 11cm weighing 3195g was resected. The postoperative course was uneventful with immediate resolution of the hypoglycemia. The immunohistochemistry diagnosis was solitary fibrous tumor of the pleura.*

Conclusions: *Solitary fibrous tumor of the pleura are very rare. Less than 5% are associated with hypoglycemia, taking the form of Doege-Potter Syndrome. Radiation therapy and chemotherapy have shown low response rate and complete surgical resection is the only procedure that offers cure.*

This case reports describes a rare giant solitary fibrous tumor of the pleura with severe hypoglycemia, successfully treated by surgery. Long-term follow-up of the patient after the surgery is necessary for detection of any possible recurrence.

INTRODUCTION

Doege–Potter's syndrome is a rare paraneoplastic syndrome that consists of the association of symptomatic hypoglycemia, as the result of excessive production of insulin growth factor (IGF) by the tumor cells, with a solitary fibrous tumor of the pleura (SFTP).[1]

SFTP are rare mesenchymal tumors representing <5% of all pleural tumours. These lesions occur predominantly in middle-aged adults with equal gender distribution.[2] Generally, there is no genetic predisposition or relationship to the exposure to asbestos, tobacco or any other environmental agents.[3]

SFTP can usually be distinguished from malignant mesothelioma by their radiographic features, gross appearance often pedunculated, immunohistochemistry characteristics and ultrastructural characteristics.[4]

Most tumors present as well-defined, slow-growing masses, which can only be cured by surgery.[5] Several case series have demonstrated complete resection to be associated with low rates of local recurrence and progression to metastatic disease.[6]

In this article, we report a case of a patient presenting with severe hypoglycemia and a SFTP occupying the entire left hemithorax.

CASE REPORT

We report the case of 54-year-old female patient that presented to the Hospital for persistent dizziness. Routine blood tests revealed glucose levels of 32 mg/dL, with no other abnormalities on the remaining parameters. Chest radiograph showed total opacification of the left hemithorax (Fig. 1a).

The patient underwent a thoracic and abdomen computed tomography (CT) scan that revealed a 28×10cm non-calcified mass in the left hemithorax, in contact with the lateral thoracic wall, well defined against the lung parenchyma, which it almost totally compressed and with

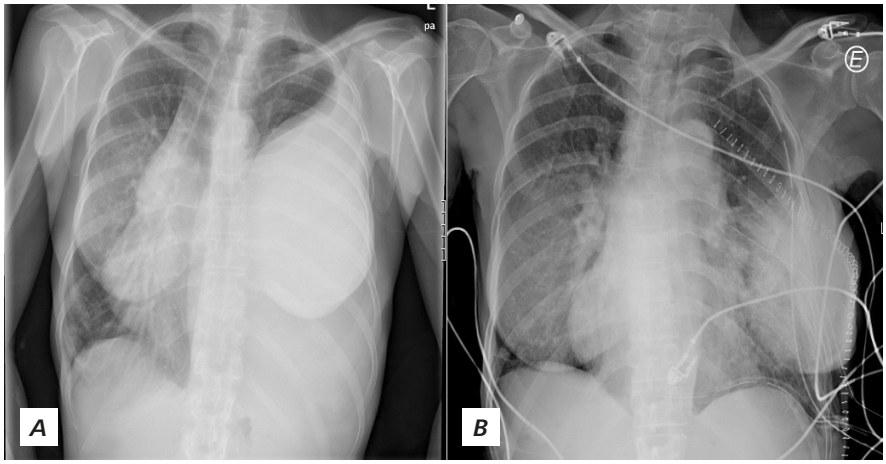

Figure 1 *(A) - Chest radiograph showed an opacification of the left hemithorax. (B) – Chest radiograph in the pos-operative, with total expansion of the left lung.*

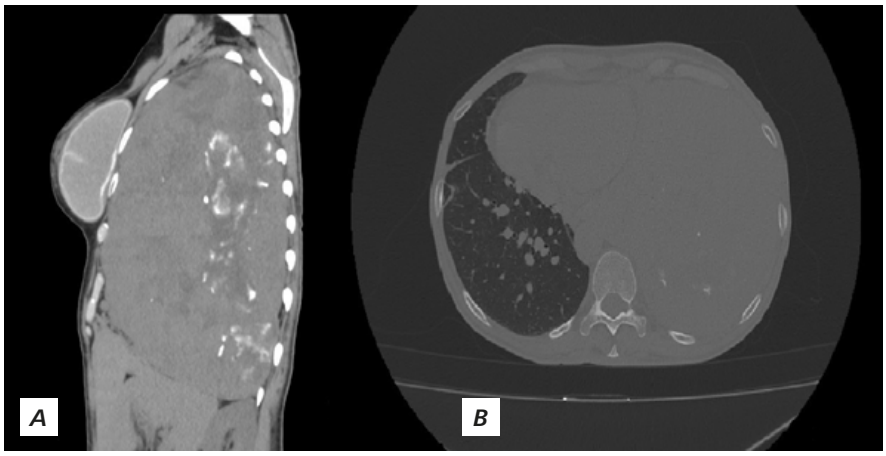

Figure 2 *Thoracic computed tomography before surgery. (A) - Mass occupying almost all the left hemithorax (sagittal view). (B) – Mass with contralateral displacement of the mediastinal structure (axial view).*

contralateral displacement of the mediastinal structures but without evidence of mediastinal or hilar lymphadenopathy (Fig. 2).

Surgery was performed under balanced anesthesia with the use of a double lumen endotracheal tube and one-lung ventilation. An antero-lateral thoracotomy through the sixth left intercostal space was performed. Resection of 2 ribs was required due to the size of the tumor (Fig. 3). Upon entering the pleura, we visualized a large encapsulated mass (Fig. 4). The tumor was attached to the superior lobe of the left lung and a wedge resection of this lobe was necessary. The main vascular pedicle of the tumor with origin in the mediastinal vessels was ligated with non-absorbable suture (Fig. 5).

The well-circumscribed, encapsulated resected mass was measured to be 30cm × 18cm × 11cm and weighed 3195 g in the fresh state (Fig. 6).

The operation took 117 min and blood loss was 250 ml. The patient remained hemodynamically stable throughout the procedure. After resection of the mass, the lung was recruited with positive pressure ventilation, achieving a good expansion of the remaining lung and no significant air leak. A thoracic epidural catheter was sited at the end of surgery and was used for post-operative analgesia. The postoperative course was uneventful, with total expansion of the lung (fig. 1b) and no respiratory complications were noted. Immediate resolution of the hypoglycemia was observed. The patient was discharged on the 6th postoperative day.

According to the morphology and cellular immunophenotype the diagnosis of malign giant pleural SFT was signed out.

The patient was observed 5 weeks after surgical resection. Follow-up chest radiography showed complete expansion of the left lung and routine blood tests were normal, with euglycemia.

DISCUSSION AND CONCLUSION

SFTP is a rare tumor with less than 800 cases reported in the literature. They can be benign (about 80%) or malign, unique or appear in multiple localizations.[7] These tumors can present with various clinical signs and symptoms, such as dyspnea, chest pain or hemoptysis.

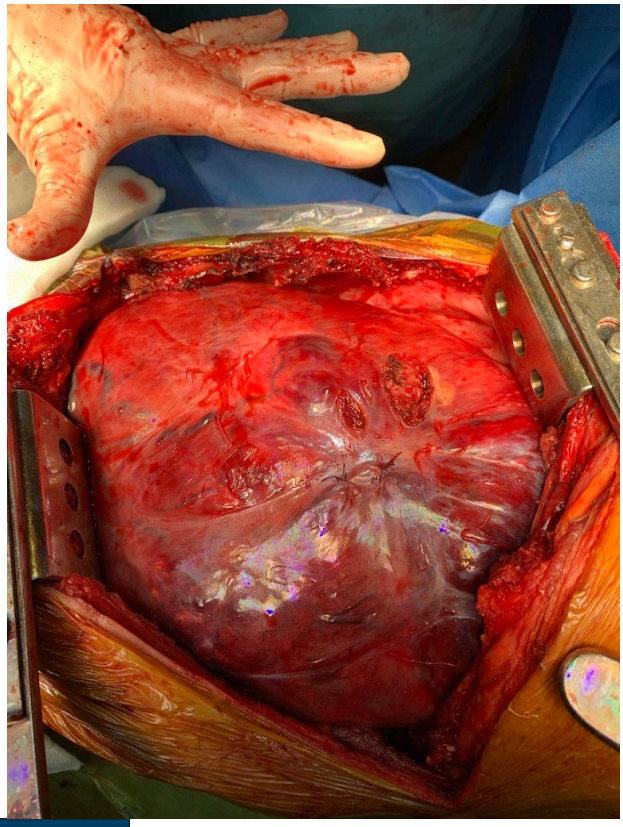

Figure 3 *Surgical approach for mass resection.*

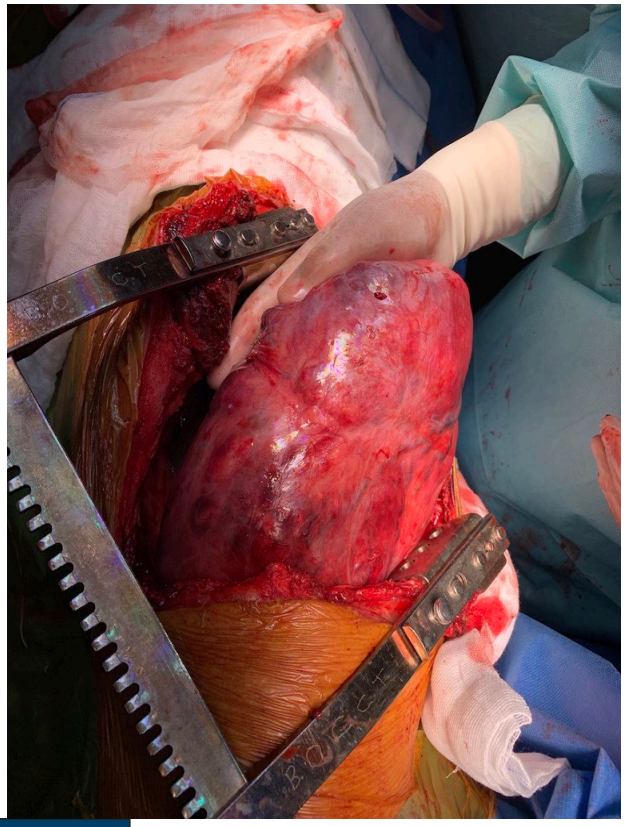

Figure 4 *SMass totally encapsulated.*

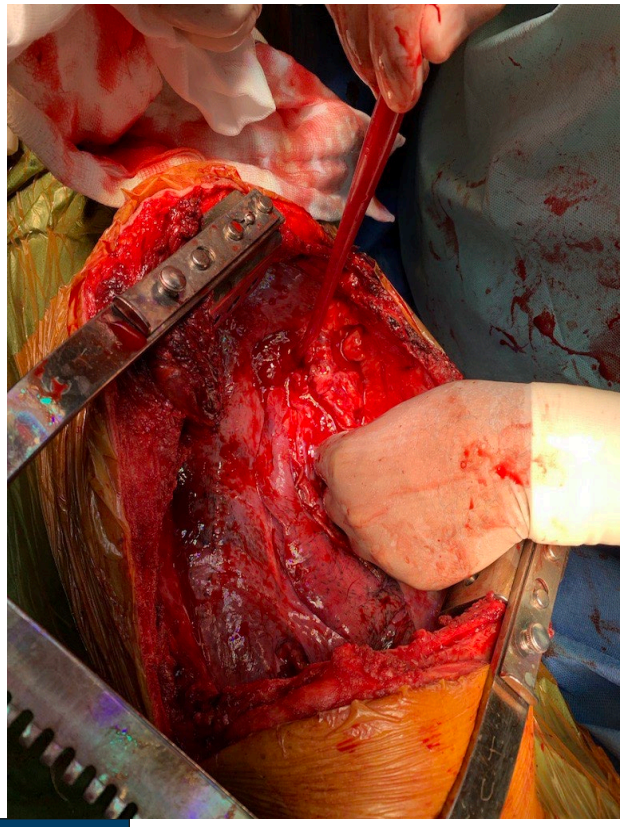

Figure 5 *Left hemithorax after mass resection.*

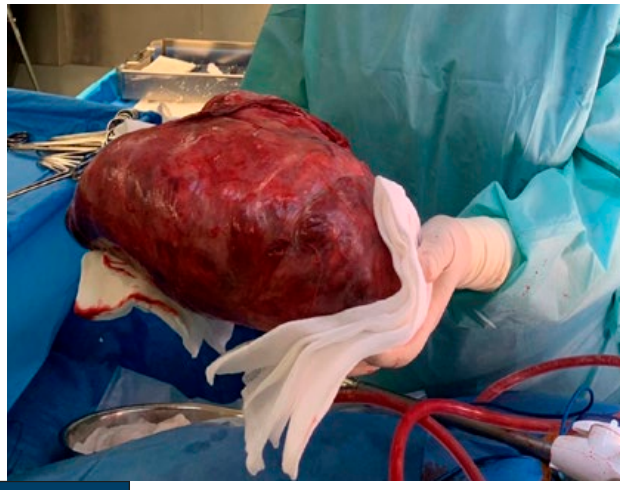

Figure 6 *A macroscopic image of the resected tumor, which weighed 3.195g.*

Less than 5% are associated with hypoglycemia, taking the form of Doege-Potter's Syndrome, a very rare entity.[8] This happens due to the ectopic secretion of IGF by the tumourcells and always resolve following resection of the tumor.[1]

A CT scan is a useful diagnostic method that can identify the localization and size of the lesion and helps to plan the surgery.

Usually SFTP are a firm and well-circumscribed mass attached by a pedicle, as in the current case.

Complete surgical resection is the procedure of choice for all the SFTP and the only procedure that offers the cure. Given the relatively indolent nature of the tumor, radiation therapy is not currently recommended after resection and chemotherapy have shown low or questionable response rate.[9] Long-term *follow-up* is necessary, even for localized benign SFTP, because of the possibility of recurrence.

In conclusion, this case describes a rare giant SFTP, detected in the context of persistent hypoglycemia that was successfully treated by surgical resection. As expected, an immediate resolution of the hypoglycemia occurred. Given the nature of the tumor a long-term *follow-up* of the patient is necessary for detection of any possible recurrence, though the post-operative period was uneventful and at 1-month follow-up the patient was clinically recovered.

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ENDOVASCULAR TREATMENT OF A SYMPTOMATIC THORACIC AORTA THROMBI

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Abstract

Aortic mural thrombus is a rare condition with 0.45% incidence in the general population, being the thoracic aorta the most affected portion. In the absence of an atherosclerotic wall lesion, other specific conditions should be studied and excluded.

The authors describe two clinical cases of a 64 years old male and a 48 years old female that despite a non-atherosclerotic diseased aorta, had a thoracic mural thrombus which presented clinically with mesenteric and lower limb microembolization, respectively.

Once presented with peripheral embolization, the aim should be to exclude the embolic source and prevent end organ malfunction. TEVAR has been developed as a therapeutic solution to exclude the embolic source, with a high rate of technical success and few comorbidities associated. Long term anti-coagulation is debatable but may prevent further embolization events.

INTRODUCTION

Thoracic aortic mural thrombus developing, in the absence of a pre-existing aortic disorder, is an uncommon pathologic process with potential devastating outcomes, once it may complicate with multi-level embolization. Literature describes a 0.45% incidence in the general population, according to autopsy reports, with 17% of them showing evidence of distal embolization and in 6% even being considered the cause of death.[1]

CASE REPORTS

Clinical Case I

A 64 years old male was admitted in the emergency department with abdominal discomfort of approximately three days of evolution. The patient had no previous findings of atherosclerotic disease with only one cardiovascular risk factor, hypertension. On clinical evaluation, he was hemodynamically stable but revealed a mildly tender abdomen without peritoneal signs, and palpable pedal pulses.

The thoraco-abdominal computed tomography demonstrated a large sessile thrombus on the descending thoracic with significant lumen narrowing, no atherosclerotic plaques and signs of embolization to the superior mesenteric artery (SMA). An electrocardiogram-Holter monitoring showed sinus rhythm, absence of arrhythmic episodes or atrial fibrillation. Transthoracic echocardiogram showed normal cardiac chambers dimensions, normal wall thicknesses, and regional contractility, with a 58% ejection fraction, and normal aortic, mitral, and tricuspid valves structure.

Under intravenous unfractionated heparin, we excluded the thoracic aortic lesion with a Valiant Thoracic Stent Graft with Captivia Delivery System™ MedtronicÒ (TEVAR). Final angiogram showed excellent positioning of the stent-graft distal to the origin of the left subclavian artery without luminal defects. The luminal thrombus could not be visualized. Additionally, the SMA was cannulated and mechanical thrombectomy was performed with a catheter-directed rhyolitic/thrombolytic system (AngioJet™ Peripheral Thrombectomy System, Boston). Final angiogram demonstrated resolution of the SMA embolic lesions and flow to all major branches. Systemic heparin anticoagulation was converted to warfarin with a target international normalized ratio (INR) of 2.0-3.0 and the patient discharged five days after the last procedure.

Follow up study was negative for thrombophilia and autoimmunity diseases but revealed deviations on hemogram that led to subsequent study and diagnosis of chronic myelocytic leukemia, so we decided to keep the patient on long-term anticoagulation.

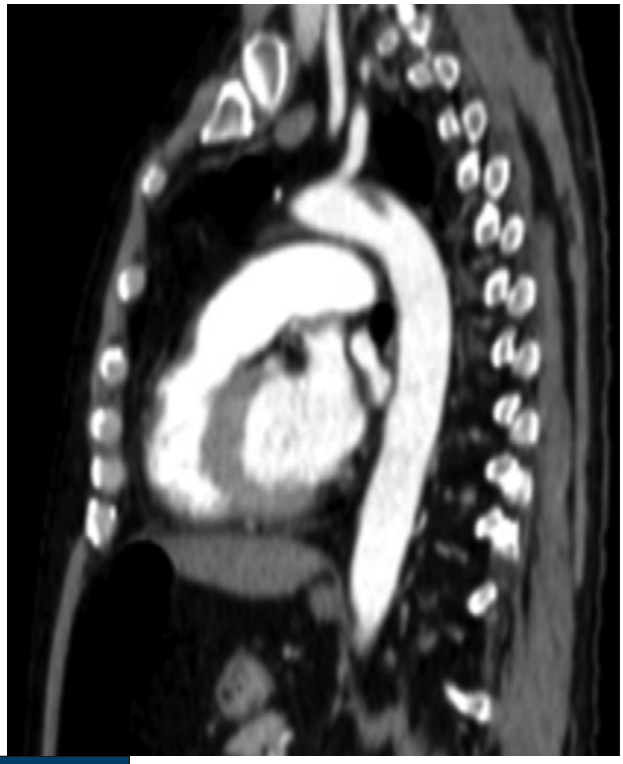

Figure 1 *Thoraco-abdominal computed tomography demonstrated a large sessile thrombus on the descending thoracic.*

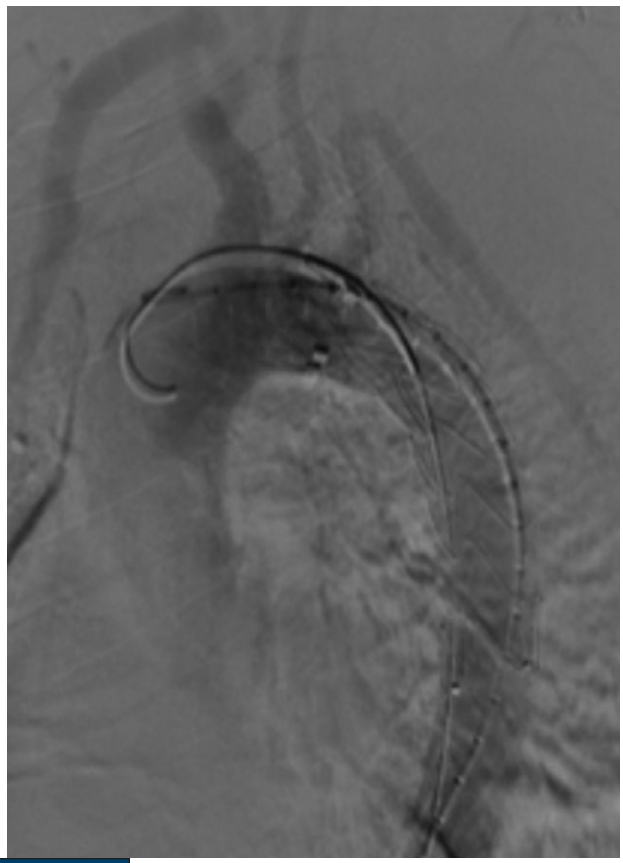

Figure 2 *Thoracic aortic lesion exclusion with a Valiant Thoracic Stent Graft with Captivia Delivery System™ Medtronic (TEVAR).*

Clinical Case II

A 48 years old female with a personal history of thyroid papillary carcinoma was admitted in the medical department with clinical signs of bilateral, acute (<24h), blue toe syndrome. The patient had no previous finding of atherosclerotic disease or cardiovascular risk factors. On presentation, she was hemodynamically stable, with bilateral, palpable distal pulses. Physical inspection also revealed a cyanotic discoloration prominently noted on right dorsum of the foot and distally on the second and third digits so as on the first and second digits of the left foot with toes being cold and painful.

Additional thoraco-abdominal computed tomography revealed a large pedicled thrombi in the descending thoracic aorta. Electrocardiogram-Holter monitoring showed sinus rhythm, absence of arrhythmic episodes or atrial fibrillation. Transthoracic echocardiogram showed normal cardiac chambers dimensions, normal wall thicknesses, and regional contractility, with a 64% ejection fraction, and normal aortic, mitral, and tricuspid valves structure.

Under intravenous unfractionated heparin, we excluded the thoracic aortic lesion with a Valiant Thoracic Stent Graft with Captivia Delivery System™ Medtronic (TEVAR). Final angiogram showed excellent positioning of the stent-graft distal to the origin of the left subclavian artery without luminal defects. The luminal thrombus could not be visualized. Completion angiogram to the lower limbs revealed peripheral micro-emboli causing, predominantly, luminal defects on the right anterior tibial artery and left posterior tibial artery. After thoracic aorta stent graft deployment, the peripheral emboli were treated with catheter-directed thrombolysis for 24 hours. Interval angiography demonstrated resolution of her embolic lesions with good runoff bilaterally and recover of bilateral pedal pulses. Systemic anticoagulation with heparin was converted to warfarin with a target INR of 2.0-3.0 and the patient discharged three days after the procedure.

Follow up study was negative for thrombophilia and autoimmunity diseases so as for malignancy recurrence. Despite these findings, attending her personal history, we decided for long-term anticoagulation.

Follow up

Patients have now 26 and 34 months after the initial event. The postoperative course of both patients was uneventful and no adverse event or thrombus recurrence was diagnosed during follow-up.

TEVAR follow up was orientated following the same guidelines from the European Society of Vascular Surgery for the intramural hematoma and penetrating aortic ulcer. They repeated thoraco-abdominal computed tomography at three and six months and then yearly. Future orientation is, once stable condition persists at three years, to extend the interval to three years.

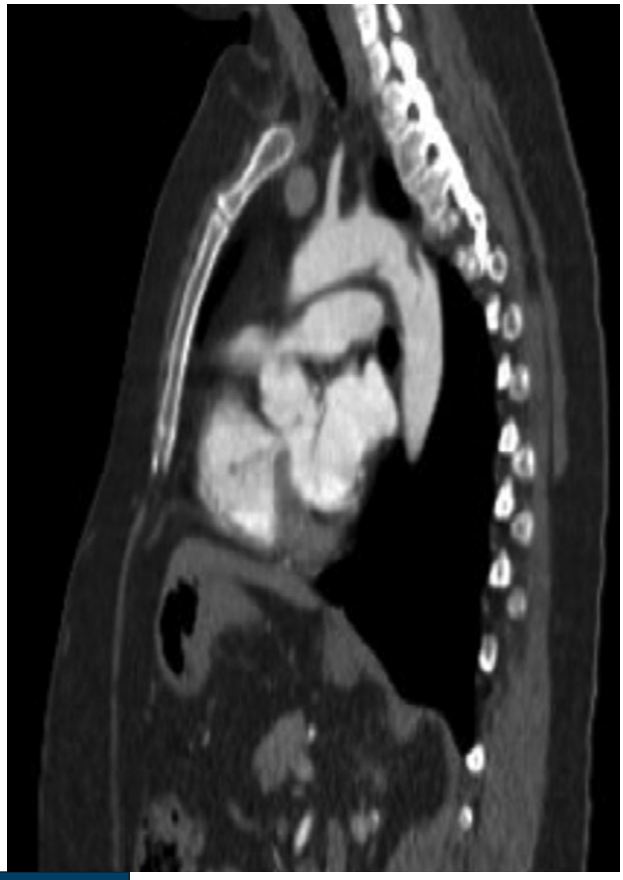

Figure 3 *Thoraco-abdominal computed tomography revealed a large pedicled thrombi in the descending thoracic aorta.*

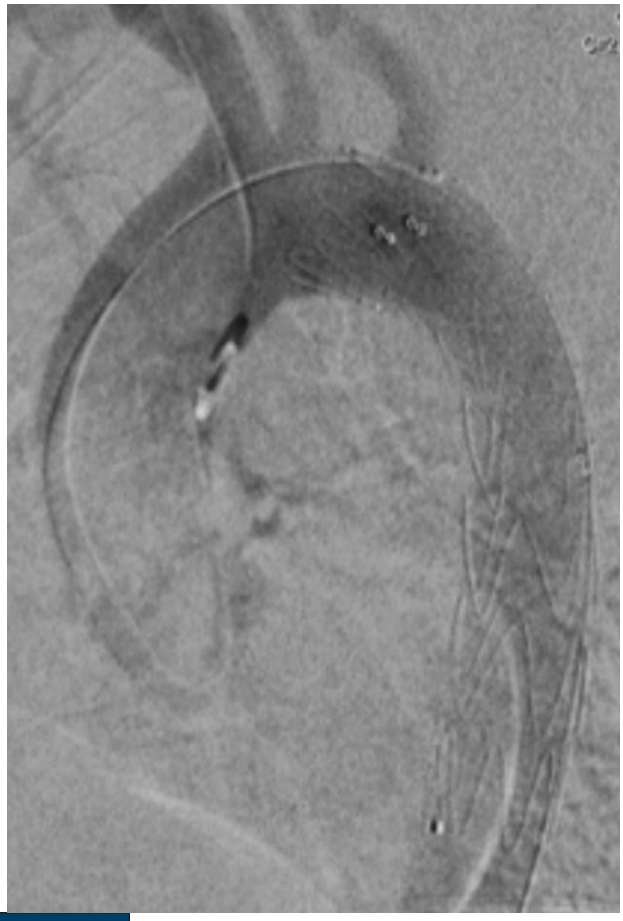

Figure 4 *Thoracic aortic lesion exclusion with a Valiant Thoracic Stent Graft with Captivia Delivery System™ MedtronicÒ (TEVAR).*

DISCUSSION

Aortic thrombus develops, mainly, from an atherosclerotic wall lesion or a hypercoagulable condition. Other, less frequent but still described causes, include smoking, steroid use, trauma, drug abuse, heparin-induced thrombotic thrombocytopenia, rheumatism, primary endothelial disorders, iatrogenic causes and history of vasculitis. Morphologically they normally present as sessile or pedunculated aortic thrombi, especially when symptomatic.

The thoracic descending aorta is the most common location, accounting for 37.5%.[2] This pathology may present asymptomatically being incidentally found, however, frequently, presents with multiple level embolism that leads to innumerous impediments including end-organ damage, acute limb ischemia and a high mortality associated. In case of embolization, there is a high risk of recurrence with potential dire consequences.[3-5]

Therapeutic options include anticoagulation alone,[6] thrombolysis, thromboaspiration, open thromboendarterectomy and exclusion using endoluminal stent grafts, nevertheless the best approach is still debatable.[7] Failure of each of the above-mentioned approaches is frequently defined by persistent thrombus, thrombus enlargement or recurrent embolization.

One of the most extensive and recent literature reviews were published by Karol Meyermann *et al*[8], with 74 patients, 43 (58%) females with a median age of 54.3 years described. In 56.8% the first presentation was lower extremity embolization. Medical therapy was found to be more likely associated with persistent thrombus compared with open thrombectomy or thoracic endovascular aortic repair (TEVAR; $P < .05$). In the open repair group which included 19 patients, 6 (31.6%) had persistent thrombus while in the endovascular group, which included 29 patients, only 3 (10%) had recurrent thrombi with recurrent emboli.

In another study by Patra *et al* recurrence was observed in 27% patients treated medically[9], and that is why we do not consider it as a good definite solution. The authors consider that anticoagulation should be started immediately once an embolization event occurred and then the embolic source excluded.

Considering these last subject, open aortic surgery has the advantage of histological examination, including immunohistochemical analysis, but comprises a recurrence rate up to 10-20% and a high morbidity and mortality up to 30%.[10]

Regarding an endovascular approach, although, experiences are still currently limited to few cases reported

in the literature, early results present a high technical success rate, approaching 100%. When bearing in mind the histological examination, intra-arterial biopsy has already been described in the interventional radiology literature[11] and may be a solution.

Reflecting about the embolization rate, the reported rate is considerably low and there are some technical aspects, that the authors believe should be taken into consideration: use a subclavian approach for the diagnostic aortography, use intravascular ultrasound for precisely identify the affected segment of the aorta, temporary balloon occlusion of selected visceral vessels to prevent embolization and a seal zone at least 2 cm proximal and distal to the thrombus.

The role of medical therapy as an adjuvant to surgical or endovascular intervention has traditionally been determined on an individualized basis. A number of reports endorse the use of continued, long-term, anticoagulation after either open surgical repair or TEVAR[12-14], which the authors believe is the best conduct.

In conclusion, when presented with a thoracic aorta thrombus complicated with distal embolization, the authors consider that anticoagulation complemented with embolic source exclusion with TEVAR should be the initial treatment strategy, whenever feasible.

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CASOS CLÍNICOS CASE REPORTS

COMPLEX AORTOILIAC, PELVIC AND VISCERAL REVASCULARIZATION

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Abstract

Aortoiliac occlusive disease (AIOD) remains an area of debate concerning open and endovascular treatment options. A case of a 63-year old female is reported, with previous known vascular intermittent claudication, that presented in the emergency room with acute ischemia of the right lower limb with 24-hours of evolution. The computer tomographic angiography unveiled occlusion of the superior mesenteric artery, occlusion of left common iliac artery (CIA), subocclusive stenosis of right CIA, occlusion of distal runoffs vessels in the right lower limb and diffuse aorto-iliac disease. The first approach was to place the patient under catheter directed thrombolysis (48h) which led to right pedal pulse recovery but the occlusion of left CIA remained. The patient was then electively submitted to Covered Endovascular Repair of Aortic Bifurcation (CERAB) with chimney to inferior mesenteric artery and with an additional bailout left iliac sandwich due to dissection. Distal pulses are still present after 18 months of follow-up. Endovascular techniques provide a low morbimortality option with similar symptomatic improvement, challenging open surgery as the standard of care even in complex AIOD.

INTRODUCTION

Complex aortoiliac occlusive disease (AIOD) was, according to the Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II - 2007), best managed by an open surgical approach.[1] However, endovascular surgery has emerged as a minimally invasive alternative, challenging or even replacing open surgery as the standard of care.[2,3] The authors report a case of extensive AIOD, presenting as acute limb ischemia treated initially with catheter directed thrombolysis, followed by a complex covered endovascular reconstruction of the aortic bifurcation with a chimney to the inferior mesenteric artery (IMA) and a left iliac sandwich (ChCERAB).

CASE REPORT

A 63-years-old female patient was admitted to the emergency department with right foot pain and cyanosis with 24-hours of duration. The patient had history of peripheral arterial disease with intermittent claudication and was an active smoker. Additional comorbidities included chronic obstructive pulmonary disease, obstructive sleep apnea syndrome, hypertension and dyslipidaemia. At clinical examination no femoral, popliteal or distal palpable pulses were detectable bilaterally. Additionally, there was no motor deficit or sensory loss. Duplex ultrasound examination detected atherosclerotic femoro-popliteal disease and popliteal monophasic flow sign while distal flow signs were inaudible. The diagnosis of acute limb ischemia grade I was established. Due to the apparent complex peripheral disease pattern, a computed tomography angiography (CTA) was performed, unveiling occlusion of the superior mesenteric artery, occlusion of the left common iliac artery (CIA), subocclusive stenosis of the right CIA, occlusion of the distal runoff vessels in the right lower limb and diffuse aortoiliac disease.

Catheter-directed thrombolysis in the infra-renal aorta was initiated through percutaneous left brachial access. It lasted for 48-hours with right pedal pulse recovery while the left CIA occlusion remained (Figure 1). Due to the limited respiratory function of the patient, an endovascular approach was planned to resolve the issue of the left CIA occlusion as well as to treat the remaining obstructive right-side disease and exclude the remaining thrombus avoiding further distal embolization.

Under general anaesthesia, bilateral retrograde 8Fr femoral accesses and a left brachial artery 7Fr access were obtained. Subtraction angiography through the brachial access was performed and followed by selective catheterization of the IMA. Via femoral access, CIA lesions were

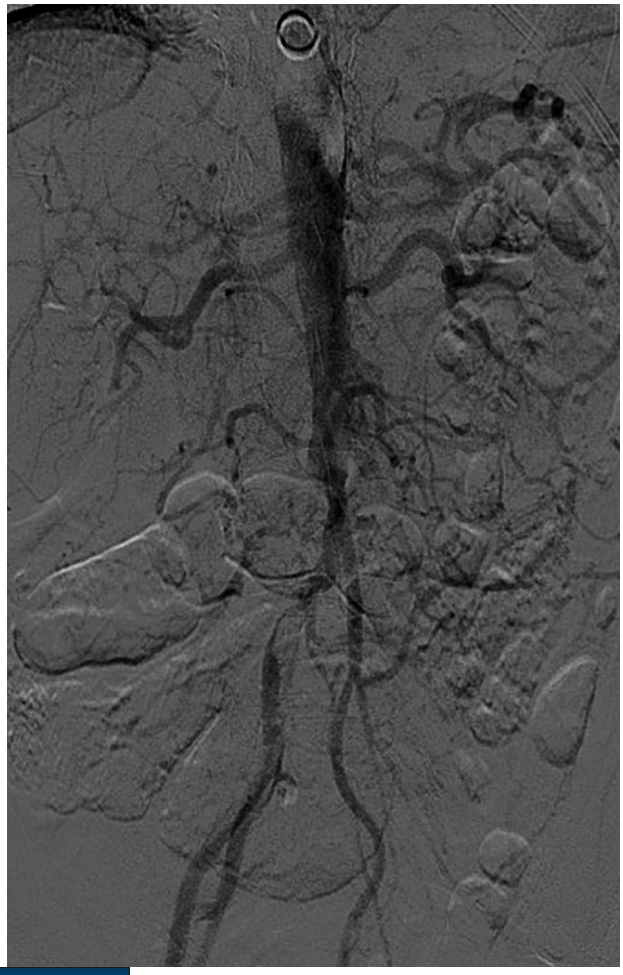

Figure 1 – *Pre-operative angiography (post-catheter direct thrombolysis)..*

crossed and a covered balloon expandable kissing stent (CBES) (Gore® Viabahn® VBX, 9x79 mm) was deployed at infra-renal aorta while actively ballooning the IMA. Both iliac pathways were stented followed by stenting of the IMA, all with CBES. Angiography confirmed patency of the stented segments however unveiled a left CIA non-occlusive thrombus and associated distal dissection. Catheterization of the left internal iliac artery was achieved via brachial access followed by an iliac sandwich-technique with two 6x39 mm CBES. Lastly, a subtraction image remained in the left external iliac artery which led to distal extension with a 6x60 mm self-expanding stent (S.M.A.R.T.® Flex Cordis) which provided a final subtraction angiogram with a good result (patency of all 8 stents and no luminal subtraction images). Distal pulses were palpable bilaterally at the end of the procedure. Postoperative complications included a brachial access site hematoma, a hospital acquired pneumonia and an inaugural diabetes. The patient was discharged home at the 32nd postoperative day. After 18 months of follow-up, distal pulses remain palpable and CTA confirmed stents patency (Figure 2).

DISCUSSION

Open surgery, namely aortobifemoral bypass (ABF), represents in many centres the gold standard for complex AIOD. It represents a durable treatment modality with high long-term patency rates although still associated with significant perioperative morbi-mortality.[4] Given this, endovascular techniques have been evolving and technical success has improved over the past years which made it as an adequate alternative to ABF even in complex (TASC

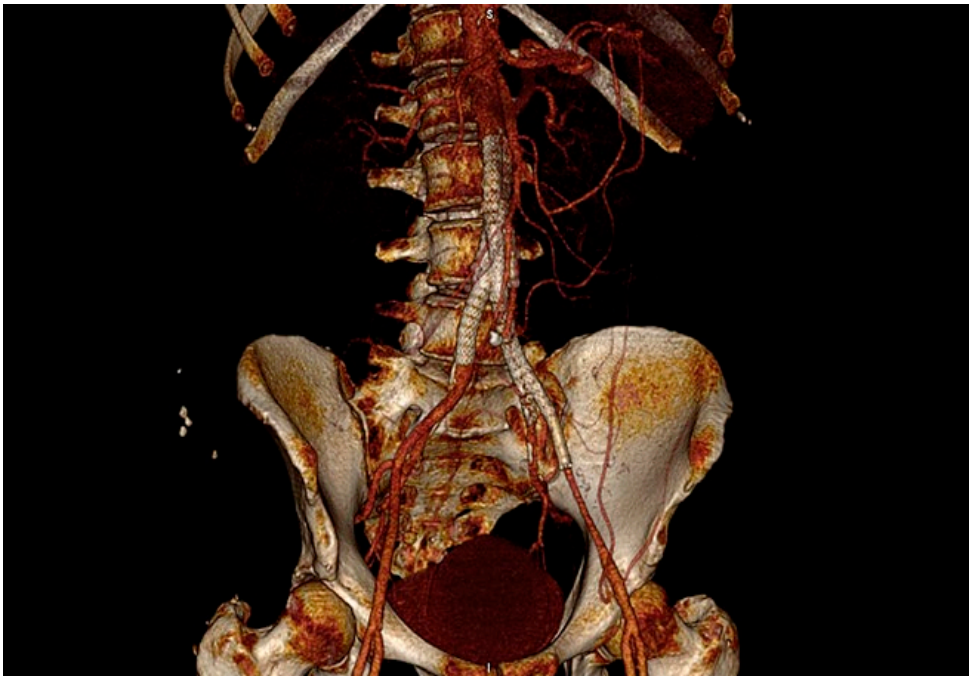

Figure 2 *Post-operative computed tomography angiography 3D reconstruction.*

II D) AIOD.[5] Many comparative studies between open and endovascular approach in AIOD have been published concerning this debate. In a cohort of patients presenting with TASC II D AIOD, endovascular surgery presented a more cost-effective therapy, without differences in postsurgical quality of life and been, at least clinically, equivalent.[6] In another cohort, with the same pattern of AOID, endovascular therapy presented high initial technical success with fewer in-hospital complications but also slightly higher re-intervention rates due to lower primary patency.[3] A systematic review and meta-analysis from 2013 that included 5358 patients (3733 and 1625 submitted to open bypass and endovascular treatments, respectively) corroborated the majority of previous finds, as open surgery demonstrated higher primary and secondary patency rates, however it was associated with longer length of hospital stay and higher complications and mortality rates at 30 days.[7]

A common argument in favour of endovascular therapy in complex aortoiliac disease was that a previous endovascular procedure would not affect negatively a future open approach. However, recently DeCarlo *et al.* retrospectively analysed 256 patients who underwent primary ABF, of which ≈ 25% had prior endovascular intervention, which revealed to be a predictor of major complications (odds ratio [OR], 2.2; 95% confidence interval [CI]: 1.2-4.1; P=0.01).[8] Although there is limited knowledge relative to the pathophysiology behind this finding, this fact needs further enlightenment and further studies are warranted.

In line with the recent literature, supported mainly by the first multicentric trial to investigate the patency of CBES and bare metal stents (BMSs) in the treatment of aortoiliac disease (COBEST)[9], in which CBES showed a patency advantage both in the short (1y) and long term (3y), the authors opted in this case for the covered endovascular repair of aortic bifurcation (CERAB).[10] It was necessary to perform a chimney to the IMA to maintain its patency due to the CTA confirmed occlusion of SMA. The literature concerning IMA stenting is scarce, with small case series. A series of four cases reported 100% primary patency of IMA stenting in patients with chronic mesenteric ischemia.[11]

Although results are promising with endovascular techniques, even in complex AIOD as shown in this case, there is still a paucity of randomized control trials in this setting.

CONCLUSION

An endovascular approach in complex aortoiliac disease, besides providing at least similar clinical results to a surgical approach, provides less procedure-related morbi-mortality as demonstrated in this case report. With the advent and continuous improvement of endovascular techniques, the endovascular approach might become the state of art in aortoiliac disease independently of the complexity. Randomized clinical trials are necessary to further address this question.

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GANGLIONEUROMA OF THE RIGHT CERVICOTHORACIC TRANSITION

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A 26 year old male, submitted to resection of a ganglioneuroma of the right pulmonary apex through a right Grunenwald approach. The mass insinuated through the innominate vessels, extending posteriorly to the subclavian artery, which it encircled for over 180 degrees, and the right thyrocervical arterial trunk, which was ligated.

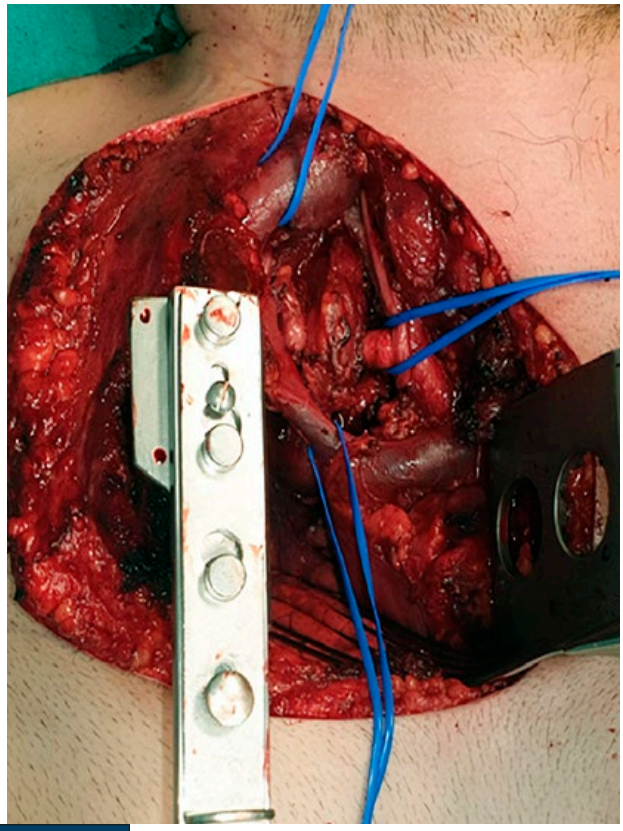

Figure 1 *After dissection of the right internal jugular vein, showing the mass encircling the right subclavian artery.*

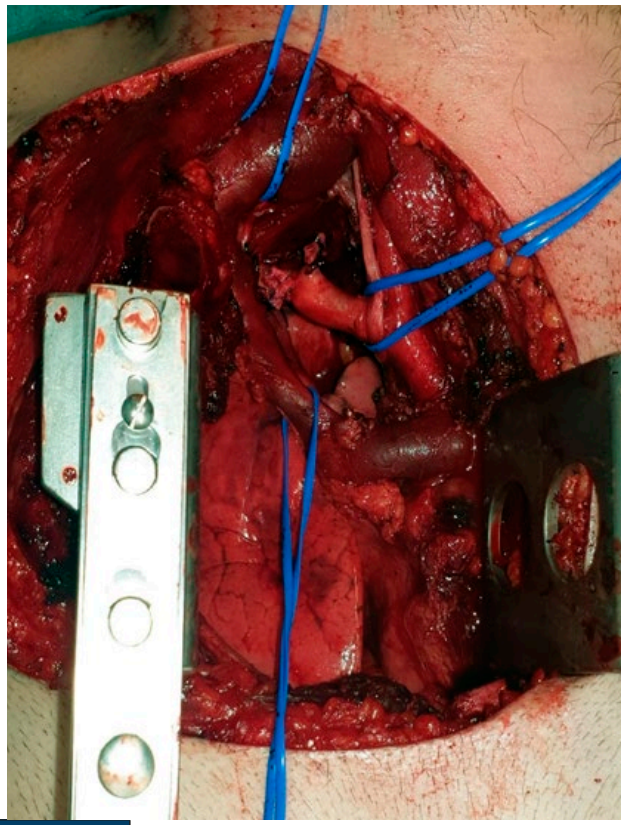

Figure 2 *After removal of the mass, the right upper lobe is visible as are the right internal jugular vein and the right subclavian artery fully dissected.*

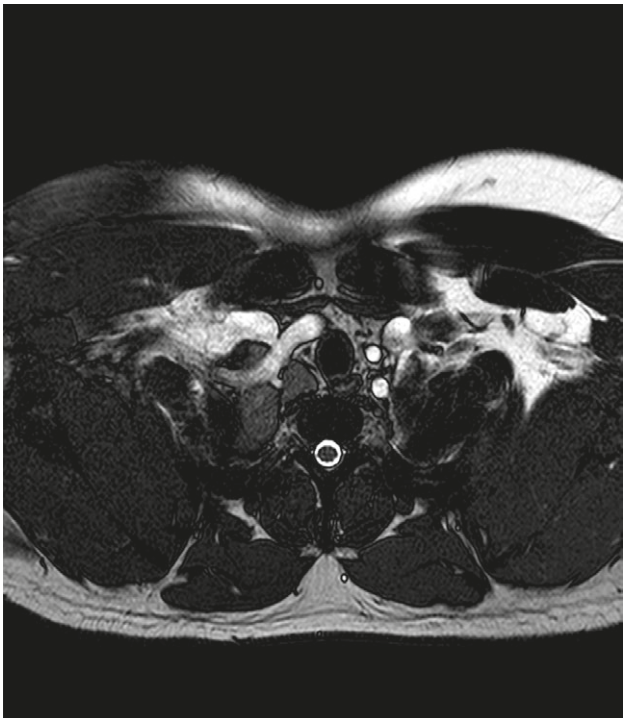

Figure 3 *Preoperative MRI scan showing the mass involving the right subclavian artery.*

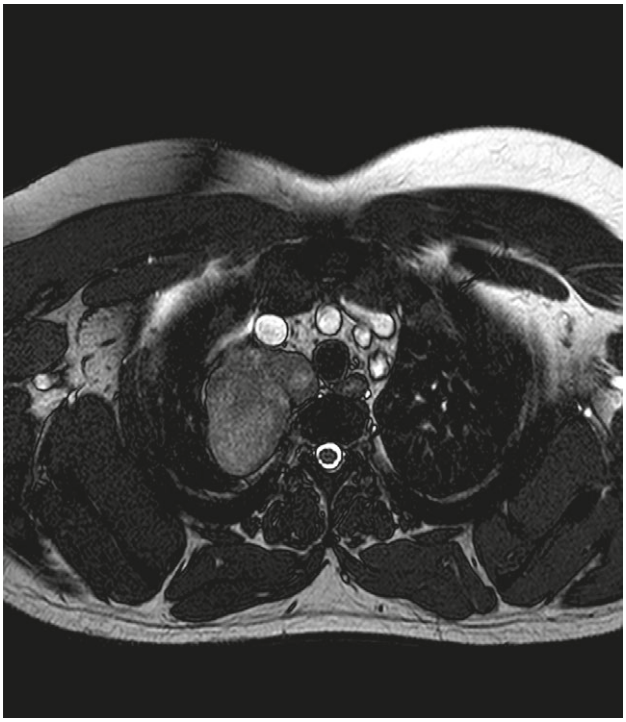

Figure 4 *Preoperatíve MRI scan showing the mass posterior to the right internal jugular vein, lateral to the trachea and compressing the right upper lobe.*

ENDOMETRIOSIS - UNUSUAL AETIOLOGY OF INGUINAL SWELLING

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A 42 years-old female presented with right inguinal swelling with one year of evolution. Magnetic resonance imaging was suggestive of inguinal endometriosis adherent to femoral vessels. Due to the rarity of this pathology (prevalence 0.3-0.6%), clinical suspicion is essential. Surgical excision is the treatment of choice.

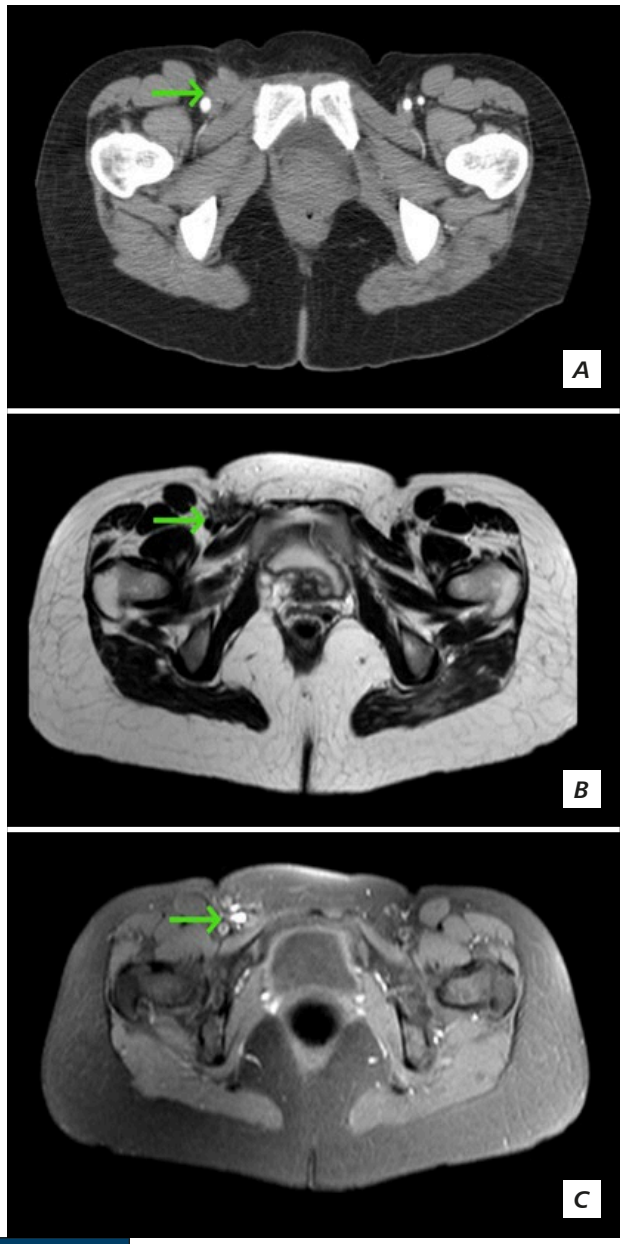

Figure 1 *(A) CT - Right inguinal lesion anterior to the femoral vessels, with infiltrative characteristics; (C) T2 MRI - Irregular lesion, heterogeneous sign, contacting the femoral vessels, with 33mm of greatest axis; (C) MRI T1 - Hypersignal millimeter focus, suggesting hemorrhagic content.*

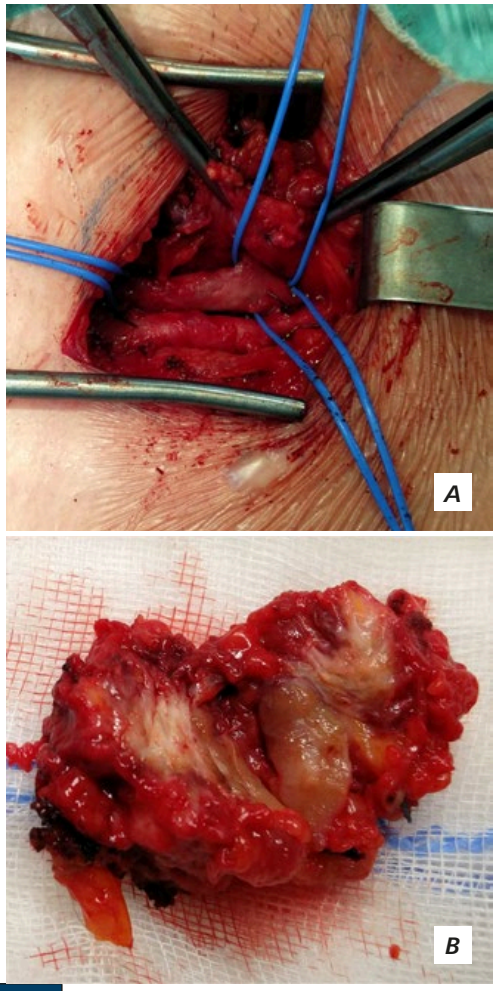

Figure 2 *(A) Lesion adherent to the femoral artery and vein and great saphenous vein, dissection of vascular structures and excision of the lesion; (B) Endometriosis focus with 3.7x3x2.5 cm.*

FIBROMUSCULAR DYSPLASIA OF THE RENAL ARTERIES

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A 48 year-old female patient presented with arterial hypertension. Computed tomography angiography revealed small stenoses alternating with areas of dilatation (due to small fusiform aneurysms) in the middle to distal portions of the main renal arteries, creating a "string of beads" appearance, findings in keeping with fibromuscular dysplasia.

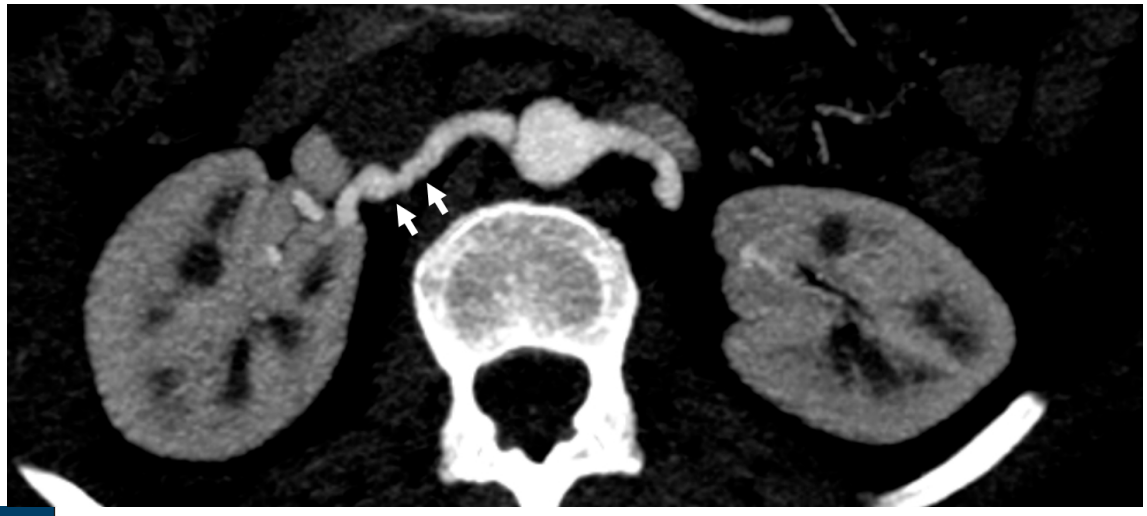

Figure 1 *Axial computed tomographic angiography image of the patient shows the "string-of-beads" appearance of the right main renal artery (arrows), which is typical of the medial fibromuscular dysplasia type.*

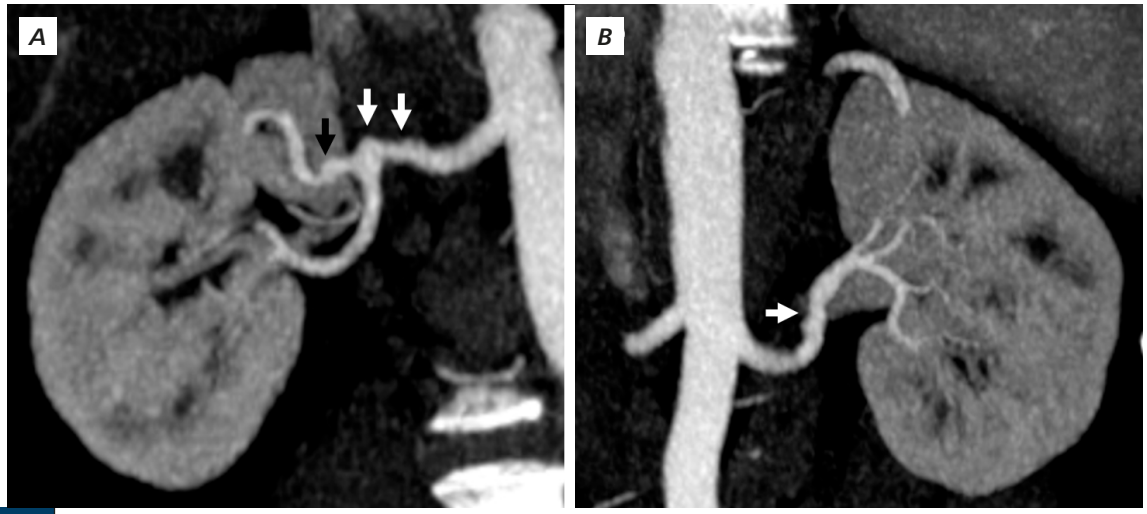

Figure 2 *Coronal **maximum intensity projection** computed tomography angiography images of the patient show the "string-of-beads" appearance of the right **(A)** and left **(B)** main renal arteries (white arrows). A small aneurysm can also be seen on a branch of the right main renal artery (black arrow).*


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