FACULDADE DE MEDICINA
UNIVERSIDADE DO PORTO

MESTRADO INTEGRADO EM MEDICINA

2012/2013

Ana Cristina Gonçalves Fragoeiro

Critical Ischemia in the Diabetic: Diagnosis and Treatment

março, 2013

FACULDADE DE MEDICINA
UNIVERSIDADE DO PORTO

Ana Cristina Gonçalves Fragoeiro

Critical Ischemia in the Diabetic: Diagnosis and Treatment

Mestrado Integrado em Medicina

Área: Angiologia e Cirurgia Vascular

Trabalho efetuado sob a Orientação de:
Doutor Roberto César Augusto Corrêa da Silva Roncon de Albuquerque

Trabalho organizado de acordo com as normas da revista:
Revista da Sociedade Portuguesa de Cirurgia Cardiotorácica e Vascular

março, 2013

U.PORTO
FMUP FACULDADE DE MEDICINA UNIVERSIDADE DO PORTO
UNIDADE CURRICULAR
PROJETO DE OPÇÃO
DISSERTAÇÃO / MONOGRAFIA

Projeto de Opção do 6º ano - DECLARAÇÃO DE INTEGRIDADE

Eu, Ana Cristina Gonçalves Fragoeiro, abaixo assinado, nº mecanográfico 200601877, estudante do 6º ano do Mestrado Integrado em Medicina, na Faculdade de Medicina da Universidade do Porto, declaro ter atuado com absoluta integridade na elaboração deste projeto de opção.

Neste sentido, confirmo que **NÃO** incorri em plágio (ato pelo qual um indivíduo, mesmo por omissão, assume a autoria de um determinado trabalho intelectual, ou partes dele). Mais declaro que todas as frases que retirei de trabalhos anteriores pertencentes a outros autores, foram referenciadas, ou redigidas com novas palavras, tendo colocado, neste caso, a citação da fonte bibliográfica.

Faculdade de Medicina da Universidade do Porto, 21/03/2013

Assinatura: Ana Cristina Gonçalves Fragoeiro

U.PORTO
FMUP FACULDADE DE MEDICINA UNIVERSIDADE DO PORTO
UNIDADE CURRICULAR PROJETO DE OPÇÃO DISSERTAÇÃO / MONOGRAFIA

Projeto de Opção do 6º ano – DECLARAÇÃO DE REPRODUÇÃO

Nome: Ana Cristina Gonçalves Fragoeiro

Email: med06238@med.up.pt

Título da Monografia:

Critical Ischemia in the Diabetic: Diagnosis and Treatment

Orientador:

Prof. Doutor Roberto César Augusto Corrêa da Silva Roncon de Albuquerque

Ano de conclusão: 2013

Designação da área do projeto: Angiologia e Cirurgia Vascular

É autorizada a reprodução integral desta Dissertação/Monografia (cortar o que não interessar) para efeitos de investigação e de divulgação pedagógica, em programas e projetos coordenados pela FMUP.

Faculdade de Medicina da Universidade do Porto, 21/03/2013

Assinatura: Ana Cristina Gonçalves Fragoeiro

Agradecimentos

Ao Prof. Doutor Roberto César Augusto Corrêa da Silva Roncon de Albuquerque, pelo tempo dedicado, disponibilidade e orientação meticulosa. A sua ajuda foi indispensável à realização desta monografia.

À minha família, pelo seu apoio incondicional ao longo de todo o curso.

Índice

CRITICAL ISCHEMIA IN THE DIABETIC: DIAGNOSIS AND TREATMENT

Roncon-Albuquerque, R.

Fragoeiro, A.

Departamento de Cirurgia

Faculdade de Medicina da Universidade do Porto

Alameda Professor Hernâni Monteiro, 4200 - 319 Porto

Nome: Ana Cristina Gonçalves Fragoeiro

Telefone: 966731838 / 919920348

Endereço de correio eletrónico: med06238@med.up.pt

Endereço Postal: Rua da Arroteia nº 463, 1º direito. 4465-027 São Mamede de Infesta. Porto.

Nº de palavras: 5009 palavras

Abstract

CRITICAL ISCHEMIA IN THE DIABETIC: DIAGNOSIS AND TREATMENT

Roncon-Albuquerque, R.; Fragoeiro, A.

Objectives: Critical ischemia plays a prominent role in the formation of diabetic foot ulcers. Despite its significance, diagnosis is difficult in diabetic patients, delaying treatment. The most feared consequence is amputation and many attempts have been made over the years to avoid this outcome. The aim of this review is to discuss the current methods of diagnosis and treatment of ischemic and neuroischemic diabetic foot ulcers.

Methods: A selective search on PubMed was conducted with the term "diabetic foot". Results were limited to publications within the last 10 years, in English or Portuguese, with available free full text and relative to humans. The search yielded 457 results and subsequent elimination was based on relevance of the information to this review.

Results: Although the prevalence of diabetes mellitus is increasing worldwide, improvement in diabetic foot ulcer outcomes has been made thanks to a protocol-driven multidisciplinary approach. A wide range of revascularization techniques are available and intensive research has been made to procure options for patients who are not candidates.

Conclusion: Treatment of diabetic foot ulcers should be multifactorial and the selection of therapy to improve perfusion should be based on the patient's general health condition, comorbidities, symptoms and clinical findings, arterial anatomy and conduit availability. Noninvasive treatment is a promising option for patients ineligible for

revascularization, but requires further trials to prove efficacy and guide potential integration in treatment.

Resumo

ISQUEMIA CRÍTICA NO DIABÉTICO: DIAGNÓSTICO E TRATAMENTO

Roncon-Albuquerque, R.; Fragoeiro, A.

Objetivos: A isquemia crítica tem um papel proeminente na formação de úlceras do pé diabético. Apesar da sua importância, o diagnóstico é difícil, atrasando o tratamento. A consequência mais temida é a amputação e várias tentativas têm sido feitas para evitar este desfecho. O objetivo desta revisão é discutir os atuais métodos de diagnóstico e tratamento de úlceras isquémicas e neuro-isquémicas no diabético.

Métodos: Uma pesquisa seletiva na PubMed foi realizada com o termo "pé diabético". Os resultados foram limitados a publicações nos últimos 10 anos, em inglês ou português, com texto integral disponível gratuitamente e relativo a humanos. Da pesquisa obtiveram-se 457 artigos e a subsequente eliminação teve base na relevância da informação para esta revisão.

Resultados: Apesar da prevalência da diabetes mellitus estar a aumentar mundialmente, uma melhoria no prognóstico tem sido obtida graças a uma abordagem multidisciplinar dirigida por protocolos. Uma grande variedade de técnicas de revascularização estão disponíveis e pesquisa intensiva tem sido feita para procurar opções para doentes que não sejam candidatos.

Conclusão: O tratamento de úlceras do pé diabético deve ser multifatorial e a escolha da terapêutica para melhorar a perfusão deve ser baseada no estado geral do doente, co-morbilidades, sintomas e achados clínicos, anatomia arterial e disponibilidade de conduto. Tratamento não invasivo é uma opção promissora para doentes inelegíveis para revascularização, mas requer mais estudos para comprovar a eficácia e guiar a potencial integração no tratamento.

List of acronyms and abbreviations

ABI – ankle-brachial index

BASIL – bypass versus angioplasty in severe ischaemia of the leg (trial)

CLI – critical limb ischemia

DFU – diabetic foot ulcer(s)

FGF – fibroblast growth factor

HbA1c – hemoglobin A1c

HGF – hepatocyte growth factor

NPWT – negative pressure wound therapy

PAD – peripheral arterial disease

PTA – percutaneous transluminal angioplasty

$TcPO_2$ – transcutaneous oxygen pressure

VEGF – vascular endothelial cell growth factor

Introduction

Peripheral arterial disease (PAD) is a manifestation of atherosclerosis that leads to arterial stenosis and occlusions in the major vessels supplying the lower limbs. The most common symptom of PAD is intermittent claudication, characterized by reproducible muscular leg pain on exercise that is relieved by short rest. In more severe cases there may be chronic ischemic rest pain, which usually indicates critical limb ischemia (CLI) [1]. PAD is 2-4 times more common in patients with diabetes than in those without [2] and in diabetic patients with foot ulcers the prevalence of PAD can reach up to 50% [3]. The most feared complication of PAD is amputation and diabetic foot complications remain the main cause of non-traumatic amputation in most western countries [4]. The diabetic foot is a challenging personal, medical, social and economic problem that is seen worldwide [5]. An effort has been made over the years to reduce diabetic foot complications and it is believed that a strategy including prevention, patient and staff education, multidisciplinary treatment of ulcers and close monitoring can reduce amputation rates by 49-85% [6]. The aim of this review is to discuss the current methods of diagnosis and treatment of ischemic and neuroischemic diabetic foot ulcers (DFU).

Material and Methods

A selective search on PubMed was conducted with the term “diabetic foot”. Results were limited to publications within the last 10 years, in English or Portuguese, with available free full text and relative to humans. The search yielded 457 articles.

Subsequent inclusion or elimination of articles was based on the information contained in the titles and abstracts. Articles which were not relevant to the pathophysiology, diagnosis and treatment of DFU were excluded. The type of publication was also taken into consideration, and letters, news and editorials were excluded.

Other articles were acquired because of their reference in reviews obtained in the first search. Also, a few smaller searches were performed to gain information on certain subjects such as therapeutic angiogenesis and drug-eluting stents, which are somewhat recent topics in investigation and possess more trials in a non-diabetic population, therefore not appearing in the first search.

To obtain recent statistics of diabetes mellitus, the International Diabetes Federation site was also consulted.

PAD and critical ischemia

PAD is a manifestation of atherosclerosis that leads to arterial stenosis and occlusions in the major vessels supplying the lower limbs [1]. CLI represents the end stage of PAD, referring to a state of arterial insufficiency that reduces distal perfusion pressure to such an extent that nutritive blood flow and microcirculation to tissues are severely reduced and tissue viability is jeopardized [7]. Patients typically present with chronic ischemic rest pain (Rutherford categories 4 to 6) and/or ischemic skin lesions such as ulceration or gangrene (Fontaine's stages III and IV). It should be remembered that CLI implies chronicity, requiring the presence of symptoms for over 2 weeks, distinguishing it from acute limb ischemia. The diagnosis of CLI should be confirmed by studies such as ankle-brachial index (ABI), toe systolic pressure or transcutaneous oxygen pressure ($TcPO_2$) [1], to be discussed later in this review.

Diabetes mellitus and diabetic foot

Diabetes mellitus is a serious healthcare problem, with an increasing prevalence worldwide. According to the International Diabetes Federation estimates of 2012, over 371 million people have diabetes [8]. The term "diabetic foot" encompasses any foot lesion occurring as a result of diabetes and its complications [6] and the lifetime risk of a patient with diabetes developing a foot ulcer has been estimated to be as high as 25% [4]. The condition constitutes a major disabling complication, with potentially limb-threatening consequences. It has been claimed that every 30 seconds a lower limb is amputated due to diabetes [9] and that over 85% of amputations are preceded by a foot ulcer [5]. The single greatest risk factor for foot ulceration is a past history of either ulceration or amputation [10].

Ischemia, neuropathy and infection are the three pathological components involved in the etiology of DFU, frequently occurring together [11]. Neuropathy and ischemia are usually the initiating factors, bearing a different weight in different patients. Infection is rarely the direct cause of an ulcer, but is strongly related to the probability of amputation, especially in combination with PAD [12]. The distinction between purely neuropathic, purely ischemic or neuroischemic ulcers is essential, as it will guide further therapy. Up to 50% of DFU are considered to be of neuroischemic origin and one-third of the patients with a foot ulcer have both signs of PAD and infection [1, 13].

It is important to recognize that the DFU is a sign of multiorgan disease. Patients frequently possess multiple comorbidities such as cardiovascular disease and end stage renal disease [14] that may be the result of the micro and macrovascular disturbances caused by hyperglycemia or integrate the metabolic syndrome common in diabetics [15, 16].

Diabetes mellitus and PAD

Both macrovascular disease and microvascular dysfunction impair perfusion in the diabetic foot, yet the most important cause of vascular impairment is PAD [17]. PAD is 2-4 times more common in patients with diabetes than in those without [2], but the true prevalence of PAD in the diabetic population is difficult to determine. Studies point to a PAD prevalence of up to 50% in diabetic patients with foot ulcers [3]. Although the major risk factors (age, smoking, hypertension, dyslipidemia, etc) are the same for diabetic and non-diabetic PAD, diabetic PAD occurs at a younger age, with a roughly

even distribution amongst men and women and characteristically advances more rapidly [17].

PAD risk is associated with duration and control of diabetes. Poor glucose control accelerates the manifestation of PAD and for every 1% increase in hemoglobin A1c (HbA1c) there is a corresponding increase of 25-60% in the relative risk of PAD [18]. There is also evidence suggesting that insulin resistance plays a key role in a clustering of cardiometabolic risk factors which include hyperglycemia, dyslipidemia, hypertension and obesity. Insulin resistance is a risk factor for PAD even in individuals without diabetes, raising the risk approximately 40 to 50% [19].

The pattern of arterial involvement differs in comparison to that of non-diabetics. Atherosclerosis is usually distally located, with a predilection for the infrapopliteal vessels. Proximal segments may also be involved, especially in diabetic smokers. The atherosclerotic process is more diffuse and there is poor collateral circulation [17].

The clinical presentation of PAD in the diabetic patient is frequently masqueraded due to concomitant peripheral neuropathy. The presence of calcification of the intimal plaque and media (Mönckeberg's media calcinosis), a condition frequently associated with diabetic PAD, may further hinder the diagnosis [17]. In all patients with diabetes and a foot ulcer, the presence of PAD must be excluded [3, 9].

A fact to be well kept in mind when managing a diabetic patient is that the presence of PAD indicates generalized atherosclerosis, including a coronary or cerebrovascular distribution that may be asymptomatic [17].

Patients with a history of DFU alone already have high mortality rates, mainly due to cardiovascular events but also due to other causes such as cancer [20]. However, PAD, especially CLI, significantly increases the mortality risk further [21].

Diagnosis

Until PAD is excluded, vascular status of the lower extremities should always be evaluated in a patient with a DFU [3]. The clinician should begin by taking a thorough history, with identification of common risk factors, family history of diabetes, personal history of ulceration or other chronic wounds, venous disease or previous vascular evaluation [17]. The presence of PAD symptoms must be questioned, such as intermittent claudication or rest pain [3]. However, less than 25% of diabetics with PAD report these symptoms, which may delay the diagnosis of ischemia [6].

Physical examination must include inspection of both legs and feet and palpation of peripheral pulses. Vascular insufficiency is suggested by absence of hair, dry, cool or fissured skin, dystrophic nails, skin pallor and dependent erythema. Signs of venous disease should also be assessed, such as varicose veins, brawny induration, or scarring. Any foot deformity, callus or scarring must be investigated and the interdigital spaces must be inspected for possible fissures, ulceration or infection. Neuropathy should be assessed by sensory, proprioceptive and vibratory testing. Pulses of the lower limb (femoral, popliteal, posterior tibial and dorsalis pedis arteries) are to be palpated bilaterally [17]. When both pedal pulses are absent, PAD is likely. A hand-held Doppler examination should be performed to assist in the vascular examination. Absent or monophasic Doppler signals from one or both feet suggest PAD [3].

The use of rigid non-invasive methods is mostly based on the hemodynamic changes in the macrovascular arterial tree. The criteria applicable to non-diabetic lower limbs are not reliable to predict the healing of diabetic foot lesions [1]. ABI is obtained by dividing the ankle systolic pressure by the brachial systolic pressure, derived from Doppler examination. ABI may be falsely elevated due to media calcinosis, and therefore can be trusted when low but not when high [17]. An ABI < 0.6 indicates significant ischemia in respect to wound healing potential, whereas an ABI > 0.6 has little predictive value and, therefore, toe pressure and/or transcutaneous oxygen pressure ($TcPO_2$) should be measured [3]. Toe pressure may give more reliable information on the level of distal flow capacity but, as reported in one study, it could not be measured in 16% of cases due to a previous amputation or gangrene of the big toe [21]. When it comes to evaluating arterial circulation of the lower limbs, measurement of toe blood pressure is superior to the calculation of ABI as media calcinosis is almost absent in the digital arteries [7]. To investigate local microcirculation and tissue viability, $TcPO_2$ of the forefoot should be measured, as it reflects local arterial blood flow and skin oxygenation [7]. DFU will often heal if toe pressure is >55 mmHg and $TcPO_2$ >50 mmHg. Healing is usually severely impaired when toe pressure is <30 mmHg and $TcPO_2$ <30 mmHg [3].

Even if initial diagnostics have suggested only questionable or mild disease, when a DFU has not healed with proper treatment in 6 weeks perfusion should be reassessed. Duplex ultrasound or angiography are the diagnostic tests to be considered [3]. Duplex ultrasound can directly visualize most vessels, but is most often used for post-bypass graft or angioplasty and stent procedure surveillance. Contrast angiography can be executed with magnetic resonance angiography, computed tomographic angiography or with conventional digital subtraction arteriography. Special precautions

must be taken due to the increased risk of contrast-induced nephrotoxicity in diabetics. These patients require hydration in preparation and monitoring of renal function after the procedure [17].

Treatment

The main goal when treating CLI and DFU is preservation of the limb. Ischemia is primarily responsible for 90% of amputations in DFU patients [22]. When left untreated, the poor arterial perfusion in CLI may lead to the need for amputation [23] and potentially fatal complications from the progression of gangrene and the development of sepsis [24].

Understanding the underlying pathophysiology of DFU is essential, as it guides in the selection of treatment options. Regardless of the type of ulcer, a multifactorial approach is necessary and provides the best results. The greatest challenge is in healing ischemic or neuroischemic ulcers, due to the low distal perfusion pressure and microvascular dysfunction. Exclusively neuropathic ulcers have a good prognosis as long as adequate and timely treatment is given [23].

The treatment of purely neuropathic and infected foot ulcers is beyond the scope of this review. Focus will be on the improvement of perfusion, by medical, endovascular or surgical means.

Medical management

Therapeutic goals in diabetic patients with foot ulcers include pain control, biomechanical off-loading, improvement of perfusion, wound bed dressings and topical treatment, frequent debridement, correction of foot deformities and reduction of edema [25]. Prevention and treatment of infection is also a key component of treatment, for infection dramatically increases the risk of amputation [12]. When ischemia and infection are presented together, "time is tissue" and urgent treatment is necessary [3]. Be mindful of the fact that reconstruction of the blood supply to the lower limb increases the body's ability to fight infections. By satisfying nutrient demand, accelerating local tissue metabolism and promoting the recovery of diseased nerves at the distal end of the limb, better control of local infection and faster healing of foot ulcers is achieved [15].

As previously discussed, poor metabolic control accelerates the development of PAD [18]. It is thus recommended that medical treatment be aimed at achieving HbA1c levels of <7.0% in most adults [26]. Patients with DFU also possess elevated cardiovascular morbidity and mortality. Cardiovascular risk factor modification is indispensable, with treatment of hypertension and dyslipidemia, control of platelet aggregation and smoking cessation [3, 25].

Negative pressure wound therapy (NPWT) and hyperbaric oxygen therapy are two treatment modalities that are not established in routine management but that may prove useful in certain cases [6]. NPWT has been shown to promote wound healing by removing excess exudates, stimulating granulation tissue, providing a closed environment, reducing edema and increasing local blood flow. The prerequisite for ideal effect is adequate blood supply and can only be considered as complementary to other

treatments [27]. Hyperbaric oxygen treatment may reduce the risk of major amputation when given as an adjunct, but the type of patient most likely to benefit from this therapy is still to be determined [14].

Vascular interventions

The crucial decision is whether revascularization is necessary in a particular patient with a particular lesion. Vascular surgery or angioplasty should be performed in any patient with PAD severe enough to impair wound healing in order to optimize peripheral arterial perfusion, improve ulcer healing and avoid amputation [3, 23]. The aim of revascularization is to restore blood flow to at least one infrapopliteal artery down to the foot, preferably the artery that supplies the anatomical region of the ulcer [3, 28]. Due to the difficulties in diagnosis, neuroischemic pattern of disease and microvascular dysfunction, the threshold for revascularization in patients with DFU should be lower [23]. Non-invasive evaluation is helpful in the decision, and revascularization is suggested when ABI < 0.6, toe pressures < 50 mmHg or $TcPO_2$ < 30 mmHg [6]. Ultimately, the decision to intervene is made according to the patient's general health status, comorbidities, symptoms and clinical findings [11, 29, 30]. Anatomical imaging of the entire lower limb circulation should be performed before vascular intervention to aid in the selection of a therapeutic strategy [3]. Atherosclerotic disease in diabetic patients frequently affects the infrapopliteal arteries, with sparing of the foot arteries. Diabetic smokers may also manifest iliac or femoral occlusions [31].

There are three revascularization techniques: open, endovascular, and hybrid [9, 11, 25]. The choice between these methods depends on comorbidity, extension and severity of the arterial lesions and expertise of the center [25]. Although mortality and

amputation-free survival may be similar at a midterm follow-up [32], these results tilt in favor of bypass surgery on the long-term if the procedure is performed on medically fit patients using quality vein grafts [33, 34]. However, bypass surgery is associated with greater morbidity and mortality, and the possibility of prolonged ulcer healing, wound complications, limb swelling, perioperative cardiac complications, hospital readmission and graft failure leading to reoperation [24]. According to the results of the Bypass versus angioplasty in severe ischaemia of the leg (BASIL) trial, angioplasty should be considered first in patients with substantial comorbidities and life expectancy under 1 to 2 years [32]. A propensity score analysis comparing surgical and endovascular techniques suggests otherwise, defending that outcomes do not differ except in respect to leg salvage (better in percutaneous transluminal angioplasty (PTA), 75.5% vs 68.0%, P = 0.042) and freedom from surgical revascularization (better in bypass, 78.8% vs 85.2%, P = 0.17) and that infrapopliteal PTA should be considered a first-line strategy when both endovascular and bypass procedures are available for a certain patient with equal outcomes to be expected [35].

Arterial bypass is an open surgery procedure and is indicated for long occlusions [25]. It must be individualized according to the patient's available venous conduit and arterial anatomy [11]. Diabetic patients usually present with arterial occlusion in the superficial femoral or the popliteal artery and the distal arteries [36]. When the distal arteries are involved, distal bypass may be an option. This may prove challenging, as the distal outflow vessels in diabetics are often calcified. Inflow to the graft may be taken from the superficial femoral or popliteal artery if the proximal vessels are free of significant wall changes [25]. The best graft material in distal bypasses is autogenous vein. A retrospective study led by the Boston Deaconess Hospital Group reports that saphenous vein grafts were more efficacious than other conduits, presenting

superior patency rates. Autogenous vein also possesses a greater resistance to infection when compared with prosthetic grafts [37].

Endovascular interventions, including PTA with or without stenting, are a less invasive alternative for revascularization. These techniques are suitable for focal, short-segment iliac stenosis or occlusions, which occur in 10 to 20% of all diabetic patients [1]. However, with the development of new angioplasty procedures and different types of stents, endovascular treatment of infrapopliteal atherosclerotic occlusions and/or stenosis is becoming the gold-standard, especially in patients with CLI [38]. There have been many attempts to evaluate the role of bare-metal, metal-absorbable, carbofilm-coated, or drug-eluting stent implantation in distal popliteal and infrapopliteal arteries, but these have yielded little information about the midterm and long-term outcomes [39]. The short lengths and the vulnerability to external compression and deformation if placed too distally are the main limitations of currently available bare or drug-eluting balloon-expandable stents. Longer length self-expanding thin-strut stents are available and more appropriate for the diffuse distribution of atherosclerosis commonly associated with CLI [38]. A retrospective study was conducted in Germany from 2005 to 2008 to evaluate the effectiveness of nitinol stent placement in long infrapopliteal lesions in patients with CLI at high risk for crural bypass and with suboptimal angioplasty. The nitinol device is relatively long (120mm) and flexible, proving beneficial in long occlusions which are common in the crural arteries. The results support this option as a durable first-choice alternative treatment in these patients, with a success rate of 97.1%, short-term (10.4+/-7.3 months) primary patency rate of 91.1% and 75.5% primary patency rate at 24 months [39, 40]. Drug-eluting stents are being investigated as an option for reducing restenosis in the infrapopliteal arteries, a recurring problem in PTA, since bare metal stents are associated with significant

neointimal hyperplasia [38, 41]. Substances such as sirolimus (with anti-inflammatory and antiproliferative properties) and paclitaxel (antimitotic cytotoxic actions) have been used, showing encouraging results [38]. Sirolimus-eluting stents appear to be superior to paclitaxel-eluting stents in terms of primary patency ($p<0.001$) and repeat revascularizations ($p = 0.014$) [42]. The major concerns are the short length and elevated price of these devices, as the need for several stents to revascularize an infrapopliteal segment is not cost-effective [39]. Fracture of a drug-eluting stent in the tibioperoneal trunk following bifurcation stenting is also a considerable risk [43]. It should be stressed that in several randomized and non-randomized trials, higher primary and secondary patency rates were obtained in comparison to bare metal stents and PTA. No significant advantage has been demonstrated with regard to limb salvage and mortality rates. These results have yet to be tested in larger cohort studies and with greater follow-up periods [44].

Randomized controlled trials comparing endovascular and surgical revascularization in the treatment of impaired perfusion or critical ischemia in diabetics are not available to this date [29]. Bypass surgery and endovascular therapy should be considered complementary techniques for revascularization in diabetic patients with non-healing ulcers [45].

Noninvasive treatment of CLI

Current treatment options for patients with DFU and CLI who are not candidates for revascularization or in which the procedure has been unsuccessful are scarce. These patients have a less favorable prognosis, with amputation possibly being the only viable choice. Recent research efforts have been made to find safe and effective

noninvasive approaches to improve peripheral arterial perfusion. Prostaglandin therapy and urokinase administration were first studied over a decade ago, but larger and more recent randomized and controlled trials are needed to better assess the value and efficacy of these treatments in this subset of patients. Stimulation of angiogenesis is a novel technique being currently explored in various studies [46].

Prostanoids prevent platelet aggregation and leukocyte activation and protect the vascular endothelium. Though treatment with local infusion of prostaglandin E_1 is still controversial, the majority of current guidelines recommend this procedure in patients with DFU and CLI without revascularization options. The Inter-Society Consensus for the Management of PAD (TASC II) however, does not [1]. Short-term studies have not shown clear results, but most long-term trials revealed a reduction in ulcer size and ischemic pain, with a decrease in amputation rates [46].

Patients with PAD have increased plasma viscosity and erythrocyte aggregation, a consequence of hyperfibrinogenemia. This condition can cause limitations in blood flow and oxygenation. Low-dose urokinase is a safe, feasible and effective therapy that improves microcirculation in diabetic patients with CLI. The most recent trial using urokinase in these patients was published in 2008 and supports this therapeutic approach [46]. Low molecular weight heparin (dalteparin 5000 U daily) has equally demonstrated significant positive effects on skin microcirculation, ulcer outcome and hemostasis, when associated with traditional medication/treatment in these patients [47, 48].

Therapeutic angiogenesis is an investigational approach to the treatment of CLI. It consists in the induced formation of a capillary network in ischemic tissues by

creating a proangiogenic environment. Two modalities have been studied: gene therapy and autologous bone marrow transplantation[49].

Gene therapy is a rising technique suitable for vascular application, and has been the subject of continued testing in many trials. Various angiogenic growth factors, such as vascular endothelial cell growth factor (VEGF), fibroblast growth factor (FGF), and hepatocyte growth factor (HGF), have been studied, with naked plasma DNA, viral genes and liposomal genes serving as vectors. Administration may be intra-muscular or intra-arterial, and can be continued over a 4- to 8-week period. Though results vary according to the different combination of vector and product, a meta-analysis of existing trials has proven the general efficacy of therapeutic angiogenesis in CLI. Mortality rates did not present significant differences in comparison to placebo, but there was a higher risk for adverse effects such as edema, hypotension and proteinuria in gene therapy [49].

Bone marrow is a rich reservoir of tissue-specific stem and progenitor cells. Studies show that endothelial progenitor cells play a part in revascularization, being mobilized to the injured tissue in response to tissue ischemia and improving collateral vessel formation [50]. Bone marrow transplantation can be achieved by intramuscular or intra-arterial injection of autologous bone marrow-derived mononuclear cells, and has been proved safe and effective in patients with CLI, accelerating wound healing and reducing major amputation rates [51, 52]. Granulocyte-colony stimulating factor which induces mobilization of bone marrow cells may be administered subcutaneously before transplantation [53]. These exploratory findings require further trials to be confirmed, using a greater number of participants and determining if and how this method may be of use to diabetics. The population subset to most benefit from this procedure is also yet to be defined.

Amputation

Amputations are urgent or curative [54]. Primary amputation should only be considered when all other options fail or are unsuitable. Indications for amputation include a non-revascularizable lower limb, bed confinement, reduced ambulation that is not worsened by amputation and a life expectancy of less than 1 year [25, 55]. Amputation should be as distal and conservative as possible to maintain functionality, as the preservation of leg length aids ambulation and decreases energy expenditure. Infected or gangrenous tissue should be removed and the surgical site should be allowed to heal [25]. When there is large volume tissue necrosis and a functionally unsalvageable foot, a need to control sepsis or the presence of non-healing wounds despite patent revascularization, amputation below the knee is necessary [55].

Prognosis

In neuroischemic legs, healing is primarily affected by the severity of ischemia [12]. Most studies report limb salvage rates after revascularization procedures between 80-85% and ulcer healing in >60% at 12 months [3]. The correct selection of revascularization method is key, as early failures often lead to rapid deterioration of the limb [56]. Comorbidity significantly increases with the severity of foot disease and is strongly related to prognosis [14]. Diabetic foot disease should be considered a life-long condition since patients with previous ulcers are always at high risk of developing a new ulcer [21].

Prevention

A strategy including regular examination of the feet, inspection and use of appropriate footwear, identification of the high-risk patient, education of patient, family and health care staff, and treatment of non-ulcerative pathology can increase the patient's awareness of his problem, his ability for self-management and reduce the number of minor foot lesions. These measures, along with a multidisciplinary treatment of ulcers and close monitoring, can reduce amputation rates by 49-85% [6].

A study conducted over a period of 20 years assessing the incidence rates of amputations indicated a decrease in the incidence of major lower extremity amputations (transtibial or higher) by more than half in diabetic patients and an increase in minor amputations (amputation below or through the ankle). The low incidence of major amputations was maintained over the years, despite the increasing prevalence of diabetes and an aging population. These results reflect the benefits of the increasing implementation and access to multidisciplinary foot care teams, as well as an increase in invasive vascular interventions [57].

Conclusion

Traditional critical ischemia criteria are not applicable in the diabetic patient. CLI is not easily suspected in diabetics due to peripheral neuropathy, as ischemic symptoms of the lower limbs may be absent and the first manifestations of PAD recognized only when foot ulcers have progressed to the point of gangrene. Also, ABI may be falsely elevated because of media calcinosis. Consequently, medical investigation and treatment may be delayed on part of both the patient and the health care professional. The implementation of a multidisciplinary management strategy with a protocol driven approach has proved to be successful in reducing amputation rates. When a diabetic patient presents with a foot ulcer, a multifactorial approach and aggressive management of underlying CLI and infection is vital. Understanding the underlying pathophysiology is also essential in selecting the best treatment options. When revascularization is necessary, the choice between an open or endovascular intervention should be based on the patient's risk (general health status, comorbidities), severity of ischemia, arterial anatomy and conduit availability. Efforts have been made to discover noninvasive therapy for patients in whom revascularization is not an option or has been unsuccessful. It should be remembered that the diabetic foot is a life-long disease, since patients with previous ulcers are permanently at high risk of developing a new ulcer.

References

[1] Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FG, et al. Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). European journal of vascular and endovascular surgery : the official journal of the European Society for Vascular Surgery. 2007;33 Suppl 1:S1-75.

[2] Beckman JA, Creager MA, Libby P. Diabetes and atherosclerosis: epidemiology, pathophysiology, and management. JAMA : the journal of the American Medical Association. 2002 May 15;287(19):2570-81.

[3] Schaper NC, Andros G, Apelqvist J, Bakker K, Lammer J, Lepantalo M, et al. Specific guidelines for the diagnosis and treatment of peripheral arterial disease in a patient with diabetes and ulceration of the foot 2011. Diabetes/metabolism research and reviews. 2012;28:236-7.

[4] Singh N, Armstrong DG, Lipsky BA. Preventing foot ulcers in patients with diabetes. JAMA : the journal of the American Medical Association. 2005 Jan 12;293(2):217-28.

[5] Boulton AJ, Vileikyte L, Ragnarson-Tennvall G, Apelqvist J. The global burden of diabetic foot disease. Lancet. 2005 Nov 12;366(9498):1719-24.

[6] Bakker K, Apelqvist J, Schaper NC. Practical guidelines on the management and prevention of the diabetic foot 2011. Diabetes/metabolism research and reviews. 2012 Feb;28 Suppl 1:225-31.

[7] Becker F, Robert-Ebadi H, Ricco JB, Setacci C, Cao P, de Donato G, et al. Chapter I: Definitions, epidemiology, clinical presentation and prognosis. European journal of vascular and endovascular surgery : the official journal of the European Society for Vascular Surgery. 2011 Dec;42 Suppl 2:S4-12.

[8] International Diabetes Federation. IDF diabetes atlas update 2012 Brussels: IDF; 2012 [07 Mar 2012]. Available from: http://www.idf.org.

[9] Apelqvist J, Bakker K, van Houtum WH, Nabuurs-Franssen MH, Schaper NC. International consensus and practical guidelines on the management and the prevention of the diabetic foot. International Working Group on the Diabetic Foot. Diabetes/metabolism research and reviews. 2000 Sep-Oct;16 Suppl 1:S84-92.

[10] Boulton AJ. The diabetic foot: from art to science. The 18th Camillo Golgi lecture. Diabetologia. 2004 Aug;47(8):1343-53.

[11] Kalish J, Hamdan A. Management of diabetic foot problems. Journal of vascular surgery. 2010 Feb;51(2):476-86.

[12] Apelqvist J. The foot in perspective. Diabetes/metabolism research and reviews. 2008 May-Jun;24 Suppl 1:S110-5.

[13] Prompers L, Huijberts M, Apelqvist J, Jude E, Piaggesi A, Bakker K, et al. High prevalence of ischaemia, infection and serious comorbidity in patients with diabetic foot disease in Europe. Baseline results from the Eurodiale study. Diabetologia. 2007 Jan;50(1):18-25.

[14] Apelqvist J. Diagnostics and treatment of the diabetic foot. Endocrine. 2012 Jun;41(3):384-97.

[15] Gu YQ. Vascular surgery and diabetic foot revascularization. Chinese medical journal. 2010 Aug 5;123(15):2116-9.

[16] Young MJ, McCardle JE, Randall LE, Barclay JI. Improved survival of diabetic foot ulcer patients 1995-2008: possible impact of aggressive cardiovascular risk management. Diabetes care. 2008 Nov;31(11):2143-7.

[17] Gibbons GW, Shaw PM. Diabetic vascular disease: characteristics of vascular disease unique to the diabetic patient. Seminars in vascular surgery. 2012 Jun;25(2):89-92.

[18] Selvin E, Marinopoulos S, Berkenblit G, Rami T, Brancati FL, Powe NR, et al. Meta-analysis: glycosylated hemoglobin and cardiovascular disease in diabetes mellitus. Annals of internal medicine. 2004 Sep 21;141(6):421-31.

[19] Muntner P, Wildman RP, Reynolds K, Desalvo KB, Chen J, Fonseca V. Relationship between HbA1c level and peripheral arterial disease. Diabetes care. 2005 Aug;28(8):1981-7.

[20] Iversen MM, Tell GS, Riise T, Hanestad BR, Ostbye T, Graue M, et al. History of foot ulcer increases mortality among individuals with diabetes: ten-year follow-up of the Nord-Trondelag Health Study, Norway. Diabetes care. 2009 Dec;32(12):2193-9.

[21] Faglia E, Clerici G, Clerissi J, Gabrielli L, Losa S, Mantero M, et al. Long-term prognosis of diabetic patients with critical limb ischemia: a population-based cohort study. Diabetes care. 2009 May;32(5):822-7.

[22] Eskelinen E, Lepantalo M, Hietala EM, Sell H, Kauppila L, Maenpaa I, et al. Lower limb amputations in Southern Finland in 2000 and trends up to 2001. European journal of vascular and endovascular surgery : the official journal of the European Society for Vascular Surgery. 2004 Feb;27(2):193-200.

[23] Jorneskog G. Why critical limb ischemia criteria are not applicable to diabetic foot and what the consequences are. Scandinavian journal of surgery : SJS : official organ for the Finnish Surgical Society and the Scandinavian Surgical Society. 2012;101(2):114-8.

[24] Lumsden AB, Davies MG, Peden EK. Medical and endovascular management of critical limb ischemia. Journal of endovascular therapy : an official journal of the International Society of Endovascular Specialists. 2009 Apr;16(2 Suppl 2):II31-62.

[25] Lepantalo M, Apelqvist J, Setacci C, Ricco JB, de Donato G, Becker F, et al. Chapter V: Diabetic foot. European journal of vascular and endovascular surgery : the official journal of the European Society for Vascular Surgery. 2011 Dec;42 Suppl 2:S60-74.

[26] Standards of medical care in diabetes--2013. Diabetes care. 2013 Jan;36 Suppl 1:S11-66.

[27] Vikatmaa P, Juutilainen V, Kuukasjarvi P, Malmivaara A. Negative pressure wound therapy: a systematic review on effectiveness and safety. European journal of vascular and endovascular surgery : the official journal of the European Society for Vascular Surgery. 2008 Oct;36(4):438-48.

[28] Faglia E, Clerici G, Clerissi J, Mantero M, Caminiti M, Quarantiello A, et al. When is a technically successful peripheral angioplasty effective in preventing above-the-ankle amputation in diabetic patients with critical limb ischaemia? Diabetic medicine : a journal of the British Diabetic Association. 2007 Aug;24(8):823-9.

[29] Hinchliffe RJ, Andros G, Apelqvist J, Bakker K, Friederichs S, Lammer J, et al. A systematic review of the effectiveness of revascularization of the ulcerated foot in patients with diabetes and peripheral arterial disease. Diabetes/metabolism research and reviews. 2012 Feb;28 Suppl 1:179-217.

[30] Apelqvist J, Elgzyri T, Larsson J, Londahl M, Nyberg P, Thorne J. Factors related to outcome of neuroischemic/ischemic foot ulcer in diabetic patients. Journal of vascular surgery. 2011 Jun;53(6):1582-8 e2.

[31] Ciavarella A, Silletti A, Mustacchio A, Gargiulo M, Galaverni MC, Stella A, et al. Angiographic evaluation of the anatomic pattern of arterial obstructions in diabetic patients with critical limb ischaemia. Diabete & metabolisme. 1993 Nov-Dec;19(6):586-9.

[32] Adam DJ, Beard JD, Cleveland T, Bell J, Bradbury AW, Forbes JF, et al. Bypass versus angioplasty in severe ischaemia of the leg (BASIL): multicentre, randomised controlled trial. Lancet. 2005 Dec 3;366(9501):1925-34.

[33] Bradbury AW, Adam DJ, Bell J, Forbes JF, Fowkes FG, Gillespie I, et al. Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) trial: An intention-to-treat analysis of amputation-free and overall survival in patients randomized to a bypass surgery-first or a balloon angioplasty-first revascularization strategy. Journal of vascular surgery. 2010 May;51(5 Suppl):5S-17S.

[34] Beard JD. Which is the best revascularization for critical limb ischemia: Endovascular or open surgery? Journal of vascular surgery. 2008 Dec;48(6 Suppl):11S-6S.

[35] Soderstrom MI, Arvela EM, Korhonen M, Halmesmaki KH, Alback AN, Biancari F, et al. Infrapopliteal percutaneous transluminal angioplasty versus bypass surgery as first-line strategies in critical leg ischemia: a propensity score analysis. Annals of surgery. 2010 Nov;252(5):765-73.

[36] Gu YQ, Zhang J, Qi LX, Yu HX, Li JX, Li XF, et al. Surgical treatment of 82 patients with diabetic lower limb ischemia by distal arterial bypass. Chinese medical journal. 2007 Jan 20;120(2):106-9.

[37] Pomposelli FB, Kansal N, Hamdan AD, Belfield A, Sheahan M, Campbell DR, et al. A decade of experience with dorsalis pedis artery bypass: analysis of outcome in more than 1000 cases. Journal of vascular surgery. 2003 Feb;37(2):307-15.

[38] Karnabatidis D, Katsanos K, Siablis D. Infrapopliteal stents: overview and unresolved issues. Journal of endovascular therapy : an official journal of the International Society of Endovascular Specialists. 2009 Feb;16 Suppl 1:I153-62.

[39] Donas KP, Torsello G, Schwindt A, Schonefeld E, Boldt O, Pitoulias GA. Below knee bare nitinol stent placement in high-risk patients with critical limb ischemia is still durable after 24 months of follow-up. Journal of vascular surgery. 2010 Aug;52(2):356-61.

[40] Donas KP, Schwindt A, Schonefeld T, Tessarek J, Torsello G. Below-knee bare nitinol stent placement in high-risk patients with critical limb ischaemia and unlimited supragenicular inflow as treatment of choice. European journal of vascular and endovascular surgery : the official journal of the European Society for Vascular Surgery. 2009 Jun;37(6):688-93.

[41] Martens JM, Knippenberg B, Vos JA, de Vries JP, Hansen BE, van Overhagen H. Update on PADI trial: percutaneous transluminal angioplasty and drug-eluting stents for infrapopliteal lesions in critical limb ischemia. Journal of vascular surgery. 2009 Sep;50(3):687-9.

[42] Biondi-Zoccai GG, Sangiorgi G, Lotrionte M, Feiring A, Commeau P, Fusaro M, et al. Infragenicular stent implantation for below-the-knee atherosclerotic disease: clinical evidence from an international collaborative meta-analysis on 640 patients. Journal of endovascular therapy : an official journal of the International Society of Endovascular Specialists. 2009 Jun;16(3):251-60.

[43] Schwarzmaier-D'Assie A, Karnik R, Bonner G, Vavrik J, Slany J. Fracture of a drug-eluting stent in the tibioperoneal trunk following bifurcation stenting. Journal of endovascular therapy : an official journal of the International Society of Endovascular Specialists. 2007 Feb;14(1):106-9.

[44] Rastan A, Noory E, Zeller T. Drug-eluting stents for treatment of focal infrapopliteal lesions. VASA Zeitschrift fur Gefasskrankheiten. 2012 Mar;41(2):90-5.

[45] Mills JL, Sr. Open bypass and endoluminal therapy: complementary techniques for revascularization in diabetic patients with critical limb ischaemia. Diabetes/metabolism research and reviews. 2008 May-Jun;24 Suppl 1:S34-9.

[46] Weck M, Slesaczeck T, Rietzsch H, Munch D, Nanning T, Paetzold H, et al. Noninvasive management of the diabetic foot with critical limb ischemia: current options and future perspectives. Therapeutic advances in endocrinology and metabolism. 2011 Dec;2(6):247-55.

[47] Kalani M, Apelqvist J, Blomback M, Brismar K, Eliasson B, Eriksson JW, et al. Effect of dalteparin on healing of chronic foot ulcers in diabetic patients with peripheral arterial occlusive disease: a prospective, randomized, double-blind, placebo-controlled study. Diabetes care. 2003 Sep;26(9):2575-80.

[48] Kalani M, Silveira A, Blomback M, Apelqvist J, Eliasson B, Eriksson JW, et al. Beneficial effects of dalteparin on haemostatic function and local tissue oxygenation in patients with diabetes, severe vascular disease and foot ulcers. Thrombosis research. 2007;120(5):653-61.

[49] Davies MG. Critical limb ischemia: cell and molecular therapies for limb salvage. Methodist DeBakey cardiovascular journal. 2012 Oct-Dec;8(4):20-7.

[50] Sata M. Molecular strategies to treat vascular diseases: circulating vascular progenitor cell as a potential target for prophylactic treatment of atherosclerosis. Circulation journal : official journal of the Japanese Circulation Society. 2003 Dec;67(12):983-91.

[51] Idei N, Soga J, Hata T, Fujii Y, Fujimura N, Mikami S, et al. Autologous bone-marrow mononuclear cell implantation reduces long-term major amputation risk in

patients with critical limb ischemia: a comparison of atherosclerotic peripheral arterial disease and Buerger disease. Circulation Cardiovascular interventions. 2011 Feb 1;4(1):15-25.

[52] Walter DH, Krankenberg H, Balzer JO, Kalka C, Baumgartner I, Schluter M, et al. Intraarterial administration of bone marrow mononuclear cells in patients with critical limb ischemia: a randomized-start, placebo-controlled pilot trial (PROVASA). Circulation Cardiovascular interventions. 2011 Feb 1;4(1):26-37.

[53] Lara-Hernandez R, Lozano-Vilardell P, Blanes P, Torreguitart-Mirada N, Galmes A, Besalduch J. Safety and efficacy of therapeutic angiogenesis as a novel treatment in patients with critical limb ischemia. Annals of vascular surgery. 2010 Feb;24(2):287-94.

[54] Frykberg RG, Zgonis T, Armstrong DG, Driver VR, Giurini JM, Kravitz SR, et al. Diabetic foot disorders. A clinical practice guideline (2006 revision). The Journal of foot and ankle surgery : official publication of the American College of Foot and Ankle Surgeons. 2006 Sep-Oct;45(5 Suppl):S1-66.

[55] Abou-Zamzam AM, Jr., Gomez NR, Molkara A, Banta JE, Teruya TH, Killeen JD, et al. A prospective analysis of critical limb ischemia: factors leading to major primary amputation versus revascularization. Annals of vascular surgery. 2007 Jul;21(4):458-63.

[56] Conte MS. Diabetic revascularization: endovascular versus open bypass--do we have the answer? Seminars in vascular surgery. 2012 Jun;25(2):108-14.

[57] Larsson J, Eneroth M, Apelqvist J, Stenstrom A. Sustained reduction in major amputations in diabetic patients: 628 amputations in 461 patients in a defined population over a 20-year period. Acta orthopaedica. 2008 Oct;79(5):665-73.

<u>Anexo:</u> Normas da Revista

Normas de publicação da Revista da Sociedade Portuguesa de Cirurgia Cardiotorácica e Vascular

A Revista da SPCCTV destina-se à publicação de artigos originais nos campos da Cirurgia Cardiotorácica e Vascular. Os manuscritos serão revistos pelos Editores e por revisores externos, e a sua aceitação dependerá do seu interesse, originalidade e validade científicas. A língua oficial da revista é o Português, mas a submissão de Artigos Originais, Artigos de Revisão, Casos Clínicos e Imagens em Cirurgia integralmente em língua Inglesa é fortemente recomendada. Caso desejem, os autores podem enviar uma versão em Inglês (para indexação) e outra em Português, para a revista impressa. E obrigatória a submissão dos resumos em Inglês.

ARTIGOS

São aceites submissões nas seguintes categorias:

Tipo de artigo	Limite de palavras	No máximo de autores	No máximo de referências	No máximo de tablas e figuras
Artigo Original	5000	8	25	8
Artigo de Revisão	s/ limite	8	s/ limite	s/ limite
Caso Clínico	1000	5	10	4
Imagens em Cirurgia	50	4	0	2
Carta ao Editor	850	4	8	2
Editorial	1000	2	10	2

A contagem de palavras deve incluir resumo e bibliografia, excluindo legendas e tabelas.

A cada edição, uma imagem seleccionada figura na capa da revista impressa.

Os editoriais apenas podem ser submetido mediante convite do corpo editorial.

As Cartas ao Editor, Imagens em Cirurgia e Editoriais dispensam o envio de Resumo.

FORMATACAO

A submissão devera ser feita integralmente em formato electrónico. Os ficheiros de texto devem ser submetidos em formato Word, com paginas numeradas no canto inferior direito, tipo de letra Times New Roman, tamanho 12, duplo espaço e justificados. As imagens devem ser submetidas em ficheiros individuais, em formato .tiff, com uma definição mínima de 300dpi.

ELEMENTOS OBRIGATORIOS

A. CARTA DE SUBMISSAO

Os manuscritos devem ser acompanhados de uma Carta de Submissão que terá de incluir:
- a declaração de originalidade,
- a concordância de todos os autores com o teor do artigo e aprovação da versão final,
- a transferência da propriedade intelectual para a Revista e,
- a declaração da presença ou ausência de conflitos de interesse. Se existentes, os Autores devem revelar as relações comerciais com tecnologias em estudo, as fontes de financiamento, a sua filiação Institucional ou Corporativa, incluindo consultadorias.

Nota: Os Autores poderão ser responsabilizados por falsas declarações.

B. PAGINA DE TITULO

Esta deve incluir o Título sem abreviações e em Maiúsculas; o nome e apelido dos autores e o(s) nome(s) e local(ais) da Instituição(ões) de afiliação de cada autor. O nome, endereço, telefone e email do autor correspondente, deve ser inscrito no fundo da página de título. No caso do manuscrito ter sido apresentado nalguma Reunião, esta deve ser discriminada juntamente com a data de apresentação. A

contagem total de palavras do artigo (incluindo os resumos, mas excluindo tabelas, figures e referências) deve ser referida.

C. RESUMO (ABSTRACT)
O Resumo, por ser a secção mais lida de todos os artigos, é fundamental. Deve ser factual, sem abreviações (excepto unidades do SI). Deve incluir o Titulo e Autores, e ser estruturado em Objectivos – problema em estudo ou objectivo do estudo, Métodos, explicando como o estudo foi realizado, Resultados, revelando os dados encontrados e sua importância e Conclusão, revelando a conclusão do estudo. O limite máximo de palavras no resumo é 250.

D. TEXTO
O texto deve ser organizado nos seguintes elementos:

Introdução: deve revelar o objectivo da investigação e fazer uma revisão bibliográfica curta do estado da arte em relação ao problema em estudo.

Material e Métodos: estes devem ser descritos em detalhe com a informação adequada sobre Estudos Humanos ou Animais como atrás referido. O uso de abreviações deve ser limitado às unidades de medida do SI ou às de uso comum. As tecnologias devem ser nomeadas através do seu nome genérico, com o seu nome comercial, nome e local do fabricante entre parêntesis. As técnicas estatísticas de analise de dados devem ser descritas em detalhe.

Resultados: estes devem ser considerados a parte mais importante do artigo. Por tal, é importante que sejam descritos de forma concisa mas simultaneamente realçando os todos os resultados de forma completa, através de tabelas ou figuras, incluindo os comentários dos autores no texto.

Discussão: a discussão, deve ser clara e breve, devendo incluir a interpretação da significância dos resultados e da sua relação com outros trabalhos publicados na mesma área. A importância dos resultados e as limitações metodológicas, se existirem, devem ser enunciadas.

Agradecimentos: a existirem, devem ser referidos no final do texto

Referências: devem ser apresentadas sequencialmente de acordo com a ordem de uso no texto e apresentadas como números entre parêntesis rectos. Comunicações pessoais e dados não publicados não devem ser incluídos na lista de referências, embora possam ser referidos no texto. Nas referências todos os autores devem ser referidos e os jornais ou revistas apresentados de acordo com as abreviações usadas no Index Medicus. As referências devem ser apresentadas do seguinte modo:

Revistas [1] Dinis da Gama A, Perdigão J, Ministro A, Evangelista A, Damião A, Garcia Alves A. The utilization of the “simplified technique” in the simultaneous management of independent thoracic and abdominal aortic aneurysms. A clinical report. RevPort Cir Cardiotorac V 2009;3:149 155.

Livros [2] Antunes M J. A Doença da Saúde. Lisboa: Quetzal 2001:167- 176. Vários Autores [3] Fragata J, Martins L. Como evitar o erro em Medicina. Em: Fragata J, Martins L, autores. O Erro em Medicina. Lisboa:Almedina, 2008:313-348. Publicações Online (O DOI é referência obrigatória e a única necessária para citações de artigos de publicações online)

Publicações Online (O DOI é referência obrigatória e a única necessária para citações de artigos de publicações online) [4] Azevedo O, Almeida J, Nolasco T, Medeiros R, Casanova J, Bartosch C, Almeida J, Pinho P. Massive right atrial myxoma presenting as syncope and exertional dyspnea: case report. Cardiovascular Ultrasound doi:10.1186/1476-7120-8-23.

E. TABELAS
As tabelas devem ser numeradas de acordo com a sequencia de aparecimento no texto, e enviadas num ficheiro conjunto a parte do texto, em formato Word. Devem incluir numero e cabeçalho, assim como legenda se necessária.

F. CABECALHO E LEGENDAS DE FIGURAS

O cabeçalho e legendas de figuras devem ser entregues num ficheiro conjunto a parte do texto, em formato Word, mencionando o numero correspondente ao ficheiro de imagem enviado.

G. FIGURAS

As figuras devem ser numeradas de acordo com a sequencia de aparecimento no texto, e enviadas em ficheiros individuais, referenciando o respectivo numero. Apenas são aceites ficheiros em formato .tiff com um mínimo de 300dpi.

SUBMISSAO ELECTRONICA

A submissão electrónica de manuscritos deve ser realizada para:

manuscritos.revista@spcctv.pt

Apenas são consideradas validas as submissões que cumpram as regras anteriormente descritas. Após a submissão, os Editores confirmarão a boa recepção do manuscrito junto do autor correspondente.

MANUSCRITOS ACEITES PARA REVISAO

Os manuscritos revistos devem ser enviados convenientemente titulados – revisão1, revisão2, etc, incluindo novas figures e tabelas caso necessário. Os comentários dos editores e/ou revisores devem ser discutidos ponto a ponto numa carta anexa e as alterações propostas discutidas. As alterações devem ser visíveis utilizando a função “track changes” do Word.