ARTICLE

SUBCRITICAL ARTERIAL LOWER LIMB ISCHEMIA

ABSTRACT:

Introduction: In 1995, John Wolfe referred to a subgroup of patients that suffered from sudden critical ischemia, considering that these patients manifested themselves by changing oxygen requirements at tissue level, and called this stage subcritical limb ischemia. Likewise, he showed that these patients had a lower amputation rate as they had used the medical treatment as opposed to that of critical ischemia.

Aim: To define the subcritical limb ischemia, diagnostic methodology and to recommend surgical medical treatment.

Materials and method: The different procedural guidelines were evaluated, taking into account clinical and diagnostic parameters; evidence-based medicine recommendations were developed.

Results: We define subcritical limb ischemia as the clinical status of occlusive arterial disease, characterized by disabling claudication (generally less than 200 mins), without pain at rest and trophic lesions, with an ankle-brachial index (ABI) higher than or equal to 0.40, ankle pressure > 50 mmHG or O2 pressures in Hallux equal to or higher than 40 mmHg and non-invasive study showing occlusion in both tibial arteries.

Conclusions: Patients with subcritical ischemia constitute a patient group that deserves greater attention than those with stable claudication.

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Firstly, we should inform the rest of the medical community of the clinical characteristics of this stage to detect patients that are included in this group, especially those medical specializations that treat elderly patients.

Palabras Clave: Peripheral arterial disease, subcritical limb ischemia, critical limb ischemia.

INTRODUCTION

The concept of critical limb ischemia[1] attempted to define the terminal stage of the peripheral arterial disease (PAD), whose most characteristic symptoms and signs are pain at rest, trophic lesions and gangrene. In a certain way, this definition tried to join the classifications made by Fontaine (1951)[2] and Rutherford (1980),[3] but, due to statistical reasons and lack of clear evidence in trying to exclude damages caused by diabetic neuropathy, the authors excluded diabetic patients;[1] therefore, in 2014, the Society for Vascular Surgery proposed a new definition based on the so-called WIfI (Wound, Ischemia and Foot Infection),[4] i.e., taking into consideration wound characteristics, ischemia level and foot infection, this being the way to include diabetic patients.

In 1995, John Wolfe[5] referred to a subgroup of patients that suffered from sudden critical ischemia, considering that these patients manifested themselves by changing oxygen requirements at tissue level, and called this stage subcritical limb ischemia. Likewise, he showed that these patients had a lower amputation rate as they had used the medical treatment as opposed to that of critical ischemia. In 2007, White and Rutherford[6] again attempted to redefine this group of patients, as a previous stage of critical limb ischemia, and stressed that, although these patients did not suffer from pain at rest, trophic lesions and tissue gangrene, they had an ankle-brachial index of 0.4, with the patients' advanced age as another relevant element. Different records have associated PAD in elder people with high morbidity and mortality rates.[7-8]

Between 25% and 30% of patients with symptomatic PAD are within this subgroup (higher than critical ischemia). They are obviously considered as population of high cardiovascular risk, as in the other PAD stages.

A recent study (SAGE)[9] shows that there are 14 million patients with PAD in South America (from the published figures, Argentina, Brazil and Colombia represent 76%

of these patients), which will reach 23 million by 2030. Nowadays, patients with critical ischemia represent 1.3 million in this region (79% of them again in Argentina, Brazil and Colombia); therefore, this subgroup under study is deemed to be even greater.

We consider that this kind of patients increasingly requires our professional assistance, and due to this we have redefined clinical characteristics, proposing a differential diagnosis and possible treatments.

DEFINITION

Clinical status of occlusive arterial disease, characterized by disabling claudication (generally less than 200 mins), without pain at rest or trophic lesions, with an ankle-brachial index (ABI) higher than or equal to 0.40, ankle pressure > 50 mmHG or O2 pressures in Hallux equal to or higher than 40mmHg and non-invasive study showing occlusion in both tibial arteries.

CLINICAL EXAMINATION

The essential characteristic is the so-called disabling claudication, which means such pain that prevents the patient from doing minimum tasks, considering it as decisive if it appears at 200 mins or less, comparable with Stage IIb in Fontaine classification[2] or Category 3 or Severe claudication in Rutherford classification.[3]

Several studies confirm that the usual symptomatology of arterial claudication and the typical pain are not always present in patients with PAD. Sometimes, patients suffer from these symptoms but do not look for medical assistance because they consider them typical pains of their age, with the advanced age (octogenarian, nonagenarian people, etc.) as one of the characteristics of this patient group.

In addition, there is still no adequate level of suspicion of this problem within the medical community, leaving out the verification of distal pulses and, in the absence of trophic lesions, little attention is paid.[6]

To further worsen the situation, many patients with a severe PAD walk very little or do not walk at all due to other diseases (osteoarticular pathology, COPD, etc.) or because they are not used to doing so, and make their clinical debut

at a very advanced stage of their disease. Therefore, they are often at the stage of subcritical ischemia.[5-6]

The most affected population is usually that of elderly patients, with other comorbidities (dyslipidemia, severe smoking, diabetes, chronic renal failure (CRDF)[6]. Special attention should be paid to younger women with diabetes, severe smoking and chronic renal failure, as a subgroup of risk.

Patients who have undergone failed previous endovascular or surgical treatments usually remain at a subcritical stage. Regarding hemodynamics and distal blood pressure, these subcritical patients have enough perfusion pressure to keep skin integrity, but in case of (major or minor) trauma, they are not able to reach cicatrization within a period of 3 to 4 weeks.

DIAGNOSIS

Diagnosis does not differ from current PAD guidelines:

Recommendation I[10-11]

a. The ankle-brachial index (ABI) is the first non-invasive study to be performed if a patient is suspected of suffering from subcritical limb ischemia. If the result is doubtful, the post exercise ABI (treadmill) with recommendation of *Grade 1 evidence A* should be added.
b. In patients with diabetes and/or chronic renal failure, the doppler echocardiography is the complementary non-invasive study, confirming the anatomic compromise and subsequent use of contrasted methods such as the angio-tomography/angio magnetic resonance with renal protection and recommendation *Grade 1 evidence B*.
c. We suggest the angiography, if possible with digital substraction, to be prescribed for those patients that will invariably undergo an invasive treatment (whether endovascular, surgical or hybrid) (*Grade 1 evidence B*).

Measuring segmental pressures (including Hallux pressures) is another study that confirms the subcritical stage of the disease.

Each of these methods will be chosen according to the speed and availability of each service. We should not forget that these patients can rapidly evolve to critical ischemia.

We should have a high level of suspicion in the high-risk patients described above.

If we consider the ABI, these patients usually have indexes between 0.4 and 0.7.

Regarding the segmental pressures in Hallux, they are above 50 mmHg.

Due to the seriousness of the clinical picture, such measurements should not delay treatment if they cannot be verified.

TREATMENT

Medical Treatment

After it is confirmed that we have a special group of patients with a large number of associated risks, such as dyslipidemia, arterial hypertension, diabetes, CRF, severe smoking, osteoarthritis, obesity, heart disease, cerebrovascular atherosclerotic disease, etc., initial treatment seeks to stabilize and treat all the above-mentioned factors. However, we should recognize that it is a group of high risk of morbidity and mortality at a subcritical stage, which means that we cannot ignore this special feature hoping that, only with the improvement of the observed risk factors, we will be able to modify their situation. Therefore, we should regularly control the patient by modifying the different treatments as needed and individually adjust them according to the patient's needs.[10-11]

The treatment for patients without critical ischemia usually consists of the control of risk factors, the use of statins, antiplatelet therapy, oral vasodilators, and walking exercises (better if supervised) for a period of 60 days. According to the response, the same treatment is continued or a more invasive treatment is implemented.

During the subcritical stage, patients are restrained by pain and there is an imminent risk of developing critical ischemia (pain at rest and/or trophic lesions). Therefore, treatment should be quick and effective, without any delay or therapeutic test period, as at the critical ischemia stage. Recognizing that revascularization is the best treatment, we should adapt to each patient's risks.

High-risk patients (diabetes, chronic renal failure or congestive cardiac insufficiency), or those who cannot be revascularized by surgical or endovascular means, first will

receive medical treatment and then they will receive invasive treatment only upon failure of the former.

Recommendation II[10-11]

a) We recommend to stop smoking habits with the assistance of multidisciplinary teams (*Grade 1 Evidence A*).
b) Aggressive treatment of dyslipidemia with statins (*Grade 1 Evidence A*).
c) Levels of glycosylated hemoglobin (Hb G) < 6.5 (*Grade 1 Evidence B*).
d) Antiplatelet therapy with acetylsalicylic acid (ASS) 75 to 325 mg/day (*Grade 1 Evidence A*).
e) Use of clopidogrel as an alternative to ASS or in combined therapies, in patients with history of PAD or another arterial line, 75 mg/day (*Grade 1 Evidence B*).
f) Use of cilostazol of progressive application reaching 200mg/day in those patients without congestive heart failure (*Grade 2 Evidence A*).
g) Use of pentoxifylline in those cilostazol-intolerant patients or to whom it is contraindicated, up to 400 mg/ 3 times a day (*Grade 2 Evidence B*).
h) We recommend the implementation of supervised walking exercises in triweekly walking sessions for 30 to 60 mins (*Grade 1 Evidence A*).

Pain management

This topic is developed in the Vascular Pain Management chapter.

USE OF PROSTAGLANDIN

The use of prostaglandin is deemed a medical treatment option. Although such use has not been supported yet by the Food and Drug Administration (FDA), many European and Asian publications confirm its usefulness in patients with critical limb ischemia. Considering that perhaps such a use in this patient group would have a better outcome since they are at a less severe stage, and especially for those patients that cannot be revascularized or have surgical high risk, intravenous E1 prostaglandin treatment is the best option.

Recommendation III[12-13-14]

Use of intravenous prostaglandin of up to 80 ug/day for 21 consecutive days, (*Grade 2 Evidence B*).

Revascularization

We consider it important in the defined patient group to exhaust medical treatment scopes. In case it does not improve the patient's symptoms after a period of 90 to 120 days (disabling claudication), we should choose the most appropriate therapeutic invasive method (endoluminal, open or hybrid surgery). This will depend on a detailed evaluation of each clinical case, considering the anatomy of the occlusive lesions, the available means and the experience of the intervening team.[10-11-15]

We should take into consideration that, in those patients with lumbar spine arthritis, coxofemoral joint compromise, severe ischemic cardiopathy, unstable heart failure, morbid obesity, stroke or advanced renal failure, invasive treatment will not have any benefit or great changes with respect to claudication, increasing the risk of morbidity and mortality.[11]

Some reports[5-6] show that patients at subcritical stages experienced better results with invasive treatments than those patients suffering from critical limb ischemia. Also, we know that we generally find lesions that compromise more than one arterial line, making it difficult to choose the strategy to be followed,[15] considering the need of inflow and outflow permeability, regardless of the invasive treatment chosen.

Recommendation IV

a) We recommend the invasive treatment for patients in whom the medical treatment has failed and the benefits of the treatment to be used exceed the possible risks of the selected procedure (*Grade 1 Evidence B*).

DISCUSSION

Pursuant to the paper by Wolfe and Wyatt,[5] in comparing two patient groups, one with critical ischemia and the other with subcritical ischemia, it was found that, although in both groups there was a mortality rate of 26% regardless of the treatment used, in the subcritical ischemia group, 27% of patients with medical treatment did not show any progress (Fig. 1), given that, in 1997, the benefits of cilostazol, coupled with antiplatelet therapy, management of statins and effectiveness of programmed walking sessions had not been proven. Also, the definition of critical ischemia was not interpreted as it is today.[4]

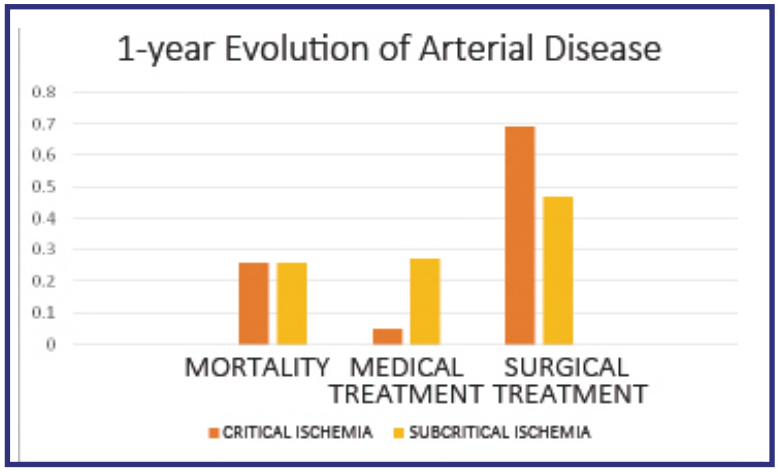

Fig 1: Modifed chart of Wolfe JHN and Wyatt MG.[5]

Considering the natural history of patients who generally suffer from intermittent claudication and only receive medical treatment over five years, the Guidelines of ACC/AHA[16] show that 20% - 30% of patients progress to disabling claudication and only 1% - 3% progress to critical ischemia; the population that is really at a subcritical stage but is not assessed should be considered (Fig. 2).

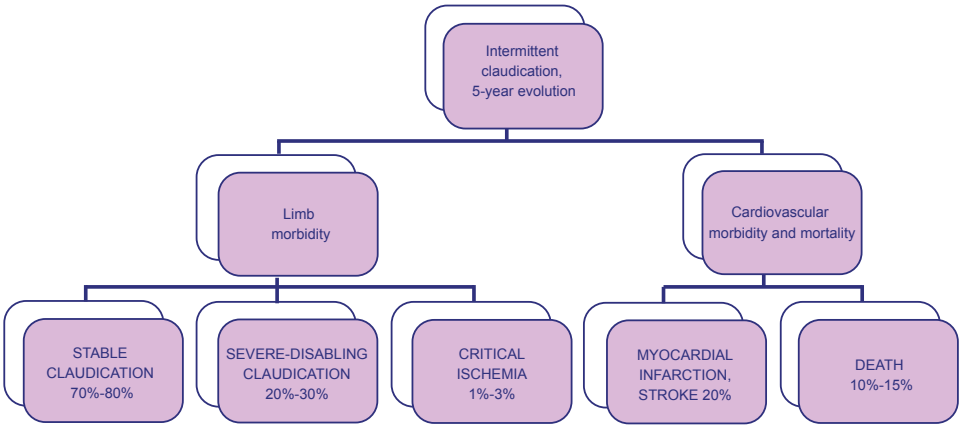

Fig.2 Modified chart of Hirsch AT, Haskal ZJ, Hertzer NR, ACC/AHA 2005.[16]

According to the foregoing, we consider subcritical limb ischemia as a stage suffered by a substantial number of patients and is underestimated. Also, as we have already mentioned, the population with arterial limb diseases in Latin American countries is increasing,[9] as well as the age of the population in our countries, meaning that subcritical limb ischemia may affect a larger number of patients.

Taking into account that in Fontaine[2] and Rutherford[3] classifications this stage is not clearly defined, we propose to create a new one.

Peripheral arterial disease classification of the III End of the World Intersocieties Consensus (EWIC)

Although the existence of these patients has always been recognized, they were never classified as another category within traditional classifications.

If we consider Fontaine classification,[2] patients would be Stage IIb; if we consider Rutherford classification,[3] patients would be Grade 3.

Therefore, we propose the following Peripheral arterial disease classification, taking into consideration symptoms (claudication severity), ankle-brachial index, O2 partial pressure of the affected foot toe, ankle systolic pressure and existence of trophic lesions and/or gangrene, thus defining four stages: (Chart 1)

Stage 1: Asymptomatic peripheral arterial disease.
Stage 2: Intermittent claudication.
Stage 3: Subcritical limb ischemia.
Stage 4: Critical limb ischemia.

STAGES	A/B Index	Claudication	PO2mmHg	Ankle Systolic Pressure	Trophic Lesions
1 Asymptomatic PAD	>0.8	> 600 m	> 60 mmHg	>100 mmHg	-
2 Intermittent Claudication	0.8-0.6	600 -200 m	60-40 mmHg	70-100 mmHg	-
3 Subcritical Limb Ischemia	0.6-04	</= 200 m	40-30 mmHg	50-70 mmHg	-
4 Critical Limb Ischemia	< 0.4	Pain at Rest	< 30 mmHg	< 50 mmHg	8,348

Chart 1: PAD classification of the III EWIC.

CONCLUSIONS

Patients with subcritical ischemia constitute a patient group that deserves greater attention than those with stable claudication. Firstly, we should inform the rest of the medical community of the clinical characteristics of this stage to detect patients that are included in this group, especially those medical specializations that treat elderly patients.

If we could compare ischemic cardiopathy with PAD patients, we would establish the following groups: those suffering from stable angor/intermittent claudication v. minimum effort angor/ subcritical ischemia v. unstable angor/critical ischemia.

Perhaps the assistance and control of these patients would allow early detection of patients with critical ischemia, thus reducing morbidity and mortality rates. Also, the definition of this patient group allows to better assess the different treatments that are applied currently.

Considering that the expected outcomes are better than those in critical patients. ■

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