Peripheral arterial occlusive disease and *ischemic disease of the lower limbs* are not the same condition. A proposed unambiguous Italian terminology for defining *Peripheral arterial disease of lower limbs* and related clinical/therapeutic implications

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Definition of *peripheral arterial disease*: not just a semantic problem

According to the American College of Cardiology/American Heart Association (ACC/AHA) Practice Guidelines,[1] peripheral arterial disease (PAD) encompasses a range of non-coronary arterial syndromes that are caused by the altered structure and function of the arteries that supply the brain, visceral organs and the limbs. Several pathophysiological processes can contribute to the formation of stenoses and aneurysms of the non-coronary arterial circulation, but atherosclerosis remains the main process affecting the aorta and its branches. The term PAD thus encompasses a large series of disorders affecting arterial districts excluding the coronary arteries, such as the aorta, renal and mesenteric arteries, carotid arteries, and arteries of the lower extremities.

The first consideration that we want to make concerns the peculiarity in the choice of defining every arterial bed that is *non-coronary* as *peripheral*. In our opinion this semantic choice, which is anatomically and physiologically questionable, testifies to and reveals the lack of consideration still reserved to non-coronary vascular syndromes, helping to not keep the real clinical impact of these hidden.

In the holistic (internistic) view, a patient suffers from *multi-morbidity* and not from *co-morbidity*: the latter term implies a hierarchy limiting the physician to manage the emerging condition first, while taking account of other conditions. However, the term used should not indicate a supposed hierarchy of importance of several diseases from which the patient, in his/her complexity, is suffering.

It is no longer hierarchically acceptable, especially in scientific nosography, to assign the coronary district a position of *centrality*, and relegate all other arterial ischemic syndromes a marginal (*peripheral*) role. Thus, while the cardiologist has the great merit of bringing his discipline to the highest levels of knowledge and ability in taking care of patients, other specialties were not so able to obtain similar attention, clinical pathways and possibilities of treatment for the different arterial syndromes. Because of this lack of attention, conditions such as PAD of the lower limbs remain *orphan* diseases, despite being major causes of acute and chronic illness, being associated with impairments in functional capacity and quality of life, leading to limb amputation and increasing the risk of death.

The term *peripheral arterial occlusive disease* is used in a manner analogous to that of PAD, although it excludes the functional (vasoreactive) and aneurysmal disorders. *Lower extremity arterial disease* only includes disorders that affect the arteries of the legs, and this term does not underline or stress the ischemic phenomenology in tissues. *Arteriosclerosis obliterans* includes those arterial diseases that are defined by the process of atheroma formation and calcium deposition in the arterial wall, but without referring to the concept of clinical expression or a syndrome, and *atherosclerotic vascular disease* includes any arterial disease that has an atherosclerotic origin and is not, therefore, limited to the legs. It should also be noted that neither of these two terms and conditions takes into account the

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possibility of vasculitic inflammatory forms, mainly *Buerger's thromboangiitis obliterans*, a non-atherosclerotic vascular disease characterized by segmental vascular inflammation, vaso-occlusive phenomena, and involvement of small- and medium-sized arteries and veins of the upper and lower extremities.

Proposal of an unambiguous Italian terminology

The Italian term usually used to refer to *peripheral arterial disease of lower limbs* is *arteriopatia obliterante periferica* [*peripheral arterial occlusive (or obliterative) disease*], although this terminology has the intrinsic limitation of shifting the focus only onto an obliterative process (mainly atherosclerotic, but also inflammatory) involving the arterial axis; moreover it is only used to refer to lower limb involvement (while PAD, although by the above-discussed questionable definition, encompasses any disorders affecting any arterial districts except the coronary arteries). Finally, this term, in itself, does not give enough emphasis to the concept of a disease or syndrome. So the term *peripheral arterial occlusive disease* seems to translate adequately only to the concept of *arteriosclerosis obliterans of the lower limbs*, which is limited to underlining the anatomical and pathological involvement of the arterial axis rather than the ischemic consequences of this in a patient.

In our opinion the Italian term *arteriopatia obliterante periferica* (and related condition) does not refer exactly to the same situation represented by *ischemic disease of the lower limbs (malattia ischemica degli arti inferiori)*, the term that we propose should be preferentially adopted when referring to a clinical syndrome that usually results from the first condition with the interaction of other determinants, primarily co-morbidities.

Towards a Copernican revolution in our way of approaching the problem

We must, therefore, put the concept of *ischemic disease of the lower limbs* at the center of our attention, that is, we must focus on the patient and clinical expression of the illness, and shift *peripheral arterial occlusive disease* among the key factors, such as co-morbidities, individual predisposition, and personal capacity of metabolic adaptation to ischemia. *Peripheral arterial occlusive disease* is surely a necessary, and perhaps even the most important, contributor to the development of ischemic disease of lower limbs, but alone it is not sufficient, it is not the only determining factor, and it is not the same condition (Figure 1).

In a similar way we classify *obstructive coronary atherosclerosis* on one side and *ischemic heart disease* on the other.[2]

Having focused our attention for a long time only on the concept of *peripheral arterial occlusive disease*, this led us to believe that the solution to the problem was always to be found in the recanalization of the diseased vessel, and for that reason several specialties have usually taken charge of this kind of patient, without adequately managing any other associated co-morbidity. Current guidelines[3] bear witness to this way of understanding and treating the condition: recommendation 22 of TransAtlantic Inter-Society Consensus (TASC) II asserts that patients with critical limb ischemia (CLI) should be referred to a vascular specialist early in the course of their disease to plan for revascularization options, and recommendation 24 affirms that revascularization is the optimal treatment for patients with CLI.

This has led to the suggestion that pharmacological therapy with prostanoids, so far the only pharmacological agents convincingly shown to have a positive influence on the prognosis of CLI patients, is proposed only as a second therapy, when the patient is not susceptible of revascularization. This aspect is emphasized in the 9th edition of the American College of Chest Physicians (ACCP) guidelines,[4] that suggest limiting the use of prostanoids in addition to previously recommended antithrombotic therapies only to patients with symptomatic PAD and CLI/rest pain who are not candidates for vascular intervention.

But is this always true and does it always represent the most correct approach to a patient affected by ischemic disease of the lower limbs?

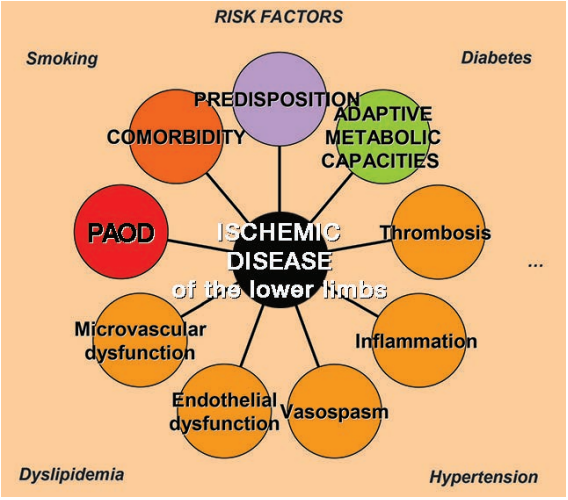

Figure 1. ***Peripheral arterial occlusive disease*** **(PAOD) and** ***ischemic disease of the lower limbs*** **- towards a Copernican revolution.**

Critical limb ischemia: not only a problem of arterial stenosis

Only approximately 20% of patients with PAD have leg-specific symptoms of claudication or CLI.[5]

Patients with intermittent claudication have sufficient blood flow at rest (and, therefore, have no limb symptoms), but with exercise occlusive lesions in the arterial lower limb bed limit the required increase in blood flow, resulting in a mismatch between the supply of oxygen and nutrients and the metabolic demand of tissues (mainly muscle). Acquired metabolic abnormalities in the muscles of the lower limbs also contribute to the reduced exercise performance, while regular exercise enables improved performance through a phenomenon of ischemic preconditioning. In CLI the mismatch is critical also at rest, and rest pain and trophic lesions appear; CLI patients also develop microcirculatory defects including endothelial dysfunction, altered hemorheology, white blood cell activation and inflammation, and maldistribution of the cutaneous microcirculation. The term CLI should be used only for patients with chronic ischemic disease, defined as symptoms present for more than 2 weeks (chronic ischemic rest pain, ulcers or gangrene) and attributable to objectively proven arterial occlusive disease. Thus, the term CLI implies chronicity and must be distinguished from acute limb ischemia (ALI), a condition caused by a sudden decrease in limb perfusion. The presentation of ALI is normally considered to occur within 2 weeks following the acute event. It is noteworthy that we often witness syndromes of *acute-on-chronic ischemia*, whose differential diagnosis from CLI is often difficult to make, since it is often based only on a temporal concept and it may not even be particularly significant from the point of view of the correct therapeutic choices.

CLI is usually caused by multilevel arterial occlusive disease (that is, *peripheral arterial occlusive disease*), sometimes triggered by rupture, destabilization or thrombosis of an atheromatous lesion, but in some cases the hemodynamic consequences of stable arterial lesions may be triggered and compounded by a critical decrease of perfusion, such as in a condition of decreased cardiac output, or by severe hypoxemia consequent to respiratory failure, or by anemia. In these cases, the solution for rebalancing the critical mismatch between supply capacity and metabolic demand must obviously be sought primarily in the management of the disease triggering the mismatch, not in the revascularization options of the stenotic, but stable, arterial axis. In brief, alleviation of the heart failure, treatment of the respiratory system, or restoration of the red cell mass is the only rational intervention for this kind of CLI.

The difference between the various situations, acute, acute-on-chronic, and progression towards critical ischemia, is not always easy to understand; what is important is to be able to determine which pathogenic situation should be tackled first in a given patient.

Vasospasm can also trigger critical mismatching and in this case a targeted pharmacological intervention is the most appropriate treatment. It should also be appreciated that inflammatory forms affecting the arteries respond better to medical treatment than to surgery.

So the statement that CLI patients should always be revascularized, and prostanoids should be limited only to patients unsuitable for revascularization, is not necessarily always correct: the concept of *revascularizability* should be initially applied to the patient, object of a holistic (internistic) assessment, and only after the judgment on eligibility been expressed for the single patient, should it be extended to include the technical feasibility of an adequate interventional approach to the stenotic arterial axis.

A key concept in this discussion is that when the chronic ischemia progresses towards the later stages (CLI), the vascular lesions may be progressing (that is, *peripheral arterial occlusive disease*), but on the other hand it may be that there is failure of the microcirculatory response, cytoprotective mechanisms and metabolic adaptation to ischemia. Co-morbidity often prevails as a precipitating factor and is the main, indeed only, problem to solve in order to save the limb from amputation. CLI represents a condition of the patient, not of his or her arterial bed.

Kinlay[6] masterfully stresses that the anatomic endpoints (such as degree of lumen narrowing and restenosis) adopted in most clinical studies on surgical interventions are arguably surrogate parameters because they do not directly affect function but rather are related to mechanisms that might affect function. In studies of PAD patients not receiving revascularization, the ankle-brachial index (ABI), a measure integrating the impact of all stenoses in a limb, is poorly associated with function.[7,8] Although measures of plaque burden correlate with walking distance, improvement in function can occur with exercise training despite no change in ABI.[9-11] Other factors, such as the development of collateral vessels and improvements in endothelial function and skeletal muscle bioenergetics may maintain function in the presence of arterial restenosis or occlusion. Thus, improving blood flow by revascularization usually has a major effect on symptoms and tissue healing, but the degree of restenosis reflects only one parameter related to the durability of these outcomes.

Overall management of CLI must, therefore, be based on an improved understanding of pathophysiology in the individual patient. Medical treatment with prostanoids acts strongly on the mechanism of adaptation to ischemia, while surgery acts exclusively on vas-

cular lesions. Antithrombotic therapies certainly act on the progression of vascular lesions and the stabilization of atheromas, but antiplatelet therapy is indicated in individuals with symptomatic, atherosclerotic, lower extremity PAD, including those with intermittent claudication or CLI, prior lower extremity revascularization or prior amputation for lower extremity ischemia, to reduce the risk of myocardial infarction, stroke and vascular death, in other words to improve their overall prognosis,[12] and not for aims of local stability.

Since 2000, the TASC guidelines[13] have highlighted that the ideal treatment for CLI is elimination or bypassing of occlusions in the larger arteries, although this is often impossible or fails. An alternative in these cases is to try to modify or modulate, by some forms of pharmacotherapy, the consequences of the low perfusion pressure on the distal microcirculation sufficiently to reverse the rest pain and avoid amputation. So the TASC guidelines state that patients who have a viable limb in whom revascularization procedures are impossible or have a poor chance of success or in whom such procedures have previously failed, and, in particular, when the alternative is amputation, may be treated with prostanoids.

Conclusions

Although *peripheral arterial occlusive disease* is the underlying and principal defect causing the ischemic phenomenon, the low tissue perfusion pressure provokes a number of complex local microcirculatory responses, which may contribute, sometimes in a decisive manner, to pain and trophic lesions. Therefore, although the primary treatment must often be surgical or endovascular correction of the *peripheral arterial occlusive disease*, pharmacological attempts to manipulate and normalize the microcirculatory changes and adaptive metabolic capacities to ischemia may enhance the results of revascularization and may be an effective option in patients in whom revascularization is impossible or has failed or is not, at that particular time, the best strategy for the management of the individual patient.

Prostanoids mainly act on adaptive metabolic capacities to ischemia and so far the only pharmacological agent that has been convincingly shown to have a positive influence on the prognosis of CLI patients is iloprost.[14] Thus, without being an alternative to revascularization, iloprost should be used: in every patient unsuitable for revascularization; in every patient suitable for revascularization as adjuvant therapy (both pre-and post-operatively, using different infusion schemes[15]); preferentially in the early stages of critical ischemia, when the damage is limited and not irreversible; in CLI patients who cannot be revascularized *immediately*, because of the limited prospects of success of the vascular rehabilitation (poor peripheral run-off, high risk of peri-operative complications, previously failed interventions), the advanced age of the patient and/or significant co-morbidities (cancer, severe congestive cardio-respiratory failure, renal failure, etc.); and in situations in which the surgical and/or endovascular procedures can be postponed without further damage to the patient.[16]

Thereafter, the favorable impact of prostanoid treatment on prognosis may have consequences on the choice of revascularization approach, because for patients with limb-threatening lower extremity ischemia and an estimated life expectancy of 2 years or less or patients for whom an autogenous vein conduit is not available, it is reasonable to perform balloon angioplasty when possible as the initial procedure to improve distal blood flow, while for patients with an estimated life expectancy of more than 2 years, it is reasonable to perform bypass surgery, when possible and when an autogenous vein conduit is available, as the initial treatment to improve distal blood flow.[12]

In conclusion, diagnostic and therapeutic strategies should always be focused on the patient and on the ischemic disease in his or her legs (*ischemic disease of the lower limbs*), rather than only on obstructive atherosclerosis (*peripheral arterial occlusive disease*). An integrated, interdisciplinary approach is the ideal strategy for controlling cardiovascular risk factors and co-morbidities. If we put the patient affected by ischemic disease of lower limbs at the center of our attention, we will reach a better understanding of the disease expressed by our individual patient and it will be easier to recognize the main emerging causative factor of the critical ischemic mismatch on which we must act. It will then be possible to develop many therapeutic strategies.

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