Part II

Definition, terminology, pathophysiology and hemodynamical aspects

Definition and Terminology

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Defining critical limb ischemia (CLI) has been and it is an extended and tiring work.
From 1981 (1), when the term "critical leg ischemia" has been coined, to 2000 when T.A.S.C. (Trans Atlantic inter Society Consensus on the management of peripheral arterial disease) (2) has established the ultimate criteria for CLI, several attempts at a precise definition of this disease have been advanced, different modifications of the originally suggested criteria have been proposed, then adopted and tested in clinical studies and trials.

It is obviously important to have objective (hemodynamic) and uniform standardized criteria for distinguishing and/or presenting the different levels of ischemia, requiring different management strategies (3).

Indeed, without this standardization it is impossible to compare the results of different treatment's procedures, particularly the limb salvage rates and mortality (i.e. loss of life or limb).

Even though the concept of CLI is now accepted, with time some authors (4) have expressed negative opinions about certain of these criteria.

Additionally, it has been pointed out the necessity of reconsidering the terminology routinely reported in clinical studies and trials, first of all the definition used of CLI.

Thus, the T.A.S.C. (2) ultimately has underlined that the "...term CLI should only be used in relation to patients with chronic ischaemic disease", i.e. the term "chronic critical ischemia" (CCI).

In this chapter, we report the definitions of CCI presented with time and their development, underlining the problems with these recent definitions and specifying the meaning of the terms used.

Development of criteria for CLI

In 1954, Fontaine et al. (5) have proposed a simple classification of ischemia, defining four stages based on clinical symptoms.

Stages III and IV, respectively rest pain and tissue loss (ulcers and limited gangrene), can represent the critical ischemic stage (6,7).

However, the cases classified as Fontaine III e IV includes "a whole spectrum of patients, from those with wild, easily controlled rest pain to patients with extensive gangrene of the foot, in whom there is no alternative to an early major amputation" (2).

For this reason, several attempts have been made to establish objective criteria for separating patients with CCI (Table I).

In 1981, an International Vascular Symposium working party in London (1), defining the concept of "limb

TABLE I

Year	Definition and criteria for CCI
1981	International Vascular Symposium working party (1)
1986	SVS/ISCVS ad hoc committee (8)
1989	First European Consensus on CCI (16)
1991-1992	Second European Consensus on CCI (6,7)
1997	Recommended standards for reports dealing with lower extremity ischemia (13)
2000	Trans Atlantic inter Society Consensus on the management of peripheral arterial diseases (2)

TABLE II
International Vascular Symposium working party definition (1)

√ Severe rest pain impairing sleep and requiring analgesia for at least 4 weeks

and either

√ Ankle systolic Doppler pressure < 40 mmHg

or

√ Ankle systolic Doppler pressure < 60 mmHg in the presence of tissue necrosis or digital gangrene

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threatening ischemia" (i. e. a grade of ischemia which in the absence of any revascularisation's procedure can require a major amputation), has coined the term critical ischemia and has suggested the hemodynamic criteria showed in Table II.

It is important to underline that, with these criteria, the Authors (1) have excluded patients with diabetes, affirming that they should be grouped separately in view of the complexity of their ischemic/septic status.

Thus, dealing with diabetics, in 1986 an ad hoc committee on reporting standards of the Society for Vascular Surgery (SVS) and the North American Chapter of the International Society of Cardiovascular Surgery (ISCVS) (8) has reconsidered the criteria of 1981 suggesting to estimate also the toe pressure and transmetatarsal or digital plethysmography (Table III).

Published both in 1991 (7) and 1992 (6), the final document of Second European Consensus on CCI has proposed the same hemodynamic criteria (Table IV) for all patients, both ischemic rest pain and non healing foot lesions.

Many authors (9,10,11,12), and more recently Rutherford (3), have underlined that these criteria did not clearly discriminate the two groups of patients because the common hemodynamic parameters are too high for ischemic rest pain and too low for foot lesion healing.

This last author has published in 1997 (13) a revised version of the standards suggested in 1986, defining a clinical categorization of chronic limb ischemia (Table V).

TABLE III
SVS/ISCVS ad hoc committee definition (8)

√ Ischemic rest pain

and either

√ Ankle systolic Doppler pressure < 40 mmHg
√ Toe systolic Doppler pressure < 30 mmHg
√ Flat or barely pulsatile ankle or metatarsal plethysmography

or

√ Minor (pedal) or major (above transmetatarsal level) tissue loss
√ Ankle systolic Doppler pressure < 60 mmHg
√ Toe systolic Doppler pressure < 40 mmHg
√ Flat or barely pulsatile ankle or metatarsal plethysmography

TABLE IV
Second European Consensus on CCI (6,7)

√ Ankle systolic Doppler pressure < 50 mmHg
√ Toe systolic Doppler pressure < 30 mmHG

and

√ Severe rest pain requiring opiate analgesia for at least 2 weeks

or

√ Non-healing ulcer or gangrene

TABLE V
Recommended standards for reports dealing with lower extremity ischemia: revised version (13)

Grade	Cat.	Clinical description	Objective criteria
0	0	Asymptomatic – no hemodynamically significant occlusive disease	Normal treadmill or reactive hyperemia test
	1	Mild claudication	Completes treadmill exercise* AP after exercise >50mmHg but at least 20mmHg lower than resting value
I	2	Moderate claudication	Between category 1 and 3
	3	Severe claudication	Cannot complete standard treadmill exercise* AP after exercise <50mmHg
II	4	Ischemic rest pain	Resting AP <40mmHg Flat or barely pulsatile ankle or metatarsal PVR Toe pressure <30mmHg
III	5	Minor tissue loss – nonhealing ulcer, focal gangrene with diffuse pedal ischemia	Resting AP <60mmHg Flat or barely pulsatile ankle or metatarsal PVR Toe pressure <40mmHg
	6	Major tissue loss – extending above TM level, functional foot no longer salvageable	Same as category 5

Legend: AP, Ankle pressure; PVR, pulse volume recording; TM, transmetatarsal ... , CCI

** Five minutes at 2 mph on a 12% incline*

Deriving objective criteria from SVS/ISCVS definition, this revised version show a subdivision of patients in 7 categories, to use in clinical trials and investigations, and in 4 grades which represent a kind of revised version of the Fontaine's classification (Table 5).

In this plan, grades II and III, categories (4, 5, 6), represent the CCI stages (13).

In 2000, the T.A.S.C. document (2) has ultimately explained that the term critical limb ischemia implies chronicity and "should be used for all patients with chronic ischemic rest pain, ulcers or gangrene attributable to objectively proven arterial occlusive disease" (Recommendation 73).

It has been suggested (2) that, to achieve this, it is necessary to use some hemodynamic criteria showed in Table VI.

TABLE VI
Trans Atlantic inter Society Consensus (2) Recommendation 74

either
√ Ankle systolic Doppler pressure < 50 – 70 mmHg
or
√ Toe systolic Doppler pressure < 30 – 50 mmHG
or
√ Transcutaneous partial pressure of oxygen < 30 – 50 mmHg

Both SVS/ISCVS revised version (8) and T.A.S.C. document 2 have pointed out the importance of using a proper and univocal terminology in the management of patients with CCI.

This topic will now be discussed.

Terminology

It is necessary to include this short paragraph because a number of terms requires definition and clarification.

Claudication means extremity pain, discomfort or weakness that is consistently produced by the same muscular activity and that is promptly relieved by cessation of that activity (13).

This clinical description distinguishes patients with CCI from those with intermittent claudication alone.

In effect, in claudicants the tissue ischemia is in the muscle and is intermittent; these patients haven't circulatory deficit or symptoms except when they exercise.

The severity of claudication can be related to time and distance walked only if speed and incline grade are standardized.

However, stratifying patients by walking distances using a standardized treadmill protocol is appropriate first of all for clinical trials (13).

The term ischemic rest pain indicates diffuse pedal ischemia (14).

It is a severe pain not controlled by analgesics that is localized to the forefoot and toes or, if more proximal, includes these distal parts (13).

Nonhealing ischemic ulcer it's a term that implies, regardless of initial cause, an insufficient arterial perfusion to support the inflammatory response required for healing (13).

The term limb salvage is commonly applied prospectively to indicate salvage of the foot, but this result can be determined only retrospectively (13).

It is most indicated to use this term only for therapeutic outcome, specifying however that the meaning of this word changes according to the level of ischemia of patient.

In fact, a revascularization procedure in a patient with established tissue loss, wich demands a minor amputation to heal, should be qualified as a success and thus a limb salvage procedure (13).

In that case, what is the meaning of the term minor amputation?

It requires the preservation of a sufficiently functional foot remnant to allow standing and walking without a prosthesis (i. e. toe or transmetatarsal amputations) (13).

The term primary patency is related to a graft which has had uninterrupted patency with either no procedure performed on it or a procedure (i.e. transluminal dilatation or a proximal or distal extension to the graft) performed for progression of the disease in the adjacent native vessel (13).

Thus, the only exceptions that do not disqualify the graft for primary patency are procedures performed for disease beyond the graft and its two anastomoses (13).

In that case, it has been also suggested (15) that it is possible to use the designation assisted primary patency.

All the procedures performed after occlusion of the graft (i.e. thrombectomy, thrombolysis, transluminal angioplasty) and/or any revision or reconstruction of the graft itself or of its anastomoses must be listed under the term secondary patency (13).

Contemporary, it has been suggested (13) that it is important to identify the terms primary and secondary operation or procedure.

A primary operation is the first of a given type ever performed on a particular arterial segment (13).

Subsequent operations, or other revascularization procedures of the same type, performed on the same arterial segment are named secondary (13).

In this group, it is necessary to distinguish between revisions and redo procedures (13).

In a revision, there is a preservation without significant modification of all or most of the graft or reconstructed segment (13).

A redo implies replacement or bypass of all or most of the graft or reconstructed segment (does not preserve at least the majority of the previous graft and one of its anastomoses) (13).

If a graft has lost its patency, it is correct to use the term failed graft (13).

On the contrary, if a graft is still demonstrably patent but has developed one or more stenoses that may lead to thrombosis, it is necessary to use the term failing graft (13).

Finally, it is important to specify the meaning of the term chronic subcritical ischemia.

This designation identifies a particular subgroup of patients with peripheral arterial disease, with perfusion pressures between 60 mmHg (required for healing) and 40 mmHg (associated with ischemic rest pain), but completely asymptomatic and thus not covered by current definition and criteria for CCI (2).

In effect, these patients are sedentary and therefore do not claudicate but they represent a high-risk group of patients that may benefit from preventive measures and need to be followed-up closely to detect the development of manifestations of CCI (2).

Problems with current definitions and criteria for CCI

Recently (2), it has been underlined that four types of problems arise from the definitions and criteria suggested for CCI.

They are summarized in Table VII.

Using objective criteria may be justified first of all in trial protocols but it is suggested (2) that these criteria are of limited use and utility for clinical management of individual patients.

TABLE VII
Problems with current definitions and criteria for CCI

√ Impossibility of defining prospectively a group of patients who will require a major amputation.
√ The division of patients with CCI between subgroups is arbitrary and of little utility in the clinical management.
√ All post-Fontaine definitions of CCI using arbitrary objective criteria exclude some patients with rest pain or ulcers.
√ It is not known what would happen to a patient with severe leg ischemia in the absence of treatment.

REFERENCES

(1) JAMIESON C. *The definition of critical ischemia of a limb.* Br J Surg 1982; 69 (Suppl): S1.

(2) ANONYMOUS. *Management of peripheral arterial disease (PAD). TransAtlantic inter-Society Consensus (TASC).* Eur J Vasc Endovasc Surg 2000; 19 (6, Suppl. A) : S1-S250.

(3) RUTHERFORD R. *The definition of critical limb ischaemia: advantages and limitations.* In: *Critical Limb Ischaemia*, Branchereau A and Jacobs M eds., New York 1999, Futura Publishing Company Inc., Armonk, NY, pp. 1-9.

(4) EARNSHAW JJ. *Neurological deficit more reliable than doppler.* Eur J Vasc Surg 1991; 5 : 106-107.

(5) FONTAINE R, KIM M, KIENY R. *Die chirurgische behandlung der peripheren durch-blutungsstörgen.* Helvetia Chirurgica Acta 1954; 5/6: 199-533.

(6) ANONYMOUS. *Second european consensus document on chronic critical leg ischaemia.* Eur J Vasc Surg 1992; 6 (Suppl. A): 1-32.

(7) ANONYMOUS. *Second european consensus document on chronic critical leg ischaemia.* Working group on critical chronic ischemia. Circulation 1991; 84 (suppl. 4): 1-26.

(8) ANONYMOUS. *Suggested standards for reports dealing with lower extremity ischaemia.* Prepared by the Ad hoc Committee on reporting standards, Society for Vascular Surgery/North American Chapter, International Society for Cardiovascular Surgery. J Vasc Surg 1986; 4: 80-94.

(9) KROESE AJ, STRANDEN E. *How critical is chronic critical leg ischemia?* Ann Chir Gynaecol 1998; 87: 141-144.

(10) THOMPSON MM, SAYERS RD, VARTY K. *Chronic critical leg ischaemia must be redefined.* Eur J Vasc Surg 1993; 7: 420-426.

(11) TYRREL MR, WOLFE JH. *Critical leg ischaemia: an appraisal of clinical definitions.* Joint Vascular Research Group. Br J Surg 1993; 80: 177-180.

(12) MATZKE S, OLLGREN J, LEPÄNTALO M. *Predictive value of distal pressure measurements in critical leg ischemia.* Ann Chir Gynaecol 1996; 85: 316-321.

(13) RUTHERFORD R, BAKER JD, ERNST C, JOHNSTON KW, PORTER JM, AHN S, JONES DN. *Recommended standards for reports dealing with lower extremity ischemia: revised version.* J Vasc Surg 1997; 26 (3): 517-538.

(14) CRANLEY JJ. *Ischemic rest pain.* Arch Surg 1969; 98: 187-188.

(15) RUTHERFORD R. *Regarding "Suggested standards for reports dealing with lower extremity ischemia [letter reply]."* J Vasc Surg 1988; 7: 718.

(16) DORMANDY JA, MAHIR MS, ASCADY G. *Fate of the patient with chronic leg ischaemia. European consensus on critical limb ischaemia.* Lancet 1989; I 737-738.

Pathophysiological and Hemodynamical Aspects

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Although the peripheral arterial diseases, or macrocirculation's lesions, represent the principal defect in patients with critical lower limb ischemia, the low tissue perfusion pressure produces a series of complex local microcirculatory responses, which are the ultimate cause of the rest pain and trophic changes.

It is possible to explain these local processes as an inappropriate response of the microcirculation, particularly of its flow regulatory mechanisms.

The principal result is a series of vicious cycles.

Thus, although the aim of the treatment must be the correction of the peripheral arterial diseases, it is possible to enhance the results of revascularization's procedures modifying pharmacologically the changes of microcirculation.

Furthermore, the pharmacological treatment may represent the best option in patients in whom revascularization is impossible or has failed.

Like all systems that depend on fluid transport, the arterial circulation of the lower limb behaves in accordance with well-defined but sometimes complicated physical principles.

The aim of this chapter is to present a brief account of the current knowledges of pathophysiology and haemodynamics of critical limb ischemia.

Simplifying, we distinguish pathophysiology of macro- and micro-circulation, understanding nevertheless the complex interaction between these two aspects of the same disease.

Atherosclerosis: inflammation, infection and macrocirculatory compensation mechanisms

In patients with critical limb ischemia (CLI), the macrocirculatory defect is atherosclerosis (1).

Epidemiological studies have revealed a number of independent risk factors associated with this disease, such as smoking, hypercholesterolaemia, hypertension and diabetes mellitus, but more recent studies have identified several additional risk factors such as homocysteinaemia, raised plasma levels of lipoprotein A, hypercoagulability and genetic markers like angiotensin-converting enzyme polymorphisms (2).

At present, it is generally accepted that plaque inflammation plays an important role in the evolution of atherosclerotic lesions (2).

These plaques are complex in composition, including a fibrous cap, lipid core, smooth muscle cells, collagen and elastin.

Immunohistochemical studies of human atherosclerotic plaques have demonstrated that macrophages, activated T cells and mast cells are present, suggesting the presence of an intraplaque immunomediated cellular response (3,4,5,6).

It has been showed unequivocally that intraplaque inflammation is a key factor in a process of plaque destabilization (7).

It is of interest that most studies focus on the role of macrophages, being that these cells play an important role not only as simple lipid scavenger cells, but also as immunocompetent cells with a profound impact on the component make-up of plaques.

The release, for instance, of matrix metalloproteinases (MMPs) is considered crucial for the breakdown processes of the fibrous cap as a prelude to plaque erosions and ruptures (2).

The role of T lymphocytes, particularly Th1 cells, is characterized by their production of interferon-gamma (IFN-_) that may profoundly affect plaque morphology by the regulation of extracellular matrix synthesis (8).

Actually, it is unknown which mechanisms are involved in the process of intraplaque immune activation.

A likely mechanism in the case of atherosclerosis operates by way of the innate immune system.

In these circumstances, non-antigen-specific immune activation may occur, for instance as a result of uptake of modified lipoproteins such as oxidized low-density lipoprotein (ox-LDL) by macrophages.

On the other hand, specific immune activation by way of the adaptive immune system may also be associated with atherosclerosis.

The simplest way to establish if such a response is generated is by measuring the levels of antibodies in the plasma.

A number of studies (9,10) have revealed a relationship between atherosclerotic disease and increased antibody titres of infectious agents. To this end, cytomegalovirus (CMV), Helicobacter pylori and Chlamydia pneumoniae are the ones most often incriminated.

The frequency of C. pneumoniae in atherosclerotic lesions appears increased when compared with normal vessels (11).

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The finding of C. pneumoniae in atherosclerotic tissue is considered specific, since these micro-organisms are infrequently identified in other tissues obtained from the same patient (12).

There are several studies in which it was shown that C. pneumoniae induces or augments atherosclerotic lesions in mice (13,14) and rabbits (15,16).

The mechanisms leading to such lesions are not clear, although several pathways have been suggested.

In the case of systemic infection, endotoxins released by C. pneumoniae induce an acute phase response which may cause endothelial injury (16).

Circulating endotoxins in the blood are bound to low-density lipoproteins (LDL), which is basically considered a mechanism of detoxification (17).

At the same time, atherosclerosis associated uptake of LDL in the arterial wall could also introduce a mechanism of endotoxin-induced vascular inflammation (17).

Once it has entered the intima of arteries, C. pneumoniae is capable of infecting several cell types involved in plaque formation, including endothelial cells, smooth muscle cells and macrophages (17).

In addition, there are also data that suggest that C. pneumoniae may contribute to atherosclerotic disease, particularly the onset of acute atherosclerotic syndromes, by increasing procoagulant properties of endothelial cells and smooth muscle cells (18).

Moreover, there is the option of an immune response against certain chlamydial antigens, such as heat-shock proteins (19).

It is obvious that much has to be learned still about the possible link between intraplaque inflammation, infection and atherosclerosis.

The risk of clinical cardiovascular events is associated with plaques at risk of rupture such as those with thin fibrous cap and large lipid cores (20).

The macrocirculation has a number of compensatory mechanisms, which may limit the effects of atherosclerosis.

In vessels affected there is an enlargement of the artery, due to the increased flow rate through the stenosis and to destruction of the mural connective tissue beneath the plaque (20).

However, the most important compensatory mechanism is the development of collateral circulation.

There are several collateral pathways involving vessels, which seem to be spared from the atherosclerotic disease such as the connections between the profunda and geniculate arteries (20).

The main stimulus for collateral development seems to be a pressure gradient that forms across the collateral bed when the main arteries are occluded (20).

This gradient increases collateral blood flow, raising wall shear stress and resulting in dilation of the vessels (20).

In patients with a single level of arterial disease, collateral circulation usually is sufficient to prevent critical limb ischemia, although the patient may have intermittent claudication (20).

Most patients with CLI have multilevel disease, for example aortoiliac and superficial femoral or superficial femoral and crural vessel atherosclerosis (20).

Microcirculation

The normal function of the skin microcirculation can be considered under two headings: a complex microvascular flow regulatory system (extrinsic neurogenic mechanism, intrinsic local mediators, modulation by circulating humoral factors) and a series of defense mechanisms (1).

The sequence of events leading to decreased capillary perfusion in patients with CLI is summarized in Figure 1.

It shows a series of auto-multiplying vicious cycles, in which the reduced perfusion pressure represents the pivotal point.

A number of techniques have improved the understanding of the skin microcirculation, which represents the pathological target tissue in most CLI patients with rest pain and trophic lesions.

These include capillaroscopy (21), fluorescence videomicroscopy (22), laser Doppler fluxmetry (23) and transcutaneous pO2 measurements (TCPO2) (24).

The management of trophic lesions in diabetic patients is more difficult than in nondiabetic patients.

Diabetic patients with CLI seem to have exaggerated changes in their microcirculation, including increased platelet adhesiveness and aggregation, decreased fibrinolytic activity, increased leukocyte free radical production, decreased red blood cell deformability and increased plasma viscosity (20).

Hemodynamical aspects

Motion of fluid from one point to another in a closed system occurs under the influence of an energy gradient.

Gravitational potential energy (GPE) represents the potential energy that is gained by raising a body or particle of fluid above the surface of the earth. It is simply the product of the mass of the fluid and its vertical displacement. Hydrostatic pressure (PH) is similar to GPE but has an opposite sign. It corresponds to the weight of a column of fluid above the point of observation. In the closed circulatory human system, this reference point is at the level of the right atrium and remains constant regardless of body position.

Normally, GPE is perfectly balanced by PH and thus it is possible usually to neglect their values in considering

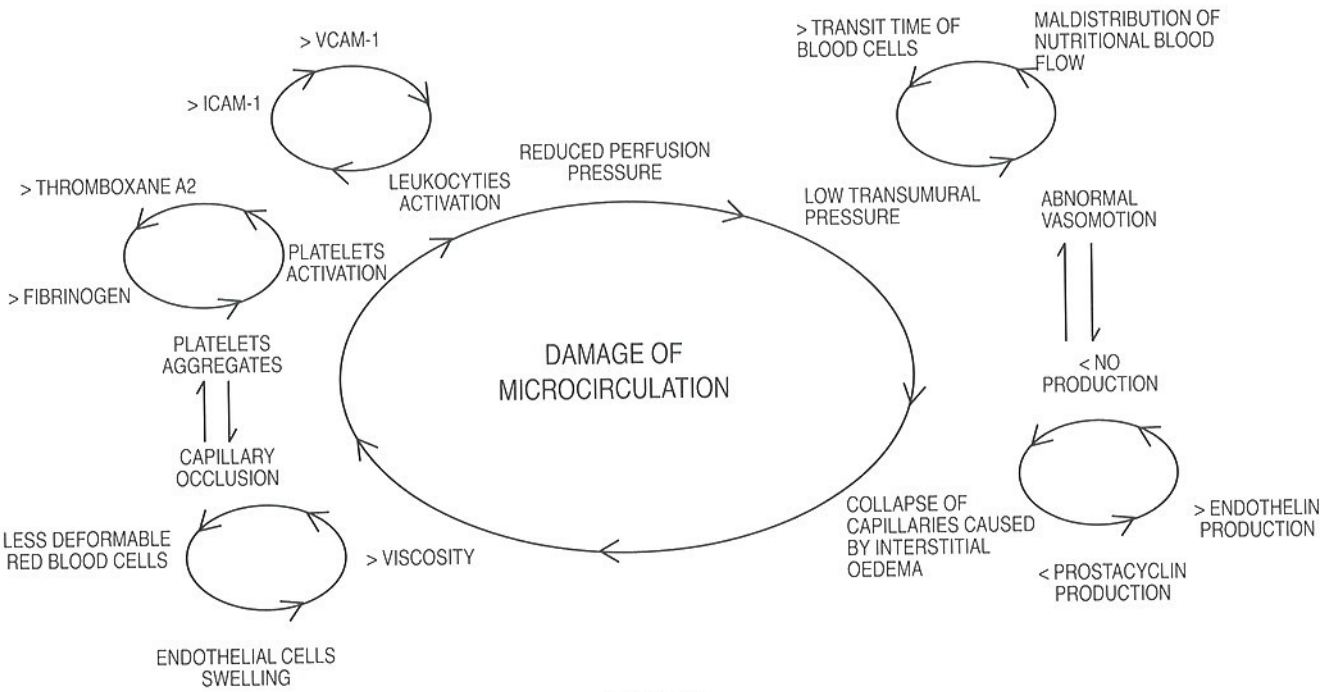

FIGURE 1

flow dynamics in humans, no matter what position the subject might assume.

However, they are situations when the two do not cancel out, for example when a patient with venous incompetence shifts from a recumbent to a standing position. In this case, blood "falls" down the empty veins propelled by GPE and unopposed by PH.

The third form of energy that must be considered is that associated with the motion of blood. This energy is known as kinetic energy (KE) and is proportional to the mass of the body or the density of the fluid and the square of its velocity (Figure 2).

The contribution of KE to the total fluid energy in the arterial system is minimal but on the venous side of the circulation, particularly in the major central veins, KE may represent an appreciable portion of the total fluid energy.

With the exception of the contribution of the muscle pump, all of the energy responsible for the motion of blood is derived from the contraction of the cardiac ventricles. In the arterial system, this energy is largely in the form of pressure and since it is produced by the motion of the heart it is convenient to use the designation of dynamic pressure (DP) to distinguish it from PH.

The total pressure at any point in the circulation is the sum of the PH and DP. While the arterial systolic pressure at the ankle of a recumbent subject might be 120 mmHg, it would rise to 210 mmHg in a standing position (120 mmHg DP + 90 mmHG PH). In the standing position, blood is able to move against a pressure gradient from the heart (where the systolic pressure is 120 mmHg) to the ankle (where the systolic pressure is 210 mmHg) because the GPE and the PH cancel (25).

Owing to friction between contiguous layers of fluid, some energy is always converted into heat and dissipated to the environment. As a corollary, energy must always be supplied if fluid motion is to be maintained. This friction, which is known as viscosity, varies from one fluid to the next.

Other energy losses relate to inertial effects. Changes in velocity occur whenever blood accelerates or decelerates (as in pulsatile flow) or when the lumen of the vessel changes diameter. Since velocity is a vector quantity, any change in direction also requires additional energy. Velocity vectors change direction at branch points, bifurcations, curves, at the entrance and exit of the stenoses and when the vessel expands or contracts during systole and diastole.

Over a short stenosis, the drop in pressure related to viscosity may be only a few millimeters of mercury, far more impressive is the loss in pressure due to inertial effects. Not only are there appreciable energy losses at the entrance to a stenosis, where the velocity vectors converge, but there are also energy losses of a much greater magnitude at the exit, where blood exits in a jet that rapidly disintegrates into a turbulent flow pattern.

Hemodynamic resistance (R) refers to the ratio of the pressure drop along a vascular segment (or stenosis) to

the flow through the segment and varies not only with the geometry of the vascular segment or stenotic lesion but also with the velocity of flow and the characteristics of the flow pattern.

The arterial supply to the lower limb may be considered to be composed of three segments: the aortoiliac, the femoropopliteal and the tibioperoneal.

In normal limbs, the hemodynamic resistance of the major arteries in each of these segments is quite low. The mean pressure drop from the aortic arch to the tibial arteries at the ankle is only a few millimeters of mercury. These arteries feed a high resistance peripheral vascular bed consisting of arterioles, capillaries and venules along which most of the dynamic pressure is dissipated. Pressure drops along the major veins from the ankle to the right atrium are again low.

Within the peripheral vascular bed, pressure drops are greatest across the arteriolar sphincters which function as valves controlling blood flow to the tissue. Under basal conditions, arterioles are relatively constricted but dilate readily in response to metabolites accumulating during ischemia and muscle contraction. Cutaneous arterioles, especially those in the feet, are well supplied by sympathetic nerve endings. Dilatation occurs in response to a lowered sympathetic tone and constriction in response to an increased tone. In the muscle, the arterioles are innervated by both sympathetic vasodilator and vasoconstrictor fibers, the former being activated by emotional stress and the latter by the assumption of an upright position.

Autoregulation is the term applied to the remarkable ability of the peripheral resistance vessels to maintain a relatively constant level of blood flow to the tissue over a wide range of perfusion pressures by constricting in response to an increased pressure and dilating in response to a decreased pressure.

Autoregulation is not present when the perfusion pressure drops below 20-30 mmHg. At these low pressures, arterioles are maximally dilated and flow responds passively to changes in perfusion pressure.

Thus, the total vascular resistance of the lower limbs is composed of a "fixed" segmental resistance and a variable peripheral resistance which includes combined resistances of peripheral vascular bed and the outflow veins.

Total blood flow to the limb is directly proportional to the pressure gradient existing between the inflow arteries and the central veins and inversely proportional to the total resistance of the interposed vascular structures.

Because the central venous pressure is low and relatively constant and the inflow arterial pressure varies within a limited range, changes in limb blood flow are primarily the result of changes in peripheral resistance.

In normal limbs, during the resting state, the arterioles are relatively constricted and the peripheral resistance far exceeds the segmental reistance. During exercise, however, the arterioles dilate, the peripheral resistance falls and blood flow increases. At rest, blood flow through the femoral artery of a normal leg is about 300-400 ml/min, but during exercise or reactive hyperemia it may increase 5 to 10 times to 1500-3000 ml/min (26).

When the segmental resistance is low as it is in normal arteries there is little additional drop in mean arterial pressure across the entire length of the limb, even when exercise evokes a massive increase in flow.

In fact, systolic pressure measured at the ankle usually rises after exercise, owing to the concomitant increase in systemic pressure.

The situation is more complicated in limbs with arterial stenoses or obstructions. Although small plaques produce no discernable alteration in pressure or total flow, once a stenosis exceeds 50% diameter reduction, compensatory mechanism come into play.

Small arteries paralleling the stenotic vessel enlarge to form collateral channels, but collaterals are seldom large enough or sufficiently numerous to reduce the segmental resistance to that of the unobstructed artery which they bypass.

Peripheral arteriolar vasodilatation is the second, and more important, compensatory mechanism. Autoregulation, occurring in response to a reduced perfusion pressure, maintains resting blood flow at normal levels until the resistance vessels are maximally dilated, at which point further pressure reduction leads to a decrease in blood flow to the tissue.

With mild to moderate disease, the increase in segmental resistance is matched by a decrease in peripheral resistance. Consequently, flow through the diseased arterial segment remains unchanged. Since the segmental resistance is increased, the distal arterial pressure falls.

This is the concept underlying the use of ankle pressure measurement to diagnose arterial disease. The lower the resting ankle pressure, the higher the segmental resistance and the more severe the disease.

Although flow in limbs with arterial obstruction increases during exercise, the increase does not match that in normal limbs. As a result, the exercising muscles are inadequately supplied with nutrients, products of metabolism accumulate, and the patient complains of intermittent claudication.

When the segmental resistance becomes too high, arteriolar dilatation in the most distally located tissues may be unable to compensate for the reduction in perfusion pressure, blood flow falls and the tissues become ischemic.

Thus, ischemia occurs in limbs with multilevel disease (especially when collateral development is poor), in limbs in which critical collateral channels are blocked at their origin or re-entry site, and in limbs with terminal arterial involvement.

In this event, the patient may experience "rest pain", a symptom that is characteristically made worse by elevation of the limb and alleviated by placing the limb in a dependent position and even, paradoxically, by walking.

Elevation reduces the total arterial pressure by an amount equivalent to the hydrostatic component.

When the foot is placed in a dependent position, the arterial and venous pressures both increase by the same amount (equivalent to the increase in hydrostatic pressure) and the pressure gradient across the capillaries remains unchanged. The relief of rest pain is explained by a reduction in the resistance of the capillary bed (which dilates in response to the increased hydrostatic pressure), permitting an increase in blood flow despite an unchanged pressure gradient.

In patients with intact venous valves, walking reduces the venous pressure by reducing the length of the effective hydrostatic column. This has the effect of increasing the pressure gradient across the capillary bed thereby increasing tissue perfusion and relieving rest pain.

REFERENCES

(1) ANONYMOUS. *Management of peripheral arterial disease (PAD).* TransAtlantic inter-Society Consensus (TASC). Eur J Vasc Endovasc Surg 2000; 19 (6, Suppl. A) : S1-S250.

(2) DE BOER OJ, VAN DER WAL AC, BECKER AE. *Atherosclerosis, inflammation and infection.* J Pathol 2000; 190: 237-243.

(3) HANSSON GK, HOLM J, JONASSON L. *Detection of activated T lymphocytes in the human atherosclerotic plaque.* Am J Pathol 1989; 135: 169-175.

(4) HANSSON GK, JONASSON L, LOJSTHED B, STEMME S, KOCHER O, GABBIANI G. *Localization of T lymphocytes and macrophages in fibrous and complicated human atherosclerotic plaques.* Atherosclerosis 1988; 72: 135-141.

(5) VAN DER WAL AC, DAS PK, BENTZ VAN DE BERG D, VAN DER LOOS CM, BECKER AE. *Atherosclerotic lesions in humans. In situ immunophenotypic analysis suggesting an immune mediated response.* Lab Invest 1989; 61: 166-170.

(6) KAARTINEN M, PENTTILA A, KOVANEN PT. *Accumulation of activated mast cells in the shoulder region of human coronary atheroma, the predilection site of atheromatous plaque.* Circulation 1994; 90: 1669-1678.

(7) VAN DER WAL AC, BECKER AE. *Atherosclerotic plaque rupture – pathologic basis of plaque stability and instability.* Cardiovasc Res 1999; 41: 334-344.

(8) FROSTEGÅRD J, ULFGREN AK, NYBERG P. *Cytokine expression in advanced human atherosclerotic plaques: dominance of proinflammatory (Th1) and macrophage stimulating cytokines.* Atherosclerosis 1999; 145: 33-43.

(9) HIGH KP. *Atherosclerosis and infection due to Chlamydia Pneumoniae or cytomegalovirus: weighing the evidence.* Clin Infect Dis 1999; 28: 746-749.

(10) MENDALL MA, GOGGIN PM, MOLINEAUX N. *Relation of Helicobacter pylori infection and coronary heart disease.* Br Heart J 1994; 71: 437-439.

(11) KUO CC, GRAYSTON JT, CAMPBELL LA, GOO YA, WISSLER RW, BENDITT EP. *Chlamydia pneumoniae (TWAR) in coronary arteries of young adults (15-34 years old).* Proc Natl Acad Sci USA 1995; 92: 6911-6914.

(12) JACKSON LA, CAMPBELL LA, SCHMIDT RA. *Specificit of detection of Chlamydia pneumoniae in cardiovascular atheroma: evaluation of the innocent bystander hypothesis.* Am J Pathol 1997; 150: 1785-1790.

(13) HU H, PIERCE GN, ZHONG GM. *The atherogenic effects of Chlamydia are dependent on serum cholesterol and specific to Chlamydia pneumoniae.* J Clin Invest 1999; 103: 747-753.

(14) MOAZED TC, CAMPBELL LA, ROSENFELD ME, GRAYSTON JT, KUO CC. *Chlamydia pneumoniae infection accelerates the progression of atherosclerosis in apolipoprotein E-deficient mice.* J Infect Dis 1999; 180: 238-241.

(15) LAITINEN K, LAURILA A, PYHALA L, LEINONEN M, SAIKKU P. *Chlamydia pneumoniae infection induces inflammatory changes in the aortas of rabbits.* Infect Immun 1997 ; 65 : 4832-4835.

(16) MUHLESTEIN JB, ANDERSON JL, HAMMOND EH. *Infection with Chlamydia pneumoniae accelerates the development of atherosclerosis and treatment with azithromycin prevents it in a rabbit model.* Circulation 1998; 97: 633-636.

(17) KALAYOGLU MV, MIRANPURI GS, GOLENBOCK DT, BYRNE GI. *Characterization of low-density lipoprotein uptake by murine macrophages exposed to Chlamydia pneumoniae.* Microbes Infection 1999; 1: 409-418.

(18) DECHEND R, MAASS M, GIEFFERS J. *Chlamydia pneumoniae infection of vascular smooth muscle and endothelial cells activates NF-kappa B and induces tissue factor and PAI-1 expression: a potential link to accelerated arteriosclerosis.* Circulation 1999; 100: 1369-1373.

(19) MAYR M, METZLER B, KIECHL S. *Endothelial cytotoxicity mediated by serum antibodies to heat shock proteins of Escherichia coli and Chlamydia pneumoniae: immune reactions to heat shock proteins as a possible link between infection and atherosclerosis.* Circulation 1999; 99: 1560-1566.

(20) SHEARMAN CP, CHULAKADABBA A. *Pathophysiology of critical limb ischemia.* In "Critical limb ischemia" Branchereau A and Jacobs M eds., Futura Publishing Company Inc., Armonk NY, USA, pp. 11-17.

(21) BOLLINGER A, FAGRELL B. *Clinical capillaroscopy: a guide to its use in clinical research and practice.* Toronto: Hogrefe & Huber, 1990.

(22) JUNGER M, FREY-SCHNEWLIN G, BOLLINGER A. *Microvascular flow distribution and trans-capillary diffusion at the forefoot in patients with peripheral ischemia.* Int J Microcirc Clin Exp 1989; 8: 3-24.

(23) SEIFERT H, JAGER K, BOLLINGER A. *Analysis of flow motion by the laser Doppler technique in patients with peripheral arterial occlusive disease.* Int J Microcirc Clin Exp 1988; 7: 223-236.

(24) FRANZECK UK, TALKE P, BERNSTEIN EF, GOLBRANSON FL, FRONEK A. *Transcutaneous PO2 measurements in health and peripheral arterial disease.* Surgery 1982; 91: 156-163.

(25) SUMNER DS. *Haemodynamics in the lower limb.* In: "Lower limb ischemia", Myers KA, Nicolaides AN, Sumner DS eds., Med-Orion Publishing Company, London.

(26) LEWIS P, PSAILA JV, MORGAN RH ET AL. *Common femoral artery volume flow in peripheral vascular disease.* Br J Surg 1990; 77: 183-190.