19. Flow dynamics and pathophysiological mechanisms of diseases of lower limb arteries

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The arterial diseases of the lower limbs are a clinical syndrome sustained by the reduction of the districtual blood flow in one or both limbs. In 80% atherosclerosis is the most important inducing factor, but in the remaining 15–20%, it is due to other diseases, such as diabetes or inflammatory arteritis. For all etiologies, a common pathophysiological understanding is valid. The disease starts when, from the anatomic phase of the atherosclerotic process, it transforms into atherosclerotic illness with a reduction of arterial diameter (stenosis) [1–4].

The arterial network of the lower limbs is a system with high resistances which makes it possible to maintain a good perfusion both at rest and during muscular work. Different factors regulate the cutaneous and muscular perfusion of the lower limbs: cardiac output, arterial blood pressure, blood velocity, the microcirculation and the un-Newtonian characteristics of blood.

The appearance of stenosis induces pathophysiological changes, involving all the determinants of flow dynamics, from the macrocirculation to the microcirculatory and metabolic patterns, that determine the compensation or decompensation of the illness [5].

Velocity

Blood velocity through the stenosis is related to its degree. For a single and small stenosis the blood velocity will be reduced downstream just after the lesion and the flux laminarity does not change; for severe (> 50%) or large stenosis the blood velocity decreases significantly, missing producing turbulences and missing the flux laminarity (Figure 19.1).

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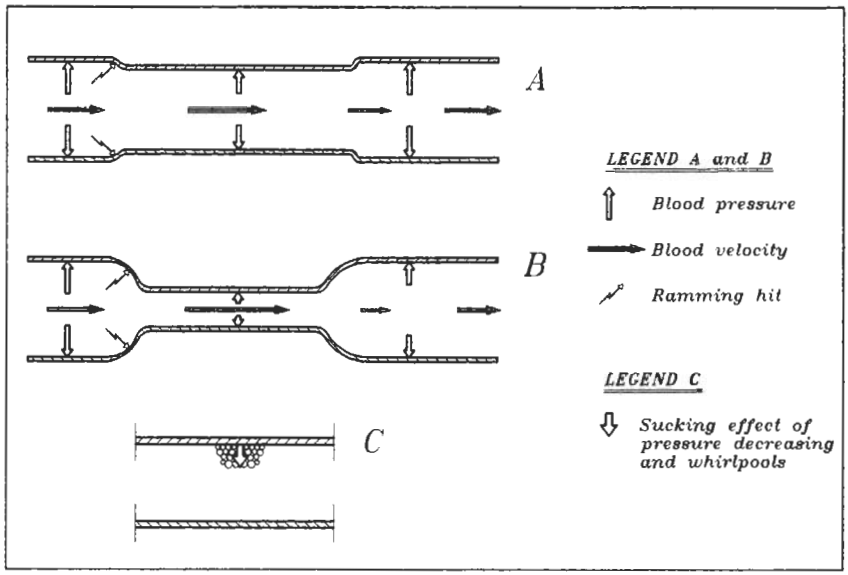

Figure 19.1. Velocity and pressure changes through the stenosis, under and over 50%. The reduction of the lateral pressure causes a *sucking effect* on the arterial wall, increasing the endothelial damage.

Pressure

The blood pressure upstream from the stenosis is equivalent to the systemic pressure; near the stenosis it is sometimes higher (*ramming hit*), downstream it is lower. The pressure also decreases within the stenosis (Bernouilli theorem), increasing the whirlpools. This causes a sucking effect on the arterial wall that takes part in the evolution of the endothelial damage, and in the growth of the atherosclerotic lesions (Figure 19.1). The drop in pressure, in the case of the isolated stenosis, diminishes proportionally leaving the lesion. This hemodynamic advantage is less important than the hydrodynamic one, due to several factors such as the post-stenotic wall conditions, the closeness of a bifurcation, and the un-Newtonian property of the blood fluid.

Flow

With reference to the variations of flow, it is necessary to take into account some peculiarities of the arterial system in the limbs. It has the capacity to work in two totally different ways: at rest and during muscular activity. The flow is determined by the Hagen–Poiseuille law ($Q = \Delta P \pi r 4/8\ \eta l$), and is therefore reduced proportionally with the drop in pressure induced by the stenosis. When the flux is low (at rest), however, the important decrease of the pressure does not show significant change in the districtual flow, because of the high resistances downstream. During muscular activity, when the flux is high due to arteriolar vasodilation, the lowering

of arteriolar peripheral resistance without increase of pressure (stenosis), causes a significant reduction of the flow.

In the advanced stages of the illness the most important organic damage is the obstruction; the blood flow is stopped along the principal arteries and the perfusion of the lower areas of the limbs is sustained by the collateral circulation and depends directly on the microcirculation [6].

Microcirculation

The teleology of the circulatory system is tissue nutrition, with exchanges between intra- and extravascular districts. The exchanges from blood to the tissues, and vice versa, require the blood flow to have a low velocity and pressure, to be proportional to the tissue requirements.

Downstream the hemodynamic features of the resistance vessels are widely varied. The Reynolds number is lower than 1.00, so the flux from inertial becomes viscous, and the denominator of the Hagen–Poiseuille law influences the flow more than does the numerator. The microhemodynamics are controlled by the central nervous system, hormones and local substances [6].

Microhemodynamics

The effectors of microcirculatory homeostasis are the arterioles. In healthy subjects they are submitted to rhythmic vasoconstriction and dilation (*vasomotion*), with consequent periodic perfusion of the tissue (*flowmotion*) (Figure 19.2). The rhythmic perfusion also induces rhythmic changes of the microhematocrit within the capillaries. This mechanism appears to control the release and reabsorption from and toward the tissue [7–9]. Local control is sustained by the homeostatic balance of several substance produced by the endothelial cells, as *prostacyclin* (PGI_2), *nitric oxide* (NO), *endothelin-1* (ET-1), *tissue plasminogen activator* (tPA) and its inhibitor (PAI-1), *heparin-like substances, heparin cofactor 2, and S-protein*.

PGI_2, derived from arachidonic acid (by the action of phospholipase A_2) and synthesized by cyclooxygenase), has a typical vasodilating and antiplatelet aggregation activity [10, 11]. NO, synthesized from L-arginine by NO synthetase, also has a vasodilating and antiaggregant activity; it is inhibited by M-mono-methyl-L-arginine [12, 13]. A specific NO agonist is acetylcholine, which induces NO release by the M_2 muscarinic receptor. The action of PGI_2 is mediated by cAMP, while NO increases cGMP, with a feedback control on PGI_2 and NO. This reaction induces dephosphorylation of the light chain of myosin with decontraction of smooth muscle cells. NO and PGI_2 are synergistic in inhibition of platelet aggregation, but it is PGI_2 which usually controls the regulation of vascular tone [14]. ET-1 contracts the smooth muscle cells in two phases. The fast phase quickly moves Ca^{++} storage, activating phospholipase C, which stimulates hydrolysis of phosphatidylinositol biphosphate and production of inositol triphosphate and diaglycerol. The slow

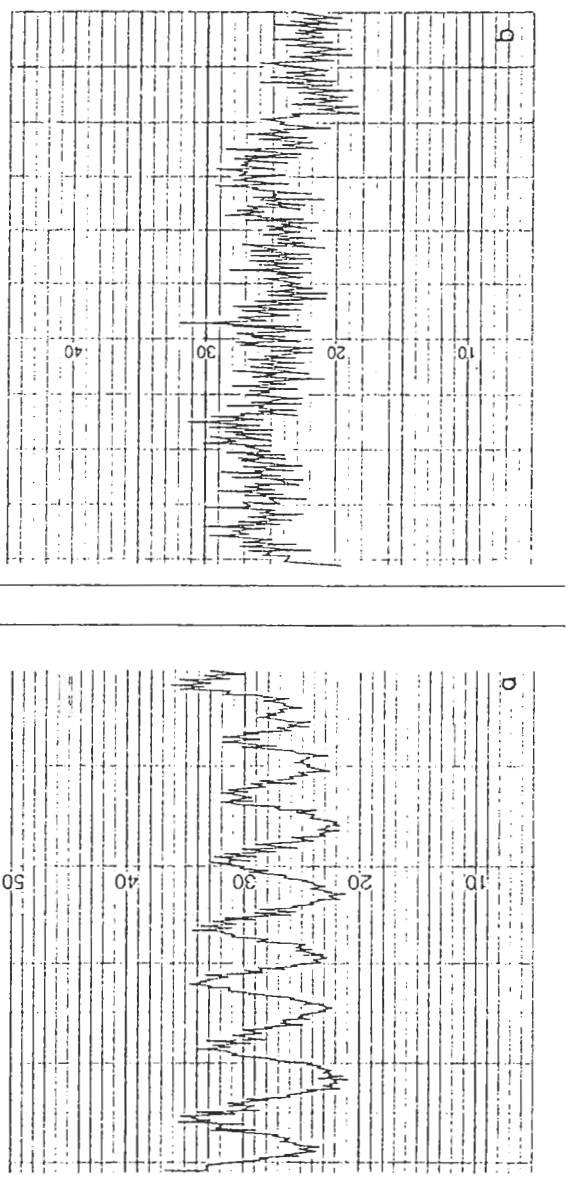

Figure 19.2. Laser Doppler output signal. Waves with different amplitude and frequency: low frequency waves (4–10 cycles/min, LFW), and high frequency waves (15–30 cycles/min, HFW). (a) Prevalence of LFW on normal skin with microcirculatory autoregulation; (b) better evidence of HFW in patient with critical limb ischemia (lost autoregulation).

phase is sustained by activation of Ca^{++} voltage dependent and independent channels. The endothelium also releases ET-1 after stimulation by angiotensin II, thrombin and adrenaline [15]; it also improves during production of superoxide anions, but the vasoconstriction from superoxide anions seems to be related to a direct action on the endothelium, to inhibition of NO and to a block of PGI_2, rather than to ET-1 release [16, 17]. Other endothelial vasocontracting factors are the cyclic endoperoxide PGH_2, thromboxane A_2 and the isoprostanes, derived from cyclooxygenation or lipoperoxidantion, which have high aggregation and constricting activity [18, 19].

All these activities of endothelial cells are continously stimulated according to the tissue metabolic requirements. At rest there is a balance between activators and inhibitors. Physiological or pathological events are characterized by the loss of this balance, with prevalence of one system. Together these systems, are part of the *microvascular flow regulating system* (MFRS) which is the basis of the local autoregulation of the microcirculation (Figure 19.2) [20].

Moreover the microcirculatory perfusion does not only depend on vasomotion and flowmotion, but is also influenced by the rheological determinants from the geometry of the vascular bed to the characteristics of the perfusion fluid and the role of the circulating cells [6].

Geometry of microvessels

The progressive reduction of vessel diameter increases the apparent blood viscosity, increasing the shear stress. Under 150 μm this apparent hyperviscosity is balanced by the *plasma skimming* (Fahraeus–Lindqvist effect) maintaining a good perfusion in the smaller vessels [21]. If the real viscosity increases over 4.5–5.0 cps, as in peripheral arterial diseases, the threshold of capillary diameter of the Fahraeus–Lindqvist effect becomes lower with subsequent perfusion reduction.

Red cells

The red cells play a very important role with reference to *hematocrit* and also *membrane deformability* [22]. The physiological stimulus to red cell deformability is the residual pressure gradient between arterioles and capillaries; in pathological conditions the residual pressure is very low and the deformability decreases significantly, proportionally to the degree of disease. In peripheral arterial disease this low deformability is secondary to the low perfusion pressure; in diabetic patients it can be primarily sustained by metabolic damage to the membrane [23–26].

Platelets

The platelet is very important for the production of vasoactive and cell stimulating substances, such as *platelet derived growth factor* (PDGF), *ADP, thromboxane* A_2, serotonin, and for the stimulation of *platelet activating factor* (PAF) release from leukocytes [27, 28].

Leukocytes

The role of the leukocyte is very important in microvascular perfusion; leukocytes have been indicated as being responsible for flowmotion, because they take a very long time to pass through microvessels, and also because of several particular interactions with the endothelial cells. The leukocyte–endothelium interaction is regulated by two mechanisms, the receptor system and the soluble substances system. The most important receptor molecules are the *integrins, selectins* and *immunoglobulins*, located on the cellular surfaces of leukocytes and endothelium; they regulate contact, rolling and adhesion of the leukocytes. To the latter group belong the *interleukins, tumor necrosis factor alpha*, PAF, leukotrienes and some fractions of the *complement system* (C4a, C5a); all these cytokines are released from endothelium and leukocytes [29]. They particularly activate recruitment, chemotaxis and migration of white cells, and other cell activities [30, 31].

Integrins, selectins and immunoglobulins do not appear on the cellular surface at the same time; GMP 140 (rolling selectin) is a molecule which appears rapidly, and ICAM and ECAM (adhesion immunoglobulin and selectin) appear 1 hour after stimulation. After stimulation the leukocyte activates these molecular systems and changes its status from *resting leukocyte* to *primed leukocyte*. If the stimulation continues it will change again into an *activated leukocyte* and will perform all the cellular reactions (chemotaxis, phagocytosis, cytolysis) [32] (Figure 19.3). This control system is defined as the *microvascular defense system* (MDS) [20]; it is activated whenever necessary (trauma, phlogosis, immunology, neoplasm). Also, recent studies involving this leukocyte mechanism in non-phlogistic diseases, such as *atherosclerosis* [3], *ischemia* [33], *shock* [34], *reperfusion syndrome* [35–37], *diabetic microangiopathy*, have shown an increase in chemotaxis and leukocyte adhesion in damaged tissue [37–39], and a correlation between tissue damage and leukocyte activation [40, 41], endothelium toxic substance and superoxide production [42–46].

To summarize, the physiology of the arterial perfusion of the lower limbs is sustained by a dynamic balance between the MFRS and MDS, with the activators and inhibitors continously being released and removed or deactivated, guaranteeing a prompt response when needed, physiologically or pathologically [6].

The presence of arterial disease with consequent changes in the pressure velocity and blood flow disturbs this dynamic balance leading to MDS prevalence. This induces a deregulation of the MFRS, with maldistribution of the local flux, free radical production and tissue toxicity [6, 47].

Pathophysiology and clinical features

Clinical evidence of peripheral arterial disease begins with a symptomatology related to all the mechanisms mentioned above. The natural history has a very slow evolution (15–20 years), due to the time needed for the anatomic damage to affect the hemodynamics, and to the efficiency of the compensation mechanism. Peripheral arterial disease has been classified into four stages (*Leriche and Fontaine classification*).

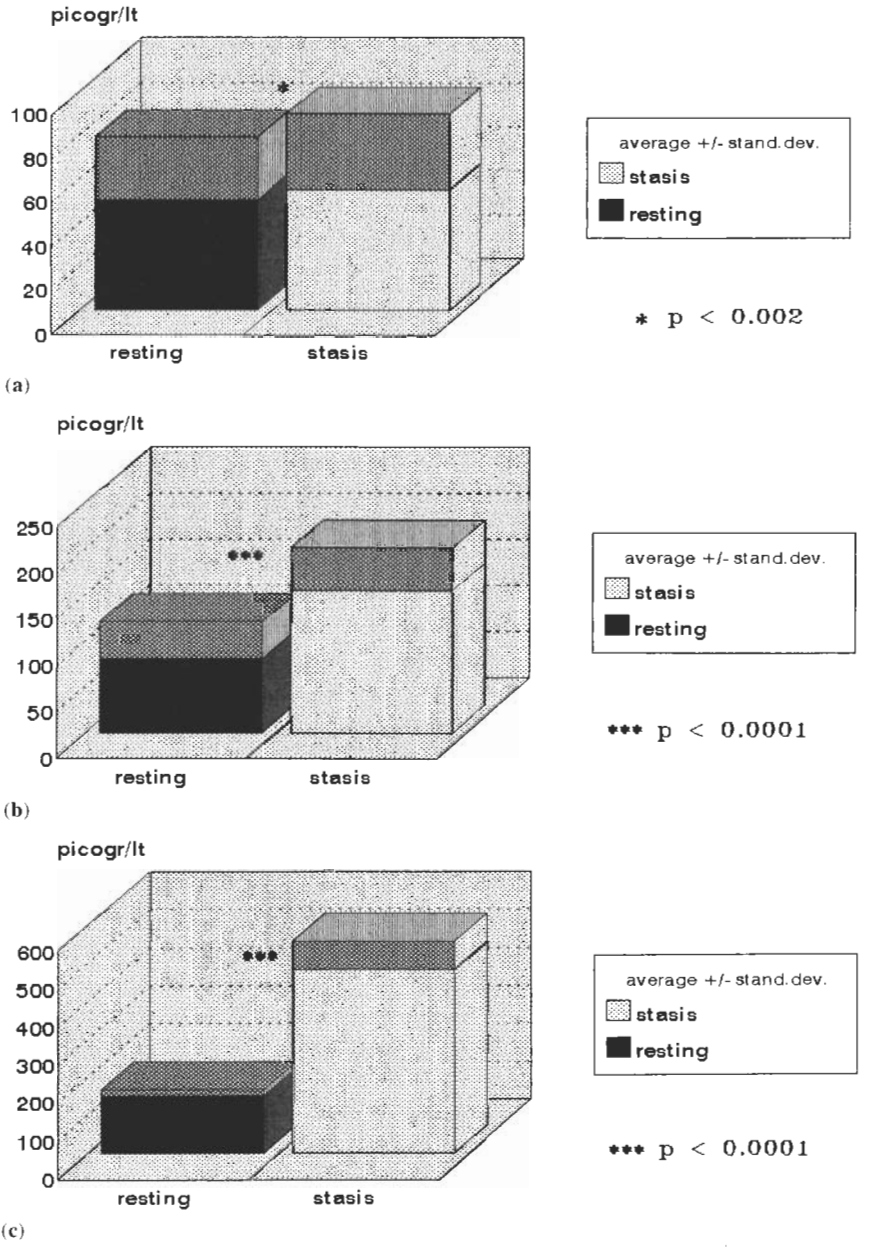

Figure 19.3. Production of interleukin-6: (a) in healthy control subjects, low level at rest (50 ± 28.87 pg/L) and small increase after 10 min of venous stasis (54.67 ± 34.64 pg/L); (b) in chronic venous insufficiency, higher resting level at rest (78.57 ± 40.62 pg/L) than in healthy controls; significant increase after 10 min of venous stasis (152.86 ± 46.38 pg/L); (c) in peripheral arterial disease, Fontaine's stage 2nd B: highest resting value of our experiment (150 ± 19.05 pg/L), and very significant increase during treadmill test (4 km/h, slope 7%) (484.16 ± 72.02 pg/L). The chronic hemodynamic damage (arterial stenosis and obstruction or venous hypertension) stimulates the leukocytes from the *resting* to the *primed* condition; every new stimulation changes the *primed leukocyte* into an *activated leukocyte*.

Stage I

This is the early phase of the illness, and is often believed to be asymptomatic, although this depends on the patient's way of life. A sedentary life rarely overlaps the mechanism of compensation. If the subject is more active, the illness will be symptomatic with pain. In this last case the patient could be classified as stage II. However we believe that patients can be classified as stage I if affected by an evident symptomatology due to a remarkable stress, e.g. walking for 1–2 km or a long climb [47].

Stage II

In this stage the illness is clinically evident after routine physical activity. At rest the patient is completely asymptomatic. Arterial disease is evident only after muscular stress because during walking the oxygen supply lowers with need. A typical symptom is *intermittent claudication*. It is a paroxystic pain, related to the level of arterial stenosis. It affects the calf, thigh, gluteus muscle and foot. Patients refer to it as a cramp (muscular acidosis) or hypostenia of the muscle (ischemic neuritis); stoping exercise without sitting makes this symptomatology disappear.

Clinical features to assess the intermittent claudication are measurement of the pain free walking distance (PFWD) and the time needed for recovery (tR). These measurements can be achieved by standardizing muscular stress with an ergometer. The treadmill test is the most useful, using constant walk and slope. Usually a 7% slope is utilized with a speed of 4 km per hour. The test must be used with care to avoid coronary problems. A study by the Italian Society for Vascular Pathology has shown that an ergometric charge with a 15% slope and a speed of 2.5 km per hour is a sensible equivalent without increasing coronary involvement [48].

At this stage MFRS deregulation to the vasoconstriction and the prevalence of MDS only occurs during muscular effort, when the blood flow cannot increase in relation to the oxygen requirement from the muscle. This leads to hypoxia and acidosis with appearance of effort pain (*claudication*). If stress is stopped the MFRS prevails, restoring autoregulation of the local perfusion. Initially it increases vasodilation and disaggregant activity, and washes out the catabolites produced during the ischemia (*reactive hyperemia*). After the hyperemia it resets in a new balance with the MDS.

In stage II, therefore, all patients with claudication can be classified, with 600–700 m or 100 m PFWD, but the pathophysiology of these two groups is very different. The first shows a direct correlation between the PFWD and transcutaneous pO_2, whilst the latter shows a decrease in this correlation and an increase of the inverse correlation with transcutaneous pCO_2 (Figure 19.4). This behavior suggests that patients with PFWD over 150 m are characterized by ischemia related to muscular work, while patients with PFWD under 150 m are characterized by a worsening of the aerobic conditions of cellular metabolism. For a better classification a stage IIA and a stage IIB have been established [47, 49].

The pathophysiology of stage IIB is sustained by blood flow reduction, permanent hypoxia, prevalence of the MDS, and low activity of the MFRS, which will

always be unable to restore the autoregulation. The perfusion will decrease both in the muscle (reduction of the PFWD) and in the skin (pallor and cyanosis).

Other symptoms frequently present in subjects suffering from peripheral arterial disease are disturbances of sexual function, particularly impotence, due to a total or partial defect of penis erection, sustained by internal iliac artery or common iliac artery occlusion or stenosis. The pudendal artery can also be affected. There may also be an inability to maintain an erection, due to hypoperfusion of the spinal cord at L5 S1, induced by stenosis of the medullar arteries coming from the aorta.

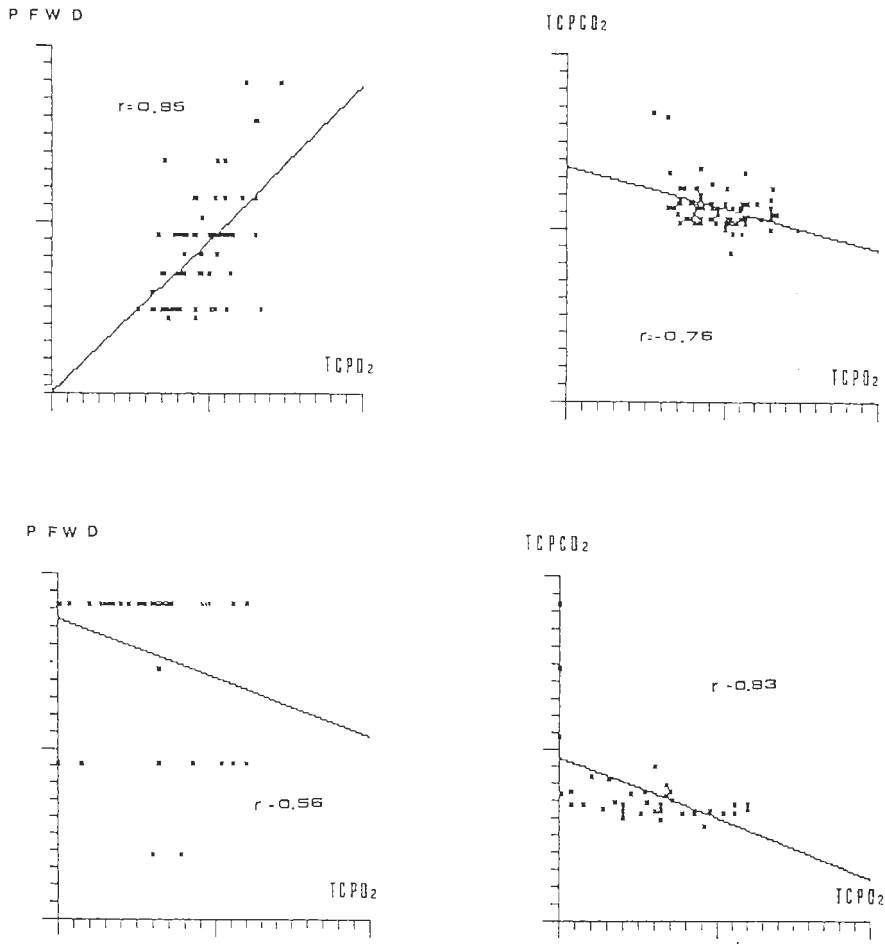

Figure 19.4. Analysis of the variance between the pain free walking distance, transcutaneous pO_2 and transcutaneous pCO_2. (a) Fontaine's stage IIA: high significant correlation between PFWD and transcutaneous pO_2 ($r = 0.85$); significant inverse correlation between transcutaneous pO_2 and transcutaneous pCO_2 ($r = -0.76$); (b) Fontaine's stage IIB: inverse and low significant correlation between PFWD and transcutaneous pO_2 ($r = -0.56$), and increase of the inverse correlation between transcutaneous pO_2 and transcutaneous pCO_2 ($r = 0.83$). This behavior indicates a worsening of the cellular metabolism, sustained by the decrease of the arterial and arteriolar inflow.

Stage III

The third stage is characterized by *rest pain* due to severe cutaneous hypoxia and ischemic neuritis. It is a continuous pain, which occurs particularly during the night, as it increases in the supine position. The patient spontaneously seeks the orthostatic position, to decrease the pain, making the leg bend out of the bed. Moreover the pain is made worse by cold and improves by heating the foot. The skin color changes gradually at this stage and often the patient does not report this symptom to the doctor. When the arteriopathy affects only one limb it is possible to note a *pale color* of the skin. In the advanced phase the pale color is always present, often with *cyanosis*. The cyanosis indicates a pathophysiological deterioration in the history of the arteriopathy. It indicates stasis and precedes gangrene [47] (Figure 19.5).

The third stage is the stage of absolute arterial insufficiency; there is no correlation between PFWD and transcutaneous pO_2 and there is a significant increase in transcutaneous pCO_2. This stage is characterized by the prevalence of the MDS with a reduction in the ability of the MFRS to restore a good perfusion. Microcirculatory reactivity disappears and stasis increases with worsening of the hypoxia and acidosis. Leukocyte activation is very strong, with great endothelial damage, and production of endothelial toxic substances and free radicals [6].

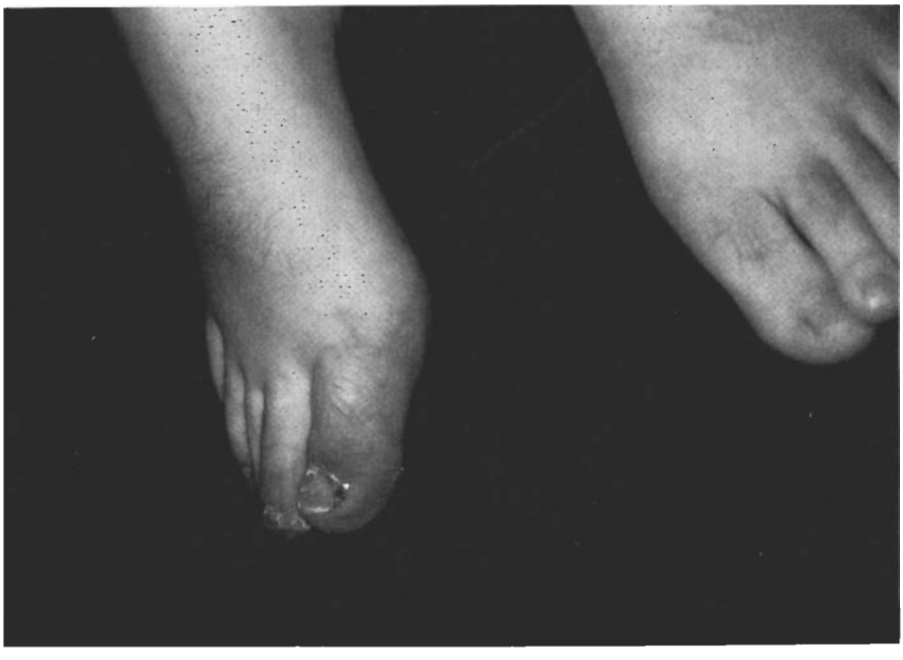

Figure 19.5. Cyanosis of the big toe, with intermittent rest pain, a prelude of critical limb ischemia (*unstable arteriopathy*).

Stage IV

This stage is characterized by *trophic injuries* sustained by hypoxia and acidosis, which hardly stress the compensation mechanisms. The trophic damage appears as different kinds of lesion, from *alopecia* to *skin lesions around the nail*, from *ulcers between fingers* to *necrosis* and *gangrene* (Figure 19.6). The gangrene can be dry or humid. Dry gangrene is sustained by a sudden death of tissues that are well demarcated from healthy areas. This can be tolerated by patients, particularly when the area is small; pain often disappears. Humid gangrene begins when the worsening of ischemia is very rapid; it is always preceded by cyanosis followed by edema and gangrene. Humid gangrene occurs even at the focus of infection in a dry necrosis. The main factor which induces the start of the trophic damage is the passage from ischemia to hypoxia and acidosis. In this stage tissue damage and free radical production is very high; the necrosis passes through a prolonged phase of necrobiosis during which reabsorption of catabolites occurs. This causes the clinical features such as fever, leukocytosis and increased erythrocyte sedimentation rate.

Critical limb ischemia

In the 40 years since the Leriche and Fontaine classification, there has been great progress in the pathological and clinical features of peripheral arteriopathies. The possibility of microcirculatory assessment, the discovery of thrombolytic drugs and prostanoids, the opening of new frontiers in surgery and angioradiology have

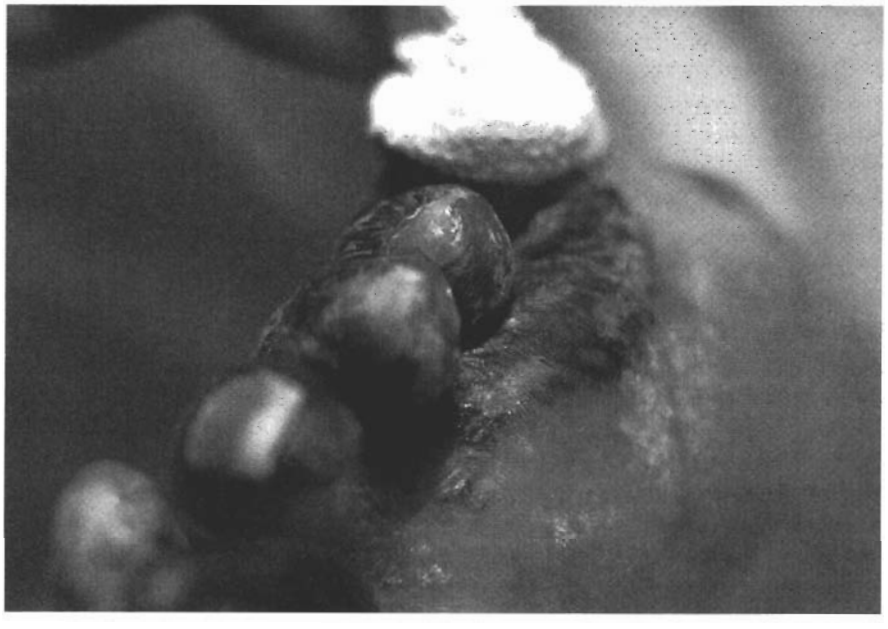

Figure 19.6. Dry gangrene: death of tissues, which are well demarcated from healthy areas.

radically changed the approach to the disease. Evolution through the four stages, from claudication to amputation can be prevented; a patient in stage III may recover to stage IIB, and even to stage IIA.

This has necessitated a revision of the Leriche and Fontaine classification. In 1989 the *European Consensus Conference* proposed the term *critical limb ischemia* (CLI), underlining the risk of the third and fourth stages leading to amputation. CLI has been defined by the following criteria:

- persistently recurring rest pain, requiring regular analgesia for more than two weeks;
- ulceration or gangrene of the foot or toes;
- ankle systolic blood pressure < 50 mmHg;
- toe systolic blood pressure < 30 mmHg (if ankle blood pressure is unreliable because of artery calcification as in diabetes; measurement with strain gauge plethysmography) [50].

This definition has been subsequently clarified, using some parameters, the most important of which are:

- transcutaneous oxygen pressure of the ischemic area ≤ 10 mmHg, which does not increase with inhalation of 100% oxygen;
- absence of arterial pulsations of the big toe (strain gauge plethysmography) after vasodilation;
- marked structural or functional changes of skin capillaries in the affected are [51].

The pathophysiology of CLI matches in the strict sense Fontaine's stages III and IV. More recently some authors have included in this risk phase the worsening of stable arteriopathy, the stage IIB. This stage, in fact, is characterized by an inverse and low significant correlation ($r = -0.56$) between PFWD and transcutaneous pO_2, while stage IIA shows a direct and very significant correlation ($r = 0.85$) (Figure 19.4). This signifies deterioration of the aerobic condition of the cellular metabolism, a prelude to CLI [47, 52]. This deterioration occurs concurrently with *cyanosis*, which can also appear without rest pain, and which is an expression of *microcirculatory stasis*.

We have suggested for this pathophysiological condition the name *unstable arteriopathy*, sustained mainly by microcirculatory decompensation, without macrocirculatory deterioration [47].

There are therefore two pathways which can lead to CLI, the micro- and the macrocirculatory pathways. The first is sustained by a lost of balance between MFRS and MDS, and increase of vasoconstrictor, aggregant and coagulative factors, with leukocyte activation. The second, while usually following the first, involves the macrocirculation with decrease of ankle systolic blood pressure, rest pain and skin necrosis. This theory suggests a possible pharmacological treatment of the unstable arteriopathy, with calcium heparin [53], prostanoids [54] or thrombolysis [55], which could restore a stable pathway, following which elective surgery will give better results than emergency surgical intervention, as in salvage surgery.

Instrumental examinations

The first diagnostic approach after anamnesis and clinical examination is measurement of systolic blood pressure along all the arteries of the lower limbs. The normal ratio between ankle and brachial blood presure is over 1.00; a ratio under 0.85 signifies a significant arterial stenosis. A decrease of more than 20–25 mmHg between two near sections (femoral and popliteal arteries) also indicates significant stenosis.

The next step is recording of the analogical signal of the Doppler continuous wave which is able to locate the stenosis and its hemodynamics (Figure 19.7). From the anatomic point of view the next examination is angiography, used for preoperative study.

Functional assessment is by measurement of district flow. The best technique is strain gauge plethysmography with venous occlusion, which can measure rest flow, peak flow after ischemia, time to peak flow and the half time of the post-ischemia hyperemia. The rest flow is not different between healthy subjects and patients because of the high peripheral resistances of the arteries of the limbs. For this reason, in clinical practice, resting flow measurement cannot distinguish patients from the controls; this can be done by assessment of blood flow after ischemic or muscular stress. After 3 min of ischemia (performed with a cuff inflated over the systolic blood pressure), is increased 3 or 4 times in healthy subjects. This ability is reduced in proportion to the degree of illness in arteriopathic patients (Figure 19.8).

The microcirculatory pathway can be investigated using the most recent techniques, laser-Doppler and transcutaneous measurement of O_2 ($tcpO_2$) and pCO_2 ($tcpCO_2$). The first is useful for investigation of microhemodynamics at rest and after ischemia, assessment of vasomotion and flowmotion, the presence of the veno-arteriolar reflex and restoration of autoregulation after ischemic stress (Figure 19.9). The latter is very helpful in assessment of some pathophysiological features. It can indicate arteriolar perfusion (*resting* $tcpO_2$), tissue damage (*resting tcp* CO_2) [49, 52], ability of the microcirculation to improve arteriolar perfusion ($tcpO_2$ *during oxygen breathing*) [56], microcirculatory hyperemia and tissue reperfusion (*oxygen recovery time* and *oxygen recovery index after ischemia*) [57, 58], tissue ability to regain a normal metabolic function (*half* $tcpO_2$ recovery time after ischemia) [49, 59], tissue resistance to ischemia, and the prognosis of patients with CLI ($tcpCO_2$ production during ischemia and $tcpCO_2$ during postural tests) [60–62] (Figure 19.10).

Addendum

Up to now, we have relied on these concepts, especially the $tcpCO_2$, for assessment of the skin necrosis risk, because this parameter measures the *tissue acidosis degree*, at rest and during ischemia. Nevertheless, in our investigation we went on to better define, in microcirculatory and tissue keys, the reactive hyperemia phenomenon.

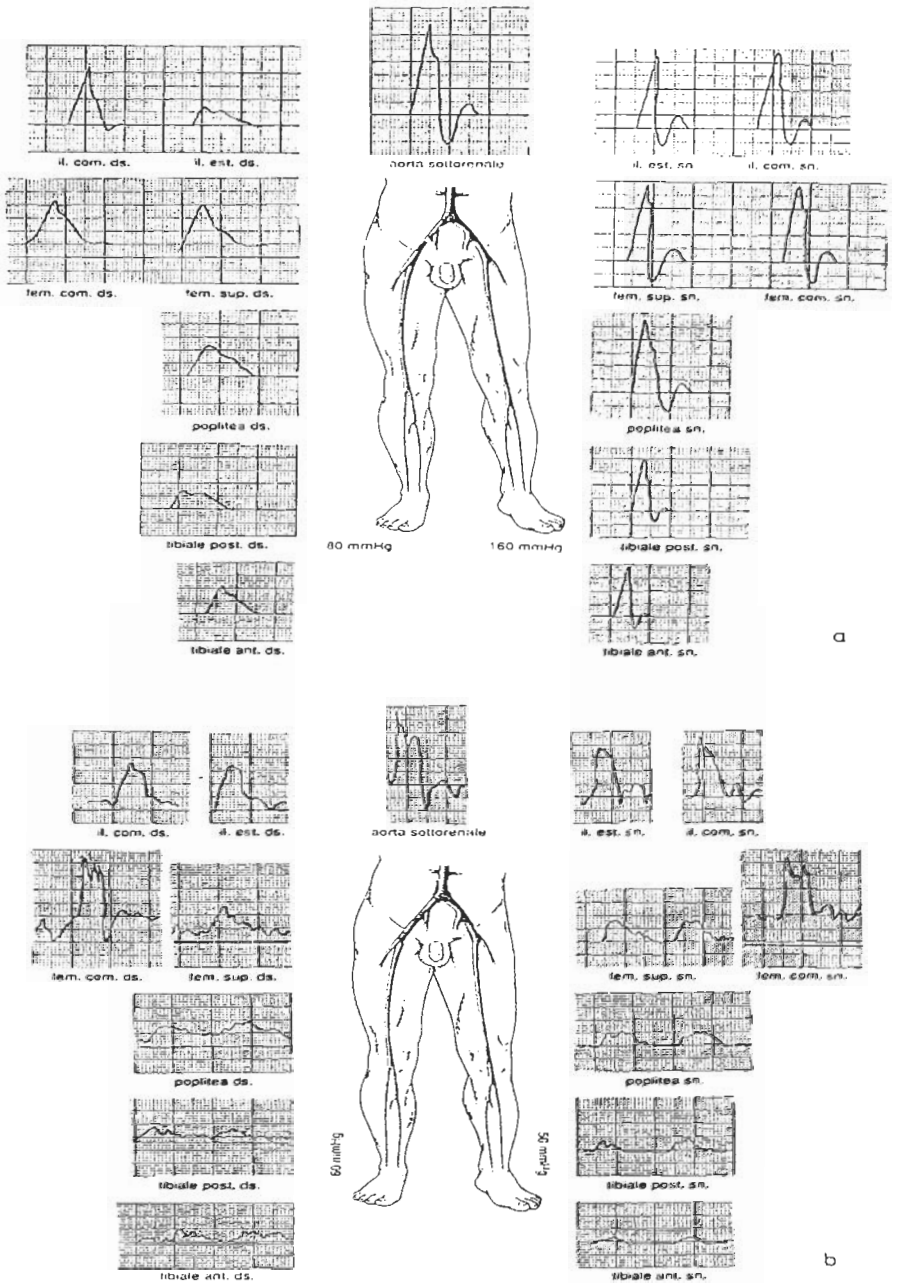

Figure 19.7. Doppler continuous wave. (a) Stenosis of the right common iliac artery, good spontaneous (collateral vessels) revascularization. Significant decrease of right ankle systolic blood pressure; demodulation of all waves on the right side; presence of continuous flow velocity in the femoral arteries, which disappears in the downstream measurements. (b) Multiple stenosis and obstruction of the right and left arterial axis. Very important reduction of the ankle systolic blood pressure; severe demodulation of all waves from the under kidney aorta to the tibial arteries.

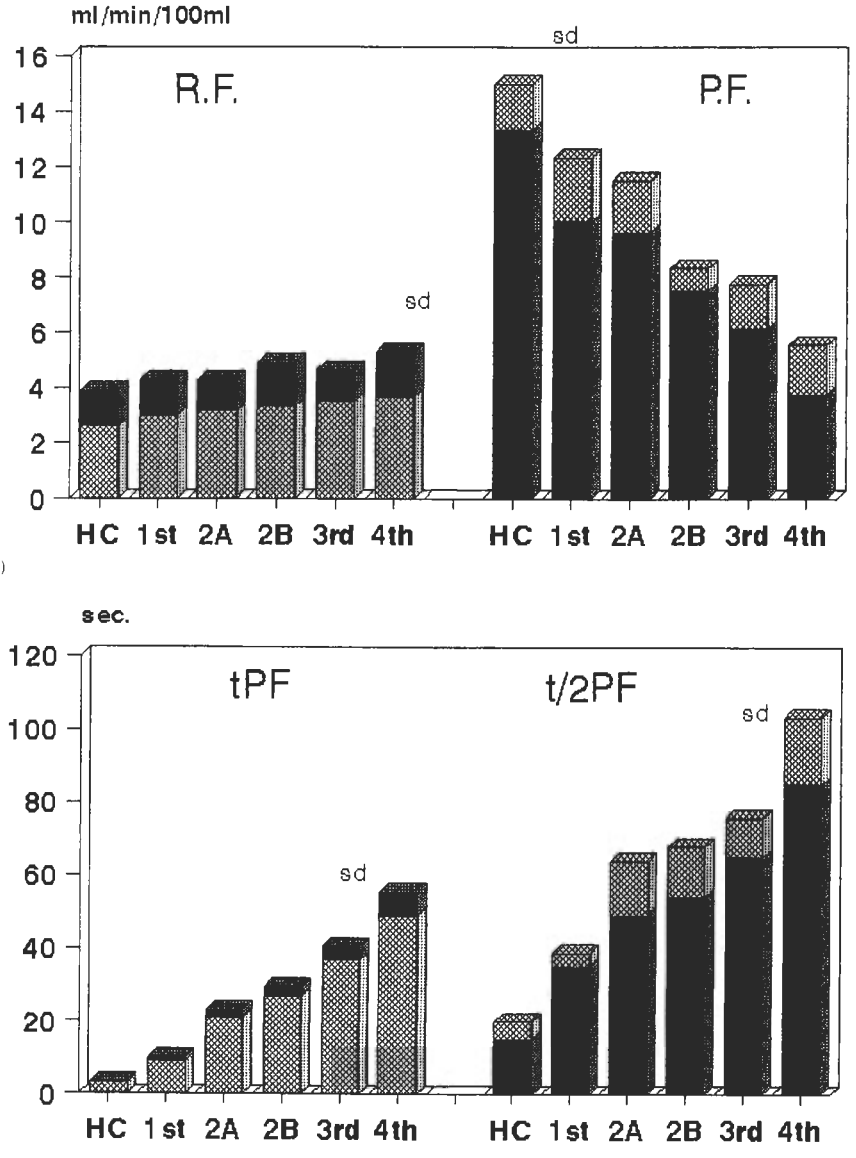

Figure 19.8. Strain gauge plethysmography. (a) Rest flow with no difference between healthy controls and patients. Peak flow (maximal reactive hyperemia after ischemic stress) with proportional decrease to the degree of disease. Note that the rest and the peak flow at the fourth stage have the same value: this is due to the permanent exciting vasodilating status of the patients, because of the high hypoxia. (b) The time parameters show an increase in the time of appearance of hyperemia after ischemia (tPF), related to the stenosis or obstruction; the duration of the hyperemia (t/2PF) is increased, related to the microcirculatory capability of washing out the ischemic catabolites.

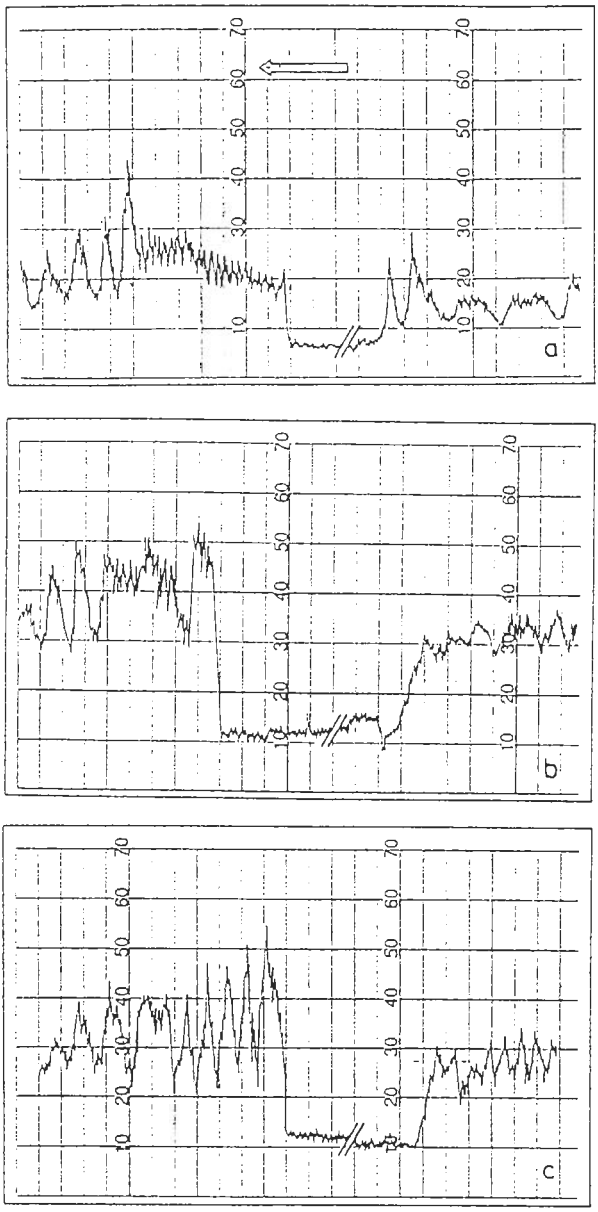

Figure 19.9. Big toe laser-Doppler output signal, in a patient with critical limb ischemia, during iloprost infusion (2.5 ng/kg/min). (a) t0, resting flow with low-frequency waves (LFW, 1.5–2.0 cycles/min) and evidence of high-frequency waves (HFW); post-ischemic flow with only HFW; restoration of autoregulation (LFW) after 80 sec. (b) t 60 min, resting flow with LFW 5 cycles/min; HFW less evidence; post ischemic flow with restoration of autoregulation after 15 sec; HFW still evident for 60 sec. (c) t 120 min, resting flow with marked increased of LFW (7 cycles/min); HFW not clearly visible; post-ischemic flow with poor evidence of HFW and restoration of autoregulation after 10 sec.

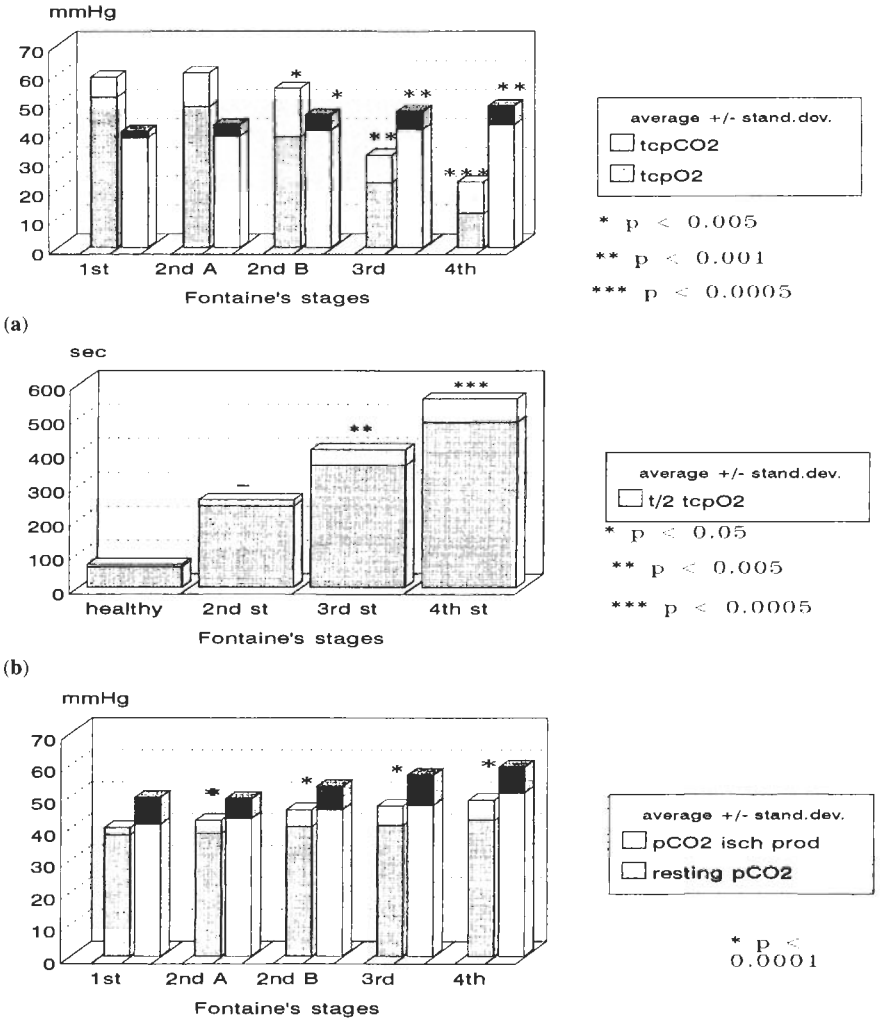

Figure 19.10. (a) Resting metatarsal transcutaneous pO_2 ($tcpO_2$) and pCO_2 ($tcpCO_2$) in patients with peripheral arterial disease. Progressive reduction of $tcpO_2$, related to the reduction of arterial and arteriolar inflow. Progressive increase of $tcpCO_2$ at Fontaine's stages IIB, III and IV, related to severe tissue damage assessing the deterioration of the cellular metabolism, sustained by reduced responsiveness of the oxidative enzymes, with lactate production. (b) Half recovery time of $tcpO_2$, after 3 min of ischemia in patients with peripheral arterial disease. During the ischemic test (calf cuff inflated over systolic blood pressure), $tcpO_2$ falls to zero-level, concomitant with the cessation of arterial inflow. After removing ischemia, in healthy controls the half value of the rest-level is restored in 60 sec. This time becomes gradually longer with different stages of peripheral arterial disease. It indicates the tissue ability to regain a normal metabolic function. (c) Metatarsal $tcpCO_2$ at rest and during ischemia in patients with peripheral arterial disease. During the ischemic test, when $tcpO_2$ falls to zero-level, $tcpCO_2$ increases. By measuring the resting value and value at 3 min, and subtracting the first from the second, $tcpCO_2$ production can be calculated. It increases proportionally with the degree of disease, and is a measure of tissue resistance to ischemia, an important prognostic value.

We are investigating this aspect by long-term continous recording of the micro-hemodynamic events (laser Doppler) and the tissue events ($tcpO_2$ and $tcpCO_2$) during ischemia–reperfusion.

The following points are the most important suggestions from our preliminary results:

(i) the 3 minutes standard ischemia is able to induce an ischemia (with laser Doppler at biological ZERO), but it hardly induces a hypoxia;
(ii) prolonging the stress until the $tcpO_2$ reaches the zero level, we noted that the time of hypoxia is longer in healthy controls than in patients;
(iii) after the reperfusion the LD reaches the peak flux immediately in healthy controls and later in patients;
(iv) during the hemodynamic reperfusion $tcpCO_2$ continues to increase and always reaches its plateau after the laser Doppler peak flux;
(v) the duration of the $tcpCO_2$ plateau is longer in patients than in healthy controls.

This behavior means that, in spite of the increasing oxygen, the cells only slowly recover their breathing capacity, proportionately to the tissue injury. If the $tcpCO_2$ production during 3 minutes of ischemia is already a reliable parameter, a higher reliability could probably be given by measuring the time of hypoxia, the $tcpCO_2$ plateau, and the recovery slope of $tcpCO_2$ [63].

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