Introduction

Intermittent claudication, the main symptomatic expression of peripheral arterial disease (PAD), affects a large proportion of the general population. Defined as cramping, aching, fatigue or discomfort in the muscles of the calves, thighs, or buttocks that occurs while walking, intermittent claudication has adverse effects on both functional status and quality of life. It represents a major cause of disability for elderly individuals who are often unable to perform their normal daily activities because of the difficulty in walking.

The history of intermittent claudication, which can be traced back to over 150 years ago, can be divided into five eras according to the pathophysiological theories postulated to explain the mechanism(s) that underlie this condition (Fig. 1).

Pre-history

The history of intermittent claudication begins in 1831 when Bouley[1], who practiced veterinary medicine in Paris, first described this syndrome in a horse affected by progressive limping and lameness. Post-mortem examination of the mare’s posterior limbs revealed that the femoral arteries were triple the volume of the femoral arteries in the natural state. They formed a fusiform tumour that contained a fibrous blood clot, which completely occluded the artery. In humans this condition was described by Brodie in 1846[2], but it was Charcot[3] who, in 1858, for the first time clearly defined and described the syndrome and termed it ‘intermittent claudication’. This term is a misnomer, however. Actually, claudication derives from the Latin word *claudicare*, which means ‘to limp’; individuals with intermittent claudication do not limp, but are forced to stop walking because of unbearable leg pain evoked by exercise.

Claudication pain is often reported by the patient as a ‘spasmodic pain’ and may be accompanied by foot blanching, lowering of skin temperature and sometimes disappearance of the pedal pulse. These are typical features of marked vasoconstriction, and thus Erb[4], who in 1898 first attributed the cause of muscle pain to reduced blood supply as a consequence of arterial occlusive disease, suggested that a functional vasospastic factor was operating in addition to organic changes. This view received support from later clinical observations and circulatory studies.

Ancient history

In 1922, Comroe[5] demonstrated that foot pulses disappeared in some claudicant patients during exercise and...
returned on resting. He believed that this phenomenon was purely vasospastic in origin, and thus called it ‘paroxysmal angiospasm dolorosa’.

The theory that vasospasm could contribute to claudication pain persisted for a long time and was widely shared. During the 1940s, many investigators reported that, contrary to observations in normal persons, claudicant patients have a reduction in oscillographical recordings with exercise\[6–8]. This was attributed to constriction of the muscle arterioles caused by abnormal substances released during intermittent claudication in place of the normal vasodilating metabolites that are produced during non-ischaemic exercise\[7].

Based on the assumption that, in claudicant patients, leg pain and blanching of the foot were conclusive evidence of the occurrence of vasospasm, vasodilator drugs were widely used to treat intermittent claudication and, more generally, ischaemic syndromes of the lower limbs. However, the spasm theory was not substantiated by animal experiments.

In 1962, Thulesius\[9] investigated exercise hyperaemia in the hind leg of the cat after ligation of the femoral artery, and found that a rapid and maximal dilatation took place. This observation helped to close the ‘vasospasm era’, and opened the door to development of a new theory to explain the clinical and circulatory phenomena that occur in intermittent claudication. Indeed, the 1960s were the years of the ‘blood steal phenomenon’, which had already been described by Lewis et al.\[10] in 1931.

### The middle ages

In 1931, Lewis et al.\[10] demonstrated that hyperaemia in a vascular district may be accompanied by simultaneous shunting of blood from other vascular territories. Those investigators suggested that, under ischaemic conditions, exercise induces production of metabolites that cause dilatation of the muscle arterioles. At the cessation of ischaemic exercise, a ‘stealing’ of blood occurs from the skin to the dilated muscle arterioles, thus causing foot blanching. In 1947, De Bakey et al.\[11] showed that this was a general haemodynamic principle that they termed ‘borrowing–lending phenomenon’, or ‘haemometakinesia’. This mechanism regulates blood flow distribution, and is appropriate and useful under particular circumstances because it allows rational utilization of circulating blood volume without relevant changes in cardiac output and arterial pressure. In contrast, in patients with intermittent claudication, this haemodynamic mechanism may be harmful because it causes a reduction in blood flow in the ischaemic skeletal muscle during exercise.

Distally to an arterial occlusion, the vascular bed is usually dilated. Therefore, the vasodilating metabolites produced by exercise act preferentially on the healthy vascular districts, with a consequent shunting of blood from the ischaemic toward the normoperfused areas. This blood steal lowers the intra-arterial pressure and, during walking, this reduced pressure may be less than the surrounding tissue pressure\[12], with consequent collapse of the arterioles in the ischaemic zones. This may induce a further reduction in the muscular blood flow\[13].

During the 1960s many investigators reported that a blood steal occurs in patients with PAD after exercise\[14,15], during reactive hyperaemia\[16] (which also induces release of vasodilating substances) and in response to vasodilators\[17]. The vascular steal phenomenon was argued to be the main mechanism responsible for intermittent claudication, and in the 1970s the use of vasodilator drugs was progressively abandoned\[18,19].

Because interventions that cause arterial dilatation in normal districts also reduce the arterial flow to ischaemic areas, it may be supposed that a drug that increases vascular resistance in the normal areas may prevent the blood steal phenomenon, or even improve the blood flow to the ischaemic areas. In effect, a reverse vascular steal was observed in the coronary bed after administration of methoxamine\[20]. Similarly, it has been demonstrated that,
in patients with PAD, propranolol inhibits the blood steal consequent to a metabolic vasodilatation after reactive hyperaemia[21] or exercise[22], and reverses that induced pharmacologically[23]. These observations did not have a therapeutic application, however.

**Modern history**

The demise of the ‘vasospasm theory’ and the consequent demise of vasodilating therapy in the early 1970s led to a new pathogenetic interpretation of intermittent claudication.

Blood flow is essentially determined by three variables: the radius of the vessels, the pressure gradient and the viscosity of the blood. Poiseuille’s law, although only an approximation of the conditions that prevail in the circulatory system, states that flow is related to the fourth power of the vessel diameter, but emphasizes also the inverse relation between viscosity and blood flow. This negative relationship is important in understanding the shift in interest from the ‘vessel’ to the ‘blood’ that marked the birth of the ‘haemorheological theory’.

In 1973, Dormandy *et al.*[24] reported that patients with PAD have a higher blood viscosity than do age-matched control individuals, and suggested that this abnormality could be the critical factor responsible for claudication symptoms. Indeed, claudicant patients with lower walking capacity had higher blood viscosity than did those with greater walking capacity, although the arteriographical lesion was similar in the two groups. Furthermore, there was a significant correlation between progressive deterioration of the peripheral circulatory disturbance and the initial blood viscosity[25].

Of the biophysical and biochemical factors that govern blood viscosity, the most influential are haematocrit, plasma fibrinogen and blood cell deformability. Erythrocytes have diameters of approximately 7–8 µm and the nutritive capillaries through which they pass have diameters of approximately 3–15 µm. In the normal circulation, under high shear stress and perfusion pressure, erythrocytes easily deform and thus pass through the capillaries. In patients with intermittent claudication, red cell flexibility is reduced[26] and thus passage of erythrocytes through nutritive capillaries might be compromised. This could result in red cell aggregation, increased blood viscosity and reduced blood flow. Also, the rheology of white cells is impaired in patients with peripheral vascular disease[27] and an increase in leucocyte rigidity has been demonstrated at the onset of intermittent claudication[28]. Furthermore, leucocytes activated by ischaemia may adhere to the endothelium of microvessels causing capillary plugging, which greatly contributes to the disturbances of microvascular circulation under ischaemic conditions.

In 1973, Hess *et al.*[29] first reported that pentoxifyline reduces whole blood viscosity. This finding was confirmed by others[30] alongside the demonstrations that pentoxifyline reduces plasma fibrinogen levels[31], increases erythrocyte flexibility[32] and improves white blood cell rheology[33]. As a consequence, this drug was extensively used to treat intermittent claudication. However, in the late 1980s critical reviews of pentoxifyline studies revealed that its efficacy was probably overestimated[34,35]. In particular, Cameron *et al.*[34] found a negative correlation between sample sizes and outcome (r = −0.79; P < 0.05), with the largest studies showing the least benefit of pentoxifyline therapy. This is probably due to the fact that small studies with negative results are not published, whereas large, multicentre trials are published even if the outcome with the active treatment is not better than that with placebo. Therefore, although impaired blood rheology is a determinant of the reduction in microvascular flow under ischaemic conditions, the overall clinical usefulness of pentoxifyline is limited by inconsistent response.

With the increasing importance assumed in medicine by molecular and cell biology, the general principle emerged that progress in the diagnosis and treatment of diseases is directly related to knowledge of basic biological mechanisms. During the 1990s research into the pathophysiology of PAD focused on the ‘chemistry’ of the metabolic regulation of the ischaemic muscle, and the inflammatory response evoked by exercise in patients with intermittent claudication.

**Contemporary history**

Although the pathophysiology of PAD is primarily accounted for by the severity of haemodynamic compromise and number of occlusive lesions in the peripheral circulation, exercise limitation in claudicant patients may not be fully explained on the basis of reduced blood flow alone. Indeed, in such patients, the ankle–brachial index correlates poorly with exercise performance[36]. Therefore, additional abnormalities that are intrinsic to the skeletal muscle may contribute to the functional impairment of claudicant patients. Accumulation of intermediates of oxidative metabolism, and alteration in fibre type distribution and in mitochondrial enzyme expression have been described in PAD[37–39]. These changes, which are typical of mitochondrial myopathies, represent a potent stimulus for early anaerobic metabolism during exercise, thus suggesting the possibility of impaired energy utilization as a secondary cause of muscle dysfunction in intermittent claudication. This concept is supported by 31P-nuclear magnetic resonance studies[40,41] that provided direct evidence of defective energy metabolism in the exercising ischaemic muscle of patients affected by PAD. Of note, the metabolic impairment appears to be independent of the peripheral haemodynamics[41].

In the skeletal muscle, adenosine triphosphate is the main provider of energy to support force production. Its mitochondrial regeneration depends on the activity of the tricarboxylic acid cycle that is fuelled by acetyl-coenzyme A (CoA). During exercise beyond the lactate threshold, the rate of acetyl-CoA formation exceeds the maximal capacity of the tricarboxylic acid cycle. As a consequence, acetyl-CoA tends to accumulate within the mitochondria,
increasing the ratio of acetyl-CoA to CoA and thus inhibiting pyruvate dehydrogenase. The reduced oxidation of glucose leads to increased lactate formation. Under these conditions, the role of carnitine is crucial. It serves as a buffer of the metabolically critical mitochondrial acetyl-CoA pool\(^\text{[42]}\). Through the action of carnitine acetyltransferase, carnitine depletes acetyl-CoA and releases free CoA and acetylcarnitine, which, unlike acetyl-CoA, may be transported out of the mitochondria and released into the blood stream. Indeed, increased levels of acetylcarnitine occur in muscle and plasma of normal persons exercising beyond the lactate threshold\(^\text{[43]}\).

Patients with PAD have alterations in carnitine metabolism that appear to be related to the severity of the disease\(^\text{[37,44–46]}\). In particular, claudicant patients with mild functional impairment have low resting levels of acetylcarnitine that normally increase with exercise, whereas the most affected patients have elevated resting levels of acetylcarnitine (reflecting acetyl-CoA accumulation) and do not form this ester with exercise\(^\text{[46]}\).

The plasma concentration of acetylcarnitine depends on two factors at least: the rate of acetyl-CoA formation and the availability of carnitine to meet the increased metabolic demand induced by walking. This hypothesis is supported by the finding that, after carnitine supplementation, such patients have an increase in plasma acetylcarnitine with exercise, as opposed to the decrease observed before treatment\(^\text{[46]}\). This implies that a corresponding amount of acetyl-CoA was removed from mitochondria with consequent stimulation of pyruvate dehydrogenase. Indeed, in patients with intermittent claudication carnitine supplementation results in a reduction in lactate concentration in venous blood leaving the exercising ischaemic muscle\(^\text{[47]}\). These findings indicate that an intervention that can improve metabolic efficiency may be effective in treating the mismatch between energy supply and demand in claudicant muscles.

Propionyl-carnitine is a carnitine analogue that, in addition to increasing carnitine availability to muscles with reduced oxidative capacity\(^\text{[45,48]}\), increases the flux in the carboxylic acid cycle by an anaplerotic mechanism\(^\text{[49]}\). In patients with intermittent claudication, propionyl-carnitine improves walking capacity and quality of life\(^\text{[50–53]}\). However, the prototype of the metabolic interventions in claudicant patients is exercise training, the beneficial effect of which was described by Foley as early as 1957\(^\text{[54]}\). Indeed, the increase in walking capacity achieved by training\(^\text{[55]}\) appears to be the consequence of improvement in oxidative metabolism, rather than of changes in blood flow\(^\text{[56]}\).

In 1990, Hickey et al.\(^\text{[57]}\) and Neumann et al.\(^\text{[28]}\) independently reported that exercise in claudicant patients incites a systemic response that is characterized by neutrophil activation. This could play a relevant role in the pathophysiology of intermittent claudication. Activated neutrophils generate oxygen-free radicals, which inactivate constitutive nitric oxide, and release arachidonic acid metabolites and activating cytokines. Increased oxidative stress\(^\text{[58]}\), and enhanced levels of thromboxane A\(_2\)\(^\text{[59]}\) and interleukin-8\(^\text{[60]}\) have been demonstrated in PAD patients during exercise. All of these events impair endothelium-dependent vasorelaxation, which, coupled with the release of endothelin-1\(^\text{[61]}\), may result in some net vasoconstriction distal to the obstruction. It is noteworthy in this regard that exogenous administration of l-arginine, the precursor of endogenous nitric oxide, increases plasma levels of cyclic guanosine monophosphate, muscular blood flow and walking capacity of patients with PAD\(^\text{[62,63]}\).

Moreover, the transient but repeated inflammatory stimuli that occur each time a patient walks may affect the endothelium at distant sites\(^\text{[64,65]}\), thereby promoting propagation of the atherosclerotic process in susceptible arteries. If this were the case, then intermittent claudication would not merely be a condition that limits exercise performance and quality of life, but also it could represent a transient risk factor that contributes to the excessive cardiovascular risk of claudicant patients. Perhaps this will be a chapter in the future history of intermittent claudication.

References

