Part I

History and epidemiology

Historical Notes

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The history of vascular surgery, particularly of the treatment of peripheral occlusive diseases, represents the history of the evolution not only of the knowledge about the etiology and pathophysiology of obliterative vascular lesions but also of the achievements in the field of anesthesia, antibiotics, anticoagulants, angiography, suture of blood vessels and vascular grafts.

However, it means the history of men with extraordinary intuitions or simple ideas that have changed the way of working and thinking of the next periods surgeons.

John Hunter (1728-1793) (Figure 1) can be considered the first vascular surgeon of the history (1,2).

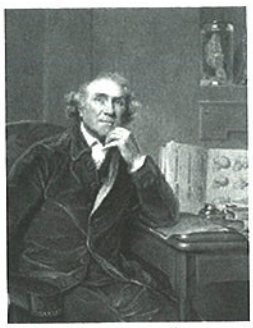

FIGURE 1
John Hunter

He is remembered for his several and important contributions, diffused in Royal College of Surgeons of England museum, but above all for the ligature of superficial femoral artery, in the area called "Hunter's canal", to treat a popliteal aneurysm (1,2).

In that period, in effect, the ligature has represented the only surgical procedure used in the treatment of arterial diseases.

Anyway, in 1759, Hallowell (3) has carried out and reported an arterial repair of a brief laceration by running a short steel pin (0.6 mm) through the edges of the wound and passing a figure – of – eight ligature around it to approach the wound edges.

Fourteen years later (1773), Asman has owed the work of Hallowell, trying to repeat the procedure in animals (4), but because of poor results he has discarded the studies criticizing arterial repair.

After Asman's critique, arterial repair has been not used again for about a century.

In fact, Jassinowsky in 1889 confirms that arterial repair represents a not successful technique, but a hope for the future (5).

From a clinical point of view, at the beginning of XIX century, gangrene from severe lower limbs ischemia, i.e. "senile gangrene" or "spontaneous gangrene", is well known but only whit Barth (6) it has been clearly understood that it's possible to observe functional symptoms less dramatic than morphological lesions of gangrene.

In 1835, he describes accurately a case of claudicatio intermittens and for this reason he has been named twenty-three years later by Charcot (7), commonly considered the first one who, thanks to his studies about horses, has connected the symptoms observed in a patient with severe claudication (pulseless, cold limb, neuropathy) with the presence of an obliterative lesion of common iliac artery.

In 1891, Jassinowsky (8) reports the results of his studies in animals with successful experiments in suturing arteries, in which anyway he avoids penetrating the intima except in vessels with thin artery wall.

Some years later, Dörfler (9) has resumed and modified Jassinowsky's method by passing the suture through all layers of the artery wall and affirming that this procedure doesn't damage the intima unless the suture isn't infected.

In 1896, Jaboulay and Briau (10) describe successful end-to-end anastomosis of the carotid artery using an inverted U-shaped suture.

The next year, Murphy (11) has successfully united the ends of a femoral artery injured by a gunshot wound.

He has excised the damaged section of the artery and has invaginated the proximal end into the distal vessel holding it in place with sutures.

One of the most convinced assertors of suturing vessels, as any other tissue, has been Alexis Carrel (Figure 2) (12), who after studing in France with Jaboulay has begun to experiment the modern technique of suturing blood vessels.

FIGURE 2
Alexis Carrel

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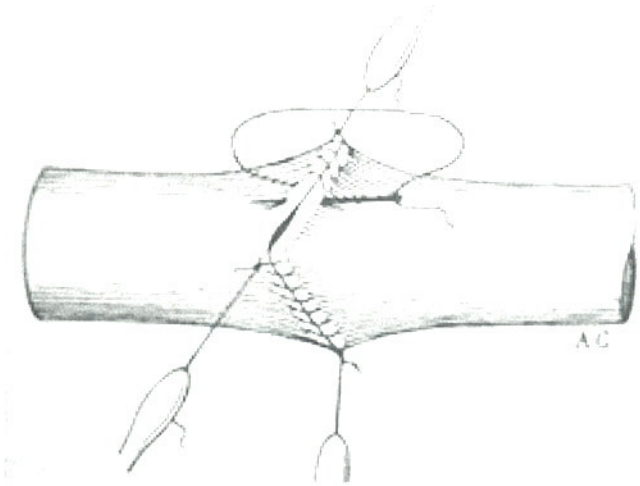

FIGURE 3
Carrel's technique of end-to-end anastomosis

His innovations in the field of end-to-end anastomosis (Figure 3), suture materials, patch graft technique and preservation of vessels in cold storage, have charmed several european and north american surgeons.

Among these, we would like to remenber the Spanish Goyanes (13), who in 1906 has removed a popliteal aneurysm using a in situ popliteal vein graft as reconstruction material, and Halsted (14) in the United States, who in the next year has used in a patient with a popliteal sarcoma the contralateral saphenous vein in a reversed position.

However, Halsted (14) if on the first side has made a proximal anastomosis between the graft and the popliteal artery, on the other side he has realized a distal anastomosis between autogenous graft and the popliteal vein.

Thus, at the beginning of XX century, the techniques necessary for suturing, anastomosing and grafting arterial vessels have been developed and are available.

After his studies in France with Jaboulay and Carrel and the end of the First World War, René Leriche (Figure 4) has given a great impulse to the development of vascular surgery, particularly to the treatment of peripheral occlusive diseases.

He first has realized the value of periarterial sympathectomy for the treatment of several circulatory and painful disorders of lower limbs (15).

After his studies about aortic endarterectomy and resection of the terminal aorta, Leriche has defined the syndrome with obliterative disease of aortic bifurcation, so-called "Leriche syndrome", describing it in 1923 (16) but reporting the first case of surgical treatment only seventeen years later (17).

Furthermore, Leriche has the merit of official beginning of the endoarterectomy's period, presenting in 1947 to the French Academy of Surgery the results of the work of J. Cid dos Santos (18), who in 1946 has performed the first successful thromboendarterectomy for peripheral occlusive disease, establishing this procedure as a feasible one.

In 1951, the procedure of aortic endarterectomy is introduced in the United States by Wylie (19), while Cannon and Barker (20) have been advocates of the use of endarterectomy for femoral atherosclerotic occlusive disease.

The procedure of endoarterectomy has gradually given way to bypass grafting, except for the carotid surgery and other localized obstructions.

In 1951, Kunlin first perform a long bypass graft of the femoral artery with a saphenous vein, using an end-to-end anastomosis (21).

In the same time, Oudot first resect the terminal aorta for Leriche syndrome and replace it with a preserved homologous aortic graft, using an end-to-end anastomoses (22).

Six months later, because of thrombosis of the right iliac limb of the graft, he places a cross-over graft from the left distal external iliac artery to the right distal external iliac artery, performing the first extra-anatomic bypass.

Like endoarterectomy procedure, also the resection of aortoiliac vessels with graft replacement has given gradually way to aortoiliac or aortofemoral bypass.

Linton, in 1952, has adopted the use of inverted saphenous vein (23), confirming Kunlin's approach.

Freeman (24), in the same year, has performed the first cross-over femoral graft using an endarterectomized segment of the left femoral artery to revascularize the right leg.

Two years later, Fontaine (25) has proposed a simple classification of patients with peripheral arterial disease, defining four stages based on clinical symptoms.

In 1961, Morris (26) has

FIGURE 4
René Leriche

emphasized the importance of the profunda femoris artery and of the proper management of lesions at this level for the success of aortofemoral bypass grafting.

In the same year, Blaisdell (27) performs an extraperitoneal thoracic aorta-to-femoral bypass graft to replace an infected aortic bifurcation prosthesis.

In 1962, the same author (27) has performed a bypass procedure for aortoiliac occlusion using a Dacron graft carried from the axillary artery subcutaneously to the femoral artery.

At the same time, Vetto (28) reports ten transabdominal subcutaneous femorofemoral graft operations to bypass iliac occlusive disease.

Thus, at the beginning of sixty years, also with the development of satisfactory materials for arterial substitutes, the picture of vascular surgery, particularly of peripheral occlusive disease treatment, shows the same surgical techniques still used today.

During the period from 1960 to 1966, we observe further improvements in distal procedures, thank to the Palma's (29), Veith's (30) and De Laurentis's (31) apports, in the use of in situ venous grafts (32) and profunda femoris artery in surgical treatment of lower limbs ischemia (33).

In conclusion, we would like to remember the important contribution of Thomas Fogarty, who in 1963 has introduced his balloon catheter for arterial embolectomy (34), which has improved the management not only of embolism but also of several vascular lesions.

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Epidemiology of Peripheral Vascular Disease

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The clinical epidemiological and public health importance of peripheral occlusive arterial disease (PAOD) has been increasingly recognised over the last decade. The definition of its specific features and severity of the prognosis in the various stage has been the task of a consensus group, with the aim of providing guidelines for testing preventive and therapeutic interventions.

The management of the patient with PAOD has to be planned in the context of the epidemiology of the disease and, in particular, the apparent risk factors or markers predicting spontaneus deterioration. It is also necessary to know the magnitude of the problem together with the likely outcome in patients with differing severity of PAOD to analyse outcome measures and to assess the socioeconomic impact of the disease.

The advanced stages of PAOD is critical limb ischemia (CLI), that have a particularly poor prognosis with respect to both mortality and morbosity. Critical limb ischemia is the term used to delineate those patients whose arterial disease has resulted in a lesion of the skin (ulcere or gangrene) or pain in the foot even at rest. The principal reason for adopting this broad inclusive definition is that most of the epidemiological data relate to this whole group. It is not possible to talk about the natural progression of these patients because they inevitably require active intervention. Little is known about the many more acute and chronic clinical and epidemiological variables in term of co-morbidity, and in relation to previous and concurrent interventions and treatments. The reasons may be sought both in the complexity of the disease itself and in the number of pathogenetic mechanism involved, as well as in the uncertainties existing with respect to the effectiveness of the currently available therapeutic interventions. This condition demand a disproportionately large commitment both in medical effort and economically. It also represents the major workload for vascular surgical units. However, it is only much more recently that data have been collected on large series of CLI patients outside the context of specific surgical procedures.

Incidence and prevalence of CLI

Knowledge of the incidence and prevalence of critical leg ischemia is essential for socioeconomic calculations and for health care planning on both regional and a national basis.

There is a little direct information on the incidence of CLI.

In Italy the only data available on incidence of CLI was assessed in North Italy (7) using three different approach. First, a prospective 7-year study on the incidence of CLI in 200 patients with intermittent claudication and 190 controls (development) which give an incidence of CLI equal to 450 per million per year in the population aged >45 years. Second a prospective 3-month study of hospitalisation for CLI in a sample of hospital in Lombardy which give an incidence of 652 per million per year in the population aged >45 years. Third, encoding the major amputation performed in the hospital in two regions (Lombardia for 6 months, Emilia Romagna for 2 years) with an incidence of 577 and 530 respectively. The results from the three approaches were substantially equivalent in order of magnitude.

Another source of data is a prospective observational study was carried out by the i.c.a.i. group (14) in order to describe the characteristics and clinical outcome of patients with CLI and to evaluate the consistency of the diagnostic and therapeutic practices with those recommended by the European Consensus.

This epidemiological approach was also undertaken with a view to identifying sizeable populations of patients as potential candidates for controlled clinical trial of various interventions. This study over a 3 months period, recruited 547 patients in 69 centres of vascular and general surgery, angiology and general medicine department of the Italian national health service. This patients had an adeguate diagnostic assessment of their vascular lesions and a high cardiovascular risk in term of prior morbidity and presence of risks factors.

Over half of the patients underwent revascularisation and the three quarters were given pharmacological treatments. At the end of the observation period 8.7% of the patients has died, 0.3% had a myocardial infarction, 1% a stroke, 12.2% a major amputation and 17.9% had persistent CLI.

This survey confirms the dramatic prognosis of patients with CLI and provides an appropriate background and setting to conduct experimental clinical studies in this field.

The second study of the i.c.a.i. (18) analysed the popu-

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lation of CLI patients enrolled in the i..c.a.i. trial, which found that prolonged treatment with i.v. prostanoids achieved only a brief benefit on CLI. This large clinical cohort was prospectively followed for up one year. Univariate analysis indicated the severity of the peripheral manifestation of the disease as associated with higher mortality; controlling for possible confounding variables the multivariate analysis highlights that the presence of trophic lesions increased the risk of amputation, ulcers and gangrene were independently negatively associated with CLI resolution. The mortality rate at 12 months (overall 19.1%) indicates that the prognosis is similar to that of myocardial infarction and stroke, once the age factor is taken into account.

In conclusion this large clinical cohort provides a reliable source of prognostic and therapeutic information that might be used in future consensus efforts and for guidelines.

Based on a national survey, the Vascular Surgical Society of Great Britain and Ireland (13) concluded that the estimated incidence of CLI was 21.450 limbs corresponding to approximately 20.000 patients; this equates to a prevalence of 1 in 2.500 of the population each year. Thirty percent of patients were diabetic, the mean mortality and amputation rate for all patients in the survey were 13.5% and 21.5% respectively. The mean duration of hospital stay was 25 days and 26.1% required long-term institutional support. Nearly 70% of patients were offered some form of revascularisation as the primary treatment option whit a 75% chance of successful limb salvage. Amputation was associated with significantly higher mortality, longer hospital stay and a larger proportion of patients requiring long-term institutional support.

The incidence of CLI can also be estrapolated from the better-documented prevalence studies of intermittent claudication (IC). If one assumes that the overall prevalence of claudication is 3% and that 5% of patients with IC will develop CLI over 5 years, this gives an incidence of CLI of 300 per million per year. Finally, the incidence of CLI can be calculated from the number of major amputations performed.

Assuming that 90% of major amputations are performed for ischemia and that only 25% of patients with CLI ever require a major amputation, it can be calculated that the incidence of CLI is approximately 500 to 1000 per million per year. Surprisingly perhaps, the incidences calculated using these different methodologies are very similar. Roughly, one new patients per year will develop CLI for every 100 patients with IC in the population.

TABLE 1
Estimated number of major amputations/annum in different countries

Country	Estimated number/million/annum
Lombardia (Italy)	172
Emilia Romagna (Italy)	154
UK	300
Sweden	500
Denmark	250
Western Finland	120
Holland	246
Scotland	142

Risk factors

In studies dealing with risk factors and risk prediction it is important to consider the validity of the data base. Risk facotrs may be erroneously measured or recorded, outcome measures may have been wrongly defined or understood. The risk factors examined represent the type of information available in routine car where no intentional selection has been done as to the possible value or use of the collected data.

The mainly risk factors for the development of CLI are age, smoking and diabetes.

Age is probably the most important factor to develope CLI and also major amputation are more common in the erderly. Some estimates the peak of incidence occurs in people aged 70-79 years, then the burden will grow progressively as the number surviving to old age increases.

Cigarette smoking increases both the risk of developing peripheral arterial disease (PAD) and its progression, in some multivariate analyses smoking has been shown to be an independent risk factor and to be more important in causing PAD that coronary artery disease (CAD). (1,2,10)

About diabetes one study (3) reported the progression of CLI to gangrene to be 40% in diabetic patients compared with 9% in non diabetic patients. The correlation between diabetes and major amputation rates is independent of other risk factors, including age and smoking. Those with diabetes generally undergo major amputation at an earlier age than those without diabetes.

In the study of i.c.a.i. group (17) the factors indipendently associated with a higher mortality, besides advanced age, were a history of stroke and major amputation.

Some considerations about economic aspect of critical leg ischemia

Economic aspect of treatment play an increasingly important role, if not in the primary choice of treatment

for the patient, then at least for decision-making in the allocation of resources.

Especiall worrying is the growing proportions of erderly persons as they have higher incidences of degenerative disease, like CLI, and need longer hospital treatments than younger patients. As resources are limited and priority decisions inevitable, it is important to evaluate the cost-efficiency and the cost-benefit of given treatments, including both hospital treatment and community care in relation to clinical results and quality of life parameters; this is cost-utility analysis where the residual life expectancy is adjusted for quality (QALYs).

The treatment of CLI is surgically demanding and resources consuming. Reconstrutions, especially infrainguinal reconstrution that are necessary for a majority of patients, frequently need further procedures.

Primary amputation is associated with a high mortality and the mobility and quality of life is reduced for the amputed patient. For society, either treatment is combined with costs that strain budgets. The treatment aim is to assure the patient of a clinically optimal solution with long-term benefit in an accetable economic frame.

Conclusion

Vascular registries have recently been established in all Nordic countries to promote quality control, scientific work, education, proper resouces allocation and health care planning. The registry data have to be valid to allow any analysis; there is always some bias in such large-scale vascular data as a result to its unavoidable incompleteness. It is important to classify correctly the patients which suffered of CLI and to define CLI with strictly criteria so the data have easily comparable.

To estimate the prevalence of CLI in Italy we propose to carry out a prospective national survey of patients. The objectives of this kind of study were: to estimate the prevalence of this condition within the community and the burden imposed by it upon health services, to determine the relative number of patients managed by the different treatment options available and to assess the average outcome in term of mortality, limb savage, duration of hospital stay and whether the patients was returned to his own home or had to be permanently accommodated in an institutions.

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