C. ALLEGRA - P.L. ANTIGNANI

Proceedings of the 21st EUROCHAP - IUA European Chapter Congress of the International Union of Angiology

Rome, Italy
(September 28 - October 1, 2013)

EDIZIONI MINERVA MEDICA

C. ALLEGRA - P.L. ANTIGNANI

Proceedings of the

21st EUROCHAP - IUA European Chapter Congress of the International Union of Angiology

Rome, Italy
September 28 - October 1 2013

EDIZIONI MINERVA MEDICA
TURIN 2013

ISBN: 978-88-7711-616-1

Sito Internet: www.minervamedica.it / *e-mail:* minervamedica@minervamedica.it

Welcome address

Dear Colleagues and Friends,
It is a pleasure to welcome you to the 21st EuroChap 2013 Meeting of IUA which is to be held in one of the world's most beautiful cities - Rome. This venue has been previously selected several times as a meeting place for vascular specialists from all around the world. With regard to the International Union of Angiology, it is even possible to say that Rome, and Italy in general, has become the most frequent destination of scientific gatherings of this society organized to date. And this is not only by chance. Italian vascular specialists belong among the most active members of the IUA. The Italian contribution to research, knowledge and clinical practice of vascular diseases cannot be in any case overlooked.
The EuroChap is organized in conjunction with the national congress of Italian Society for Vascular Investigation and prof. Antignani, prof. Allegra and their team have been working for many months to organize this congress and I am glad to have the opportunity to congratulate them for preparing such a wonderful and outstanding program. Allow me to express my gratitude and conviction that we will spend together a pleasant and fruitful time in this exciting city. I am sure we'll return enriched not only by scientific news but also with a feeling of mutual friendship.
Welcome again and may we have a nice meeting in Rome!

Prof. Karel Roztocil
President of International Union of Angiology

Presidents' Congress welcome address

We would like to welcome you all to Rome which, despite its familiarly hospitable side, encloses the past greatness not only of ancient Rome but also of all the cultural and architectural movements that it has hosted over the ages.

It is often said that this great city is humble and unassuming in appearance, but this is only true because it is the one city in the world that encompasses 4,000 years of history scattered freely in every corner. Walking around Rome is like buying a ticket to an enormous museum that one may observe and admire at a stroll.

All of this is in addition to the world's largest place of worship, St. Peter's, beacon of greatness and caritas, a hand stretched out to lighten the world's suffering and steer science and technology between good and evil.

With a bit of care, each of you attendees will be able to find a piece of his or her history in this venue for the Congress, which looks out on Michelangelo's great dome.

This European chapter of the IUA will focus on the problems currently faced by Angiology, with the aid of those best versed in the subjects concerned and with the goal of harmonising language, rules and international regulations: not a banal globalisation of the problems, but a shared language rationally accepted by all, within the due limits imposed by sustainability.

Welcome and please accept our apologies in advance if everything is not perfect, but perfection is not of this world.

Prof. Claudio Allegra
Prof. Pier Luigi Antignani

Contents

The power and limitations of guidelines

P. Poredoš, M.K. Ježovnik
Department of Vascular Disease, University Medical Centre Ljubljana, Ljubljana, Slovenia

Introduction

Recently numerous clinical guidelines appeared. Nevertheless, there is considerable uncertainly whether this will improve clinical practice.[1] However, it is easier writing guidelines than introduce them in everyday clinical practice. If guidelines are to achieve the health gain some criteria have to be fulfilled. Firstly, purchasers and providers should identify scientifically valid guidelines in the sense that when followed, they lead to the health gain projected for them.[2] Further, validity of guidelines is more likely if they are based on systemic literature review and are written by independent groups including representatives of all key disciplines and of explicit link between recommendation and scientific evidence.[2] Secondly, providers should ensure that scientifically valid guidelines are successfully introduced in medical practice, thus leading to health gain. Therefore, clinical guidelines should produce explicit recommendations that are both scientifically valid and helpful in clinical practice.

Who should do it and how guidelines should be developed?

Guidelines can be developed by internal groups composed entirely of the clinicians who will use them, intermediate groups or external groups. In last case, none of them will use proven guidelines. Most of studies evaluating the clinical applicability of guidelines in dependency on authors concluded that there is a greater compliance if they were developed by users of proven guidelines and not by others.[3] For local guidelines also fewer resources are needed to disseminate and implement them than for intermediate or external guidelines.

For clinical applicability it is also important how they are presented. There is considerable diversity in their presentation. The Harvard Community Health Plan has established quality assurance program based exclusively upon algorithms.[4] However, doctors are often reluctant to use algorithms in every day clinical practice because of their apparent complexity and the lack of flexibility. In contrast, other groups like guidelines which are concrete (making specific recommendations), offering practical advice to the clinicians, and dividing patients into specific subclasses. To meet these different demands, many groups now produce guidelines containing a short summary of principle recommendations in combination with the detailed presentation of proven topic.

Also the dissemination strategy is important to influence target physicians, awareness attitudes and knowledge. Implementation strategies are intended to encourage clinicians to change their own clinical practice in line with guidelines. The simple strategy of distribution is to provide clinicians with easily accessible copies of the guidelines: tables or guidelines packed in a format that can be easily carried.[5] There are different implementation strategies of guidelines and the studies confirmed that implementation strategies operating within the consultation that focus on the management of individual patients are more likely to lead to changes in medical practice. There is little evidence about relative effectiveness of strategies operating outside the consultation, but it seems that they contributed substantially to the success of guidelines when they were used.

The role of clinical guidelines

Clinical guidelines represent very important and useful tool for providing efficient, rational, and safe medical care. They represent general opinions and suggestions which don't completely cover the needs of each individual patient. However, to fulfil expectations and mission, guidelines should fulfil some basic criteria: they cannot achieve health gain unless they are scientifically valid and consistent with the available scientific evidence for best clinical judgment. Clinical guidelines can achieve health gains if appropriate development, dissemination, and implementation strategies are adopted during their introduction. However, guidelines cannot achieve health gains and influence every day clinical practice unless they are not introduced and implemented. Research is needed to determine the barriers to implementing the recommended guidelines and perhaps more practical details for a simpler approach for development of guidelines may be required.[6]

Conclusion

In spite of considerable uncertainty whether clinical guidelines will improve clinical practice they represent very important role in management of patients with different diseases and provide safely and scientifically proven international health care. Clinical guidelines cannot achieve health gain unless they are scientifically valid and implemented. Successful introduction needs leadership, good communication and above all, time.[7]

References

1. Guidelines for doctors in the New World. Lancet 1992;339: 1197-8.
2. Grimshaw J, Russell I. Achieving health gain through clinical guidelines. I: Developing scientifically valid guidelines. Qual Health Care 1993;2:243-8.
3. Medical audit in general practice. I: Effects on doctors' clinical behaviour for common childhood conditions. North of England Study of Standards and Performance in General Practice. BMJ 1992;304:1480-4.
4. Schoenbaum SC, Gottlieb LK. Algorithm based improvement of clinical quality. BMJ 1990;301:1374-6.
5. Landgren FT, Harvey KJ, Mashford ML *et al*. Changing antibiotic prescribing by educational marketing. Med J Aust 1988;149:595-9.
6. Turner T, Misso M, Harris C *et al*. Development of evidence-based clinical practice guidelines(CPGs): comparing approaches. Implement Sci 2008;3:45.
7. Grimshaw JM, Russell IT. Achieving health gain through clinical guidelines II: Ensuring guidelines change medical practice. Qual Health Care 1994;3:45-52.

The role of associations of vascular patients

M. Catalano
Research Center on Vascular Diseases and Angiology Unit, University of Milan. L. Sacco Hospital, Milan, Italy

Aim

Prevention, patients' centrality and compliance [1, 2] are three different tools based on awareness and active participation of patients that interact and contribute as individuals as well as members of the society, to develop effective health prospects and necessary measures.
The process to obtain this active participation requires clear and shared aims related to the different steps and methods with interactive procedures to keep a check on the process.
Up to few years ago (still existing in most of our health realities) the relationship doctor/sanitary personnel-patients, hospital-patient, NHS-citizen were completely asymmetrical,[3] not only caused by psychological factors but also by traditional education and training of the sanitary staff, by the organization of the health institutions and by the strategies of the NHS.
The following facts in particular have contributed to modify realty: world development of the consciousness of rights, the Web 2.0 revolution which spreads out information and shares experiences, the employment of a new generation of health personnel brought up with a democratic view of knowledge, the improvement of research on the effectiveness of compliance as well as of prevention, the economic crisis itself with the need of reducing costs.
This process has both driven to well codify and rigid expressions (*e.g.* information for patients, informed consent and the respect of privacy etc.) as well as innovative experimental formulas to concretely revise the role of the patient in the treatment process and his role as a citizen on the pathway to good health.
Focusing on vascular patients, one of the most consistent elements to be added to these general considerations is that they are affected by chronic disease and that a weighty familiarity exists making their active involvement even more relevant.

Material and methods

There is a lack of accepted efficacy indicators to evaluate results in this area. Health outcomes and patient satisfaction have been proposed,[4] but they don't cover the whole experience.
The first method we used was focused on the patients' education centering on the disease and on the personal clinical condition. As described in literature the results were positive if compared to the most traditional approach, using compliance as the main indicator. However, the self-identification as a "patient" remained the prevalent attitude.
The second approach was opposite to the first. Patients were requested to take part in social activities related to the disease. In the first phase, that seemed to be a superb approach, patients were asked to concentrate on the social side of their experience. After a short period we found a reduction in the number of patients involved and some of them left our Unit as they felt a contrast between their own needs and the activities proposed.
Following the previous results a 7 step protocol was defined, leaving the interaction and agreement with the patients as how to put it into practice:

- Step 1. Conventional clinical visit with invitation to educational meetings.
- Step 2. Conventional clinical visit + individual educational meetings.
- Step 3. Educational group meetings with exchange of experience.
- Step 4. Educational group meetings with exchanges of experience and evaluation of the assistance offered by the Unit- Patients requested to help.
- Step 5. Meetings with both education and exchange of experience as well as the organization of patients support to the Units activity. Patients requested to help in citizen awareness projects.
- Step 6. Vascular Patient Groups founded as part of AmaVas National Association.
- Step 7. Continuous collaborative activities, mixing personal needs of knowledge, rehabilitative activity as a group, to support the Unit if necessary (including student training), national activities. Hence, natural links to the European projects.

Personal clinical follow-up visits remain in the usual clinical protocols.

Results

This multistep approach respects the needs and the patients' rights ensuring safe and quality care, improving their knowledge, their responsibility, and their ability to self-evaluation and at the same time improve quality of life, well-being, satisfaction and self-confidence. The approach to their disease seems to change from a self-related responsibility to a more social responsibility based both on examples in life style and in active commitments at different levels.

Asymmetry has been deeply reduced, notwithstanding the different competences and roles carried out, due to the common aims. The most demanding and relevant social experiences are those in AmaVas (Italian no-profit Association linking doctors, researchers, patients and the general population) and the commitment to the international awareness projects of VAS-Vascular-Independent Research and Education-European Organisation (http://www.vas-int.net) and the "PAD&Vascular European Days" (every 3rd Wednesday and Thursday of March from 2014) where, along with training, palpation of arteries is taught (FooTest). For the first time learning "self-examination" of the arteries of the feet, will be introduced (in analogy to breast tumor prevention etc.) to contribute to discover a suspected PAD.

Discussion

The basic element is the changing central figure, from the position of a patient to an informed man and citizen, with the right and the social duty to cooperate on the prevention and/or improvement of his own health and hopefully contribute to the development of a healthier society, offering quality and equity-friendly services.

Quality is not only guaranteed and measured by professional figures and structures and the NHS, but is evaluated and improved by those using the Services.

Patients organizations make these changes permanent.

Conclusion

The social dimension and active participation is strongly enhanced by the involvement of the patient flanked by other figures.

A multi-step process is required to create such involvement without creating conflict with the need to focus on their lives and the definitions through which the illness is expressed.

Skills in individual roles are respected, but do not create asymmetry. Scientific and clinical knowledge, sanitary aspects and direct experience become different sides of a common task.

Collaboration among Patients' Organisations increases confidence and leads to relevant results both in personal terms and that of awareness.

References

1. Michie S, Miles J. Weinman. Patient-centredness in chronic illness: what is it and does it matter? Patient Educ Couns 2003; 51:197-206.
2. Thompson AGH. Moving beyond the rhetoric of citizen involvement: Strategies for enablement. Eurohealth 2003-2004;9:5-8.
3. World Health Organization. Adherence to long-term therapies: evidence for action, Geneva: WHO; 2003.
4. Lewin SA, Skea ZC, Entwistle V *et al.* Interventions for providers to promote a patient-centred approach in clinical consultations. Cochrane Database Syst Rev 2001;(4):CD003267.

Point on: metabolic syndrome and asymptomatic carotid lesions predict future cerebro and cardiovascular events beyond the cards of risk

S. Novo, A. Peritore, R.L. Trovato, L. Arvigo, V. Evola, M.C. Sinacori, G. Novo

Cardiovascular Disease and Centre for the Early Diagnosis of Preclinical and Multifocal Atherosclerosis and for Secondary Prevention - Department of Internal Medicine and Specialities, University of Palermo and Division of Cardiology, Department of Internal Medicine and Cardiovascular Disease, Palermo, University Hospital "P. Giaccone" of Palermo, Italy

Introduction

Atherosclerosis is a significant cause of death in the developed world and quite frequently it presents as a fatal event, hence the interest in detecting it in its subclinical stages. The atherosclerotic process starts in childhood and proceeds silently over a long period of time before clinical manifestations.

Subclinical disease can be measured using non-invasive B-mode ultrasound in order to assess common carotid artery intima-media thickness (IMT) that reflects the structural deterioration of the arterial wall, and it is considered a significant predictive marker of generalized atherosclerosis and future cardiovascular events in adults.[1]

Several studies have shown that a thicker IMT predicts coronary heart disease,[2] stroke,[3] and myocardial infarction.[3, 4] In particular, a 5.5 years-follow-up showed that the risk of myocardial necrosis increases for about 10-15% just if IMT increases for 0,1 mm while the risk of stroke increases for about 13-18%.[5]

The metabolic syndrome (MetS) represents a clustering of several cardiovascular (CV) risk factors including abdominal obesity, impaired glucose intolerance, dyslipidemia, and hypertension, with insulin resistance as a major characteristic.[6-8] Several clinical studies recognized MetS as responsible for the endothelial dysfunction, which is the first "step" in atherothrombotic disease and, in addition, it has been observed the association between an increased carotid IMT (C-IMT) and MetS.[9-12]

Personal experience

We assessed the influence of carotid atherosclerosis on prediction of cardiovascular events during a 20-years follow-up in a population of 529 asymptomatic, middle-aged subjects, and we also evaluated the role of the metabolic syndrome on the risk of cardiovascular events comparing groups with equal atherosclerotic lesions. Differences between groups were compared by the *Chi-square test* for categorical variables.

During the follow-up there were 242 cardiovascular events: 144 in patients with MetS (251 patients) and 98 in healthy controls (278 patients); (57.4% *vs*. 35.2%; P<0.0001).

As to the presence or absence of carotid atherosclerosis, 63 events occurred in patients with normal carotid arteries (198 patients), while 179 events occurred in patients with subclinical atherosclerosis (increased IMT/asymptomatic plaque; 331 patients); (31.8% *vs* 54.1%; P<0.0001). In the 144 total events occurred in patients with MetS, 36 happened in the subgroup of patients with normal carotid arteries and 108 happened in the subgroup of patients with subclinical atherosclerosis (45% *vs* 63.15%; P=0.0099). Similarly, in the 98 total events occurred in patients without MetS, 27 developed in the subgroup with normal carotid arteries and 71 in the subgroup with subclinical atherosclerosis (22.88% *vs.* 44.37%; P=0.0003). So, atherosclerosis produced a significant increase of the risk of events, especially in presence of MetS (Table I).

Furthermore, in the 63 total events occurred in patients without atherosclerotic lesions, 36 events were recorded in the subgroup with MetS and 27 events in the subgroup without MetS (45% *vs.* 22.88%; P=0.0018). Among 179 total events recorded in patients with atherosclerotic lesions, 108 events happened in the subgroup with MetS and 71 events in the subgroup without MetS (63.15% *vs.* 44.37%; P=0.0009). So, both in patients with atherosclerosis and in patients without atherosclerotic lesions the presence of MetS increased the risk of CV events (Table I).

Finally, comparing the subgroup without MetS and without atherosclerotic lesions to the subgroup affected by MetS and subclinical atherosclerosis, the second group showed a higher incidence of cardiovascular events (22.88% *vs.* 63.15%; P <0.0001); (Table I).

Our data confirm the results of other clinical studies (nationals and internationals) that have examined the relationship between atherosclerosis, MetS and CV risk.[13-16]

Table I. – Distribution of CV events in each subgroup of population.

	MetS (251 patients)	No MetS (278 patients)	P	Subclinical Atherosclerosis (331 patients)	108 events / 171 patients (63.15%)	71 events / 160 patients (44.37%)
Normal vessels (198 patients)	36 events / 80 patients (45%)	27 events / \ 118 patients (22.88%)	P=0.0018	P=0.0009	P=0.0099	P=0.0003

We demonstrated that the presence of subclinical atherosclerosis lead to an increased incidence of cardiovascular events, especially if it is associated with MetS. In fact, total cardiovascular events were more frequent in the group of patients with carotid atherosclerosis compared to patients with normal carotid arteries (P<0.0001). Similarly, both in patients with MetS and in patients without MetS, cardiovascular events were more frequent in presence of carotid atherosclerosis than without these lesions. Moreover, also the importance of MetS resulted significant, in fact, both in patients with atherosclerosis and in patients without atherosclerotic lesions the presence of MetS increased the risk of CV events. In addition, according to the recent ESC 2012 guidelines on cardiovascular prevention, the detection of an asymptomatic carotid plaque put subjects in the very high risk category.[16]

Conclusion

In conclusion we suggest to investigate the presence of subclinical atherosclerosis in all patients >45 years old, by a carotid echo-color-Doppler test, because the assessment of Subclinical atherosclerosis can improve the cardiovascular risk definition,[5, 17] especially in presence of metabolic anomalies.

References

1. Dahl-Jørgensen K, Larsen JR, Hanssen KF. Atherosclerosis in childhood and adolescent type 1 diabetes: early disease, early treatment? Diabetologia 2005;48:1445-53.
2. Bots ML, Hoes AW, Koudstaal PJ *et al.* Common Carotid Intima-Media Thickness and Risk of Stroke and Myocardial Infarction: The Rotterdam Study. Circulation 1997;96:1432-7.
3. O'Leary DH, Polak JF, Kronmal RA *et al.* Carotid-Artery Intima and Media Thickness as a Risk Factor for Myocardial Infarction and Stroke in Older Adults. Cardiovascular Health Study Collaborative Research Group. N Engl J Med 1999;340: 14-22.
4. Salonen JT, Salonen R. Ultrasound B-Mode Imaging in Observational Studies of Atherosclerotic Progression. Circulation 1993;87:156-65.
5. Novo S, Visconti CL, Amoroso GR *et al.* Asymptomatic carotid lesions add to CV risk prediction. Eur J Cardiovasc Prev Rehabil 2010;17:514-8.
6. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation 2002;106:3143-421.
7. Novo S, Balbarini A, Belch JJ *et al.* The metabolic syndrome: definition, diagnosis and management. Int Angiol 2008;27:220-31.
8. Novo G, Corrado E, Muratori I *et al*. Markers of inflammation and prevalence of vascular disease in patients with metabolic syndrome. Int Angiol 2007;26:312-7.
9. Koskinen J, Kähönen M, Viikari JS *et al.* Conventional CV Risk Factors and MetS in Predicting Carotid Intima-Media Thickness Progression in Young Adults. The CV Risk in Young Finns Study. Circulation 2009;120:229-36.
10. Kawamoto R, Tomita H, Inoue A *et al.* Metabolic syndrome may be a risk factor for early carotid atherosclerosis in women but not in men. J Atheroscler Thromb 2007;14:36-43.
11. McNeill AM, Rosamond WD, Girman CJ *et al.* Prevalence of coronary heart disease and carotid thickening in patients with metabolic syndrome (the ARIC study). Am J Cardiol 2004;94: 1249-54.
12. Sipilä K, Moilanen L, Nieminen T *et al.* Metabolic syndrome and carotid intima media thickness in the Health 2000 Survey. Atherosclerosis 2009;204: 276-81.
13. Nambi V, Chambless L, Folsom AR *et al.* Carotid intima-media thickness and presence or absence of plaque improves prediction of coronary heart disease risk: the ARIC (Atherosclerosis Risk in Communities) study. J Am Coll Cardiol 2010;55:1600-7.
14. Sehestedt T, Jeppesen J, Hansen TW *et al.* Risk prediction is improved by adding markers of subclinical organ damage to SCORE. Eur Heart J 2010;31:883-91.
15. Mookadam F, Moustafa SE, Lester SJ *et al.* Subclinical atherosclerosis: evolving role of carotid intima-media thickness. Prev Cardiol 2010;13:186-97.
16. European Guidelines on Cardiovascular Disease Prevention in Clinical Practice (version 2012): the Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts). Eur J Prev Cardiol 2012;19:585-667.
17. Shah PK. Screening asymptomatic subjects for subclinical atherosclerosis: can we, does it matter, and should we? J Am Coll Cardiol 2010;56:98-105.

News in diagnostic evaluation of Horton disease

M. Amitrano [1], F. Cannavacciuolo [2], S. Mangiacapra [2]
[1]UOS Angiologia, Dipartimento Medicina Interna e Specialistica, AORN Moscati, Avellino, Italy
[2]Dipartimento di Medicina Interna, Seconda Università degli Studi di Napoli (SUN), Italy

Aim

Giant cell arteritis (GCA) is a chronic systemic vasculitis affecting large and medium-sized arteries with an elastic lamina. It was first described by Horton, in 1932, and so it is even called "Horton disease". It usually involves cranial vessels, in particular the branches of the external carotid artery, including the posterior ciliary arteries that supply the optic nerve. In these vessels, inflammation can cause intimal hyperplasia, thus giving the most dreaded complication, *i.e.* visual loss, occurring in almost 15% of patients. That's why early diagnosis and prompt initiation of steroid treatment is mandatory. GCA can also affect large vessels outside the cranium, particularly the aorta and its proximal branches. Involvement of extra-aortic large vessels most often affects the upper extremities, in particular the subclavian, axillary, and proximal brachial arteries. Otherwise, inflammation of lower extremities vessels and mesenteric arteries is less common. These extracranic forms are defined as "Large Vessel GCA" (LV-GCA), and clinically differ from classic GCA, since they are often lacking of signs and symptoms of cranial arteries involvement (i.e. headache, visual impairment, jaw claudication), while arm claudication (due to upper extremity vascular insufficiency) or constitutional symptoms (fever of unknown origin, systemic inflammatory syndrome) are frequently observed. The aorta and its branches can be involved, but aortic inflammation often goes undetected, since there are no symptoms until complications arise. While in the other vessels GCA causes stenosis and occlusion, thus resulting in ischemic manifestations, when Horton disease affects the aorta it can cause aortic dilatation and aneurysm formation, which may lead to aortic dissection or rupture. In particular, aortitis is associated with an increased risk of aneurysms of the thoracic aorta, therefore routine screening for aortic involvement is necessary, as well as a monitoring of aneurysms at regular intervals, even after steroid treatment discontinuation. There is considerable overlap between GCA and polymialgia rheumatica (PMR). This one is characterized by aching and morning stiffness in the neck, shoulder and pelvic girdle, accompanied by a systemic inflammatory response. About pathogenesis, some factors (geographical variation, seasonal fluctuations) suggest an environmental, possibly infectious, etiology of the disease, but no clear association with a particular infectious organism has been found. Moreover, there is probably a genetic component too, probably some particular HLA genotype. Effectively, HLA-DRB1*0404 and HLA-DRB1*0401 are associated to GCA in some populations.[1] Histopathology typically shows an inflammatory infiltrate in all three tunics of the arterial wall, with giant cells in the media, with intimal hyperplasia and partial or complete occlusion of arterial lumen with consequent ischemia. The infiltrate in the arterial wall is composed primarily by T-cells and macrophages. T-cells are predominantly CD4+. These two kind of cells play a central role in the inflammatory damage in GCA.

As regards clinical presentation, temporal arteritis is the most typical one, with the onset of headache, scalp tenderness and jaw caludication. Signs of systemic inflammation are often observed, such as general malaise, fever, anorexia, weight loss and elevated acute phase reactants. Visual manifestations are also frequent and range from transient diplopia and amaurosis fugax to sudden unilateral or bilateral visual loss, with permanently visual loss affecting approximately 15% of patients. In LV-GCA the most common manifestation of upper extremities vasculitis is arm claudication; Raynaud's phenomenon and digital ischemia can also occur. Aortic involvement, on the other hand, is often clinically silent or may manifest with systemic signs such as fever of unknown origin.

As for diagnosis, there are no official diagnostic criteria. American College of Rheumatology's (ACR) 1990 criteria for GCA are: 1) age >50 years; 2) new onset of localized headache; 3) temporal artery tenderness on palpation or decreased pulsation; 4) ESR >50 mm/h; 5) abnormal temporal artery biopsy.[2] The presence of three of these criteria is necessary for diagnosis of GCA. Nevertheless, the diagnostic accuracy of these criteria is uncertain, since they were established as classificative (not diagnostic) criteria, in order to distinguish a specific type of vasculitis among patients with various vasculitides, not to differentiate patients who have vasculitis from those who don't have vasculitis.[3] Temporal artery biopsy is still considered as the "gold standard" for the diagnosis of GCA, of which the typical histopatology consists of an inflammatory infiltrate in all three tunics of the arterial wall, with

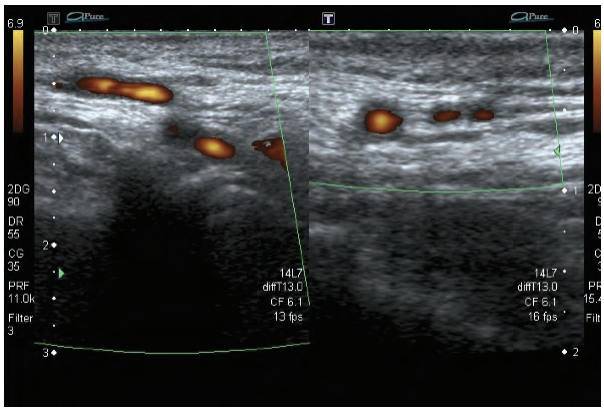

Figure 1. – Halo.

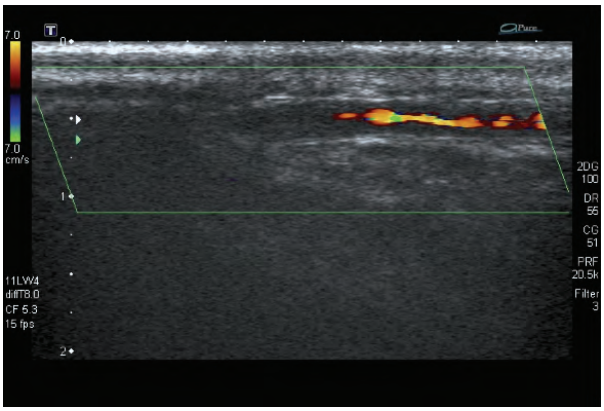

Figure 2. – Stenosis and occlusion.

giant cells granulomas in the media (especially at the intima-media border). The recommended length of the biopsy sample is between 1 cm and 2 cm. Anyways, biopsy has a lot of limitations. First of all, even if it is safe enough, there are some complications such as skin necrosis, damage of facial nerve, drooping of the eyebrow and stroke due to the interruption of collateral circulation.[4-9] Moreover, biopsy has low sensitivity with a percentage of false negatives between 9% and 44%,[10] probably due to the segmental inflammation of the artery, that could be not involved in the sampled segment. Furthermore, in the so-called Large Vessel GCA (LV GCA), temporal arteries are often spared, and this can result in a false negative biopsy. So, it is necessary to have new diagnostic tools in order to make an earlier diagnosis of this vasculitis, thus preventing its severe complications (blindness, stroke, aortic aneurisms rupture).

Materials and methods

Schmidt *et al.*, in 1997, were the first to study the use of ultrasonography in the diagnosis of GCA. In particular, they found that in inflamed temporal artery, ultrasonography may show: 1) halo sign, that is a dark hypoechoic circumferential wall thickening around the artery lumen (Figure 1); 2) stenosis (segmental increase of blood flow velocity); (Figure 2) 3) occlusions (absence of flow in the temporal artery). In this study halo sign was the one that showed specificity for GCA.[11] Many other studies have been published about this item, including a metanalysis that showed that halo sign is useful for diagnosis of GCA with a sensitivity of 68% and a specificity of 100%, if bilateral.[12] In other studies, ultrasonography was compared with biopsy in clinical practice. In particular, in one of these studies they compared clinical decision made after temporal artery biopsy versus negative temporal artery duplex, and also the effects on patients' outcome. Therefore, there were no differences between the two groups in terms of clinical decision and final outcome, but we must remember that biopsy exposes patients to additional potential morbidity, while ultrasonography is well tolerated, more accessible, less expensive, more rapid and easier to perform.[12]

Results

These data suggest that US can play a central role in diagnosis and treatment of GCA. Moreover, it can be useful for follow up of patients in steroid therapy, since it has been shown that the "halo" disappears 14-16 days after the beginning of treatment. So, biopsy should be used in limited circumstances, that is when clinical picture is not consistent with US findings. In particular, some suggest that in patients with high clinical probability we can start treatment and no more test is required. Patients with low and intermediate clinical probability, instead, should undergo a bilateral temporal artery duplex followed by biopsy only when a positive duplex result is not consistent with the clinical picture. In this case, the area of abnormality at the duplex can be sampled with biopsy.[12] But temporal arteries are not the only ones that can be studied with US for suspected GCA. Ultrasound, indeed, can show characteristic abnormalities (i.e. stenosis, occlusions and halo sign) even in the upper extremity arteries, especially in LV-GCA, where the axillary artery involvement is more frequent.[14] So, extending the US examination to these districts in patients with PMR, temporal arteritis, arm claudication, unclear inflammation or fever of unknown origin (FUO), can bring to a greater number of diagnosed cases with LV-GCA.

In our experience, moreover, we found halo sign and the other less specific US findings in some cranial arteries other than the temporal one such as facial artery, thus suggesting that a systematic study of other cranial and extracranial districts could increase sensitivity of US for Horton disease's diagnosis and allow an early treatment of these patients. Nevertheless, more studies are required to better analyze this aspect. In this context, however, there are some criticalities. First of all, ultrasonography is still strictly dependent on the performer.

Discussion and conclusion

Furthermore, we lack of a truly standardized method of examination, since, except for temporal and axillary arteries, all other districts (cranial and extracranial), that anyway could show the typical alterations, are not systematically analyzed at duplex. So there is a great necessity of ultrasonographic guidelines for the detection and evaluation of this disease, that could increase diagnostic accuracy of this procedure, thus leading to a validation of a revised set of diagnostic criteria for GCA that could include the halo sign or other US finding.

References

1. Ly KH, Regent A, Tamby MC *et al*. Pathogenesis of Giant Cell Artheritis: more than just an inflammatory condition? Autoimmune Rev 2010;9:635-45.
2. Hunder GG, Arend WP, bloch DA *et al.* The American College of Rheumatology 1990 criteria for the classification of vasculitis. Arthritis Rheum 1990;33:1065-7.
3. Rao JK, Allen NB, Pincus T. Limitations of the 1990 ACR Classification Criteria in the Diagnosis of vasculitis". Ann Intern Med 1998;129;345-52.
4. Ikard RW. Clinical efficacy of temporal artery biopsy in Nashville, Tennessee. South Med J 1988;81:1222-4.
5. Slavin ML. Brow droop after superficial temporal artery biopsy. Arch Ophthalmol 1986;104:1127.
6. Bhatti MT, Goldstein MH. Facial nerve injury following superficial temporal artery biopsy. Dermatol Surg 2001;27:15-7.
7. Siemssen SJ. On the occurrence of necrotising lesions in arteritis temporalis: review of the literature with a note on the potential risk of a biopsy. Br J Plast Surg 1987;40:73-82.
8. Fisher CM. Discussion. Giant cell arteritis (temporal arteritis). Trans Am Neurol Assoc 1971;96:12-5.
9. Haist SA. Stroke after temporal artery biopsy. Mayo Clin Proc1985;60:538.
10. Hall S, Persellin S, Lie JT *et al*. The therapeutic impact of temporal artery biopsy. Lancet 1983;2:1217-20.
11. Schmidt WA, Kraft HE, Vorpahl K. Color duplex ultrasonography in the diagnosis of the temporal arteritis. N Engl J Med 1997;337:1336-42.
12. Arida A, Kyprianou M, Kanakis M *et al.* The diagnostic value of ultrasonography-derived edema of the temporal artery wall in giant cell arteritis: a second meta-analysis. BMC Musculoskelet Disord 2010;11:44.
13. Alberts MS, Mosen DM. Diagnosing temporal arteritis: duplex *vs.* biopsy. Q J Med 2007;100:785-9.
14. Schmidt WA, Seifert A, Gromnica-Ihle E *et al.* Ultrasound of proximal upper extremity arteries to increase the diagnostic yield in large-vessel giant cell arteritis. Rheumatology 2008;47:96-101.

Contrast carotid ultrasound for the detection of plaque at higher risk of embolism

P. Rispoli, G. Varetto, P. Garneri, A. Gattuso, C. Castagno, L. Gibello

Department of Surgical Sciences Division of Vascular Surgery, Città della Salute e della Scienza, Molinette Hospital, Torino, Italy

Aim

The traditional morphological parameters for the description of a carotid atherosclerotic plaque (degree of stenosis and systolic peak velocity) are insufficient for the prediction of the risk of embolization. An important study published in 2001 concluded that subjects with echolucent atherosclerotic plaques have increased risk of ischemic cerebrovascular events independent of the degree of stenosis and cardiovascular risk factors.[1] Another method of morphological evaluation of the plaque has been historically represented by Gray Scale Median. Many authors found a significant correlation between GSM values <25, corresponding to an echolucent plaque, and an increased risk of cerebral infarction and symptoms of cerebrovascular disease.[2] There is growing evidence for a strong connection between neovascularization, plaque vulnerability and cardiovascular events and contrast enhanced ultrasound (CEUS) seems to have a great potential in the quantification of these characteristics. According to the current status of literature CEUS appears to be a powerful, not expensive and easy to perform procedure for the discrimination of "unstable" carotid atherosclerotic lesions.

Materials and methods

Contrast enhanced ultrasound (CEUS), based on the theory of inflammation and neoangiogenesis, consists of the evaluation of the enhancement of the carotid plaque after venous injection of a not-iodinate mean of contrast. Patients with carotid stenosis ≥70% with indication for surgical/endovascular treatment were enrolled in the study. The study protocol consisted of a pre-operative imaging study with B-mode echo-Doppler ultrasound and with CEUS. For each patient we calculated the echogenicity of the plaque at baseline (Grey Scale Median; GSM), and the plaque enhancement after injection of a bolus of mean of contrast (SonoVue, Bracco®, Milan, Italy) through a peripheral venous access. The images of CEUS were acquired during the arterial phase and saved on the hard disk of a portable computer and processed using Quontrast4.0 (Bracco®) software specifically designed to study contrast enhancement of the plaque. Afterwards patients underwent carotid endoarterectomy (CE) or carotid artery stenting (CAS) procedure according to the national and international guidelines. All the atherosclerotic plaques removed from CE were sent to the pathology laboratory for the measurement of the neoangiogenesis (Vessel Density; VD). The CAS group was additionally studied with diffusion-weighted MR (DW-MR) before and after the procedure for the evaluation of microembolization after CAS procedure.

Results

This work is the continuation of our study published in 2012 in which we analyzed 51 patients (all of them with indication for CE) with the protocol of study previously mentioned.[3] This study showed that there was a difference statistically significative between symptomatic and asymptomatic patients for GSM, contrast enhancement of the plaque (evaluated with two parameters of signal intensity; SI max and SI mean), and neovascularization of the atheroscelrotic plaque. Moreover a cut-off value was determined between the two groups for each parameter: GSM:25, SImax: 28%, SImean: 20%, and VD:25/mm^2. Combined analysis showed that plaques with greater contrast enhancement had more newly formed capillaries and that plaques with lower GSM values correlated with greater vascularization. The extended case study, with 29 new patients (total 80 patients) undergoing CE confirmed the trend seen so far and data are in process of validation for scientific publication. Twenty two patients underwent CAS, 12/22 (54%) presented a post-procedural microembolization detected with DW-MR. One patient presented a controlateral microembolization (right carotid plaque, left microembolization) probably due to periprocedural arch embolization. 1/11 patient with omolateral embolization (9%) presented a post-procedural neurological symptom with hypoesthesia and weakness of the right upper extremity. 6/11 presented three or more distinct microembolization regions at DW-MR. We found a difference of GSM ($P<0.05$), SI max ($P<0.01$) and SI mean ($P<0.01$) between patients with post-procedural microembolization compared to the ones without microembolizations. Afterwards we analyzed the group of patients with microembolization but we did not found a statistically significant difference between patients with 3 or more lesion compared with patients with less than 3 cerebral lesions.

Discussion

The degree of stenosis and the peak of systolic velocity (PSV) are insufficient predictors of stroke risk. For this reason it becomes mandatory to find a reliable method that could disclose asymptomatic atherosclerotic plaques with high emboligenic risk before that a cerebral event occurs. CEUS is a relatively new method to evaluate carotid plaque morphology, identify intraplaque microvessels and surface ulcerations, and define plaque vulnerability with greater emboligenic potential.[4, 5] The purpose of our study is to emphasize the potentiality of CEUS for the discrimination of "at risk" carotid plaques for patients undergoing CE and for the risk of microembolization in patients undergoing CAS, correlating the results of this second technique with the findings of the DW-RM. For the patients undergoing CE (80 patients), our results are in line with data from previous similar studies and corroborate those from an earlier study by Giannoni *et al.*[6] who showed that atherosclerotic lesions in symptomatic patients are more vascularized than those in asymptomatic patients. GSM values ≤25 were significantly correlated with high VD, SImax and SImean ($P<0.01$). Our data suggest that a threshold GSM of 25 could be used to discriminate an instable plaque irrespective to symptoms in patient's history as proposed by Biasi *et al.*[7] The difference in the mean of contrast uptake (SImax and SImean) and VD between the two groups was also statistically significant ($P<0.01$). Combined analysis of data on contrast enhancement (SI) and neoangiogenesis (VD) showed a close correlation between the two: lesions with greater contrast uptake have more newly formed capillaries, as demonstrated in previous studies.[8] In addition, analysis of GSM in relation to neoangiogenesis showed that plaques with a lower GSM value were generally more vascularized. Data of patients undergoing CAS revealed that plaques with high contrast enhancement detected with CEUS have greater risk of peri-post-procedural microembolization ($P<0.01$). The results are in line with the ones expressed in literature.[9] We did not found a correlation between CEUS and the number of the cerebral lesions nor between the CEUS and the symptomatic patient respect to the asymptomatic ones with microembolization. Despite the promising results of CEUS for the prediction of microembolization, it is necessary to collect more data to confirm the results obtained.

Conclusion

CEUS is a powerful tool for the evaluation of the stability of the plaque. Our study revealed a great potential of this technique for the definition of " at risk" atherosclerotic plaques not only for patient undergoing CE but also for the detection of atherosclerotic lesion with high risk of embolization in patients with indication of CAS.

References

1. Mathiesen EB, Bønaa KH, Joakimsen O. Echolucent plaques are associated with high risk of ischemic cerebrovascular events in carotid stenosis: the Tromsø study. Circulation 2001; 103:2171-5.
2. Biasi GM, Froio A, Diethrich EB *et al.* Carotid plaque echolucency increases the risk of stroke in carotid stenting - The Imaging in Carotid Angioplasty and Risk of Stroke (ICAROS) study. Circulation 2004;110:756-62.
3. Varetto G, Gibello L, Bergamasco L *et al.* Contrast enhanced ultrasound in atherosclerotic carotid artery disease. Int Angiol 2012;31:565-71.
4. Staub D, Partovi S, Schinkel A *et al.* Correlation of carotid artery atherosclerotic lesion echogenicity and severity at standard US with intraplaque neovascularization detected at Contrast-Enhanced US. Radiology 2011;258:618-26.
5. Ten Kate G, Van Dijk A, Van den Oord S *et al.* Usefulness of contrast-enhanced ultrasound for detection of carotid plaque ulceration in patients with symptomatic carotid atherosclerosis. Am J Cardiol. 2013;112:292-8.
6. Giannoni MF, Vicenzini E, Valentini FB *et al.* Contrast Carotid Ultrasound for the Detection of Unstable Plaques with Neoangiogenesis: A Pilot Study. Eur J Vasc Endovasc Surg 2009;37: 722-7.
7. Biasi GM, Froio A, Diethrich EB *et al.* Carotid plaque echolucency increases the risk of stroke in carotid stenting: the Imaging in Carotid Angioplasty and Risk of Stroke (ICAROS) study. Circulation 2004;110:756-62.
8. Ten Kate G, Van den Oord S, Sijbrands E *et al.* Current status and future developments of contrast-enhanced ultrasound of carotid atherosclerosis. J Vasc Surg 2013;57:539-46.
9. Ritter MA, Theismann K, Schmiedel M *et al.* Vascularization of carotid plaque in recently symptomatic patients is associated with the occurrence of transcranial microembolic signals. Eur J Neurol 2013;20:1218-21.

Incidence of anatomical compressions of the internal jugular veins with full block of their flow in patients with chronic cerebro-spinal venous insufficiency and multiple sclerosis

S. Mandolesi [1], E. Manconi [2], T. Niglio [3], A. D'Alessandro [4], A. Orsini [5], D. Mandolesi [6], F. Fedele [1]
[1]Department of Cardio-vascular and Respiratory Sciences, Sapienza University, Rome, Italy
[2]Department of Cardiovascular and Neurological Sciences, University of Cagliari, Italy
[3]Istituto Superiore di Sanità
[4]Ospedale "Masselli-Mascia", San Severo (FG), Italy
[5]Gioia Hospital, Sora (FR), Italy
[6]Medicina del lavoro Sapienza, Rome, Italy

Aim

Multiple sclerosis (MS), the most common neurological disorder in young adults, is traditionally considered to have autoimmune determinants.[1] The multistep mechanism of the disease involves inflammation, demyelination, and neuro-degeneration of the central nervous system.[1-3] Interestingly, from the time of the first histological description by Charcot, MS plaques are known to be venocentric.[2, 4] Both magnetic resonance imaging (MRI) venography [5-9] and post-mortem studies show a central vein oriented on the long axis of the inflammatory lesion.
In addition, as in several neurodegenerative disorders, the brain and spinal cord of MS patients contain abnormally high levels of redox-active metals, particularly iron,[10] documented by advanced MRI [1, 12] and enhanced histo-chemical methods.[13, 14]
There are several diagnostic tools to identify the different MS types.[1, 2, 18-20] Magnetic resonance imaging (MRI) of the brain and spine shows areas of demyelination (lesions or plaques) in the absence or in the presence of gadolinium.[21, 22] Analysis of cerebrospinal fluid may provide evidence of chronic inflammation of the central nervous system by showing oligo-clonal bands of IgG,[23] while evoked potentials study putative demyelination of the optic and sensory nerves.[24] A clear demonstration of a topographic correspondence between Multiple Sclerosis plaques and the cerebral venous system has been shown by magnetic resonance venography (MRV) [7, 25] and post-mortem studies.[26]
Such new nosological vascular pattern, defined as chronic cerebrospinal venous insufficiency (CCSVI), is strongly associated with MS.[27] CCSVI is characterized by multiple stenosis/obstructions affecting the principal extra-cranial outflow pathways of the cerebrospinal venous system, the internal jugular veins (IJVs) and the azygos vein (AZY), distributed in four main hemodynamic patterns.[29] Furthermore, CCSVI determines significant changes in cerebral venous hemodynamic, with a very high incidence of reflux in both intra- and extra-cranial venous segments as well as loss of the postural regulation of cerebral venous outflow.[29-32] Recently, Zamboni suggested five echo-color-Doppler (ECD) venous criteria that characterize this syndrome.[35] The presence of two of them is enough to diagnose CCSVI.
We created a software to collect morphological venous anomalies and hemodynamic ECD data named Morphological Hemodynamic Map (www.mem-net.it, Figure 1). WE designed an algorithm for data analysis of patients with CCSVI, following Zamboni's ultrasound criteria.[27-31-35] First we identified in CCSVI patients , by using such hemodynamic morphological map (MEM-net), the compression syndrome of IJVs (Mandolesi *et al*. 2011). This study provides the hemodynamic basis for an more appropriate assessment of our new CCSVI classification.

Methods

We investigated from 2010 by echo-color-Doppler (ECD) 789 patients with CCSVI and MS (490 females, 299 males), mean age 45.4. We found 728 positive and 61 negative for CCSVI. Morphological and hemodynamic ECD data were recorded by a computerized MEM-net maps , and they were analyzed by MEM-net Clinical Analysis programs (Table I). Furthermore, the patients were divided into two groups, the first one with intravenous anomalies and the second one with extrinsic vein compression according to our classification of IJVs Compression Classification shown below.

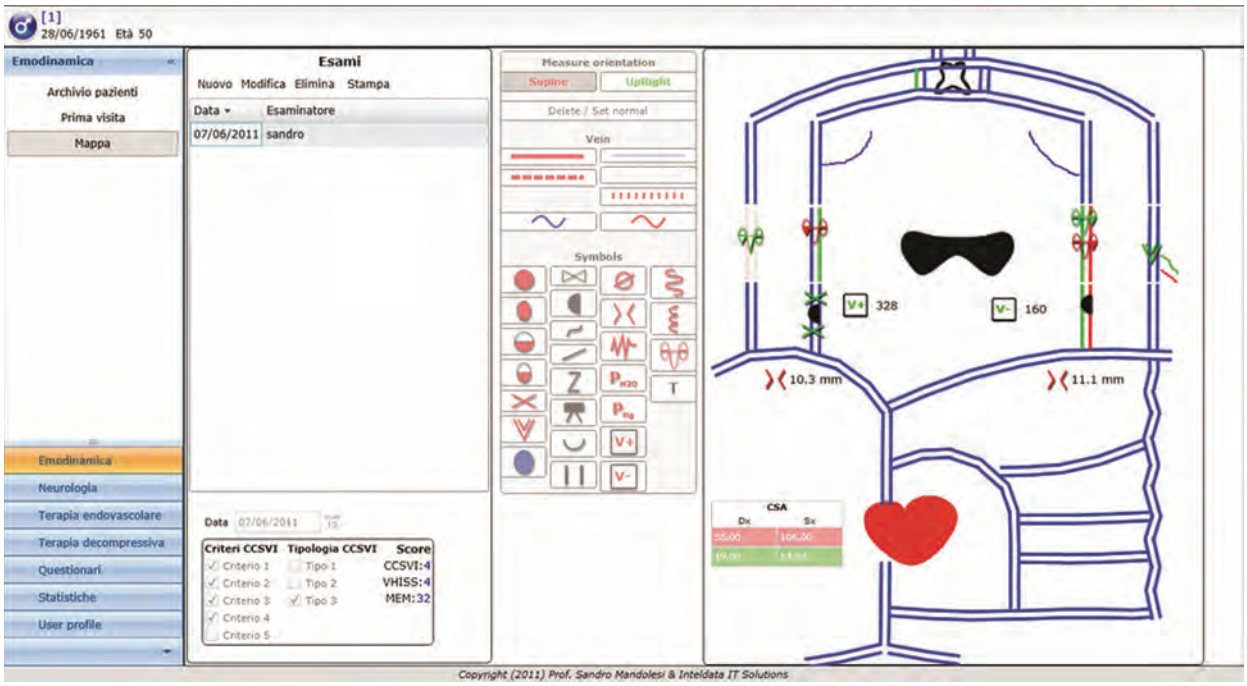

Figure 1. – Morphological Hemodynamic Map (MEM) scheme representing pattern of ECD venous cerebrospinal drainage, CCSVI types, hemodynamic severity score and patient data.

Echo-color Doppler (ECD) assessment of cerebral venous hemodynamics

The patients underwent a non-invasive study of cerebral venous return. A combined trans-cranial and extra-cranial ECD provided valid measures of venous hemodynamic (VH) parameters enabling an assessment of CCSVI cerebral venous return. The subjects were investigated in both supine and standing positions (0° and 90°) in consideration of the postural effect on the main route of cerebral outflow. We focused on the detection of three anomalous VH patterns affecting cerebral venous return according to the Zamboni's criteria and our CCSVI types Classification.[27-31]

Beside the Zamboni's criteria our population was studied using new hemodynamic patterns to complete the evaluation of the cerebro-spinal venous drainage: the venous compression of the IJVs and/or VVs not visible in supine and/or standing posture. We define venous compression as a normal vein not visible with ultrasound, because collapsed, which may expand with neck position changes and/or Valsalva maneuver such a vein presents a block of blood flow. In all our ECD assessments we performed the following ECD dynamic tests: neck movements, on right, on left rotation and anterior/ posterior intrusion of the neck; Valsalva's maneuver, performed by moderately forceful attempted exhalation against a closed airway, usually done by closing one's mouth and pinching one's nose shut.

According to these new hemodynamic parameters, we classified our patient population in three different CCSVI types. Block and/or stenosis and/or reflux of the IJVs and DCVs as Type-1; compression of the IJV and/or VV not visible as Type-2. The mixed form composed by patients with block and/or stenosis of IJVs and/or reflux of the IJVs and DCVs and compression of the IJVs and/or VVs not visible as Type-3. These parameters were used to draw up our algorithm.

Our center designed and developed for the first time the Morphological Hemodynamic Map (MEM) of the CCSVI. The MEM is made by a scheme reproducing the intracranial and extra-cranial venous circulation. The operator can insert in a few seconds different symbols to define the aforementioned hemodynamic conditions and also venous anomalies including hypoplasic veins, veins with stiffness of walls (not compliant), septum, membrane, web, annulus, twist and valve stiffness. The collected ECD data were analyzed by MEM-net software (www.mem-net.it), which includes the data analysis algorithm.

We utilized morphological and hemodynamic symbols of Consensus Conference of National Epidemiological CCSVI Observatory February 2013 (Table I).

According to Consensus Conference we subdivided the vein compression in two type : white and black compression. The compression is defined white when the vein is completely compressed and we can not detect any flow by ECD. The compression is defined

Table I. – Symbols and terminology to be used in reporting on map EchoColorDoppler examination of the veins draining the brain (Consensus Conference of National Epidemiologic CCSVI Observatory -2013).

	Symbol	Description	MEM Score
	Calcification	Endo or extra vascular	0
	Full block	When the block involve one or more segments with caliber equal or greater than the previous level or the following level	2
	Empty block	When the block involve one or more segments with caliber much lesser than the previous level or the following level	2
	Emi Full block	When the time of the drainage flow detected by Pulsed Doppler is longer than the stop flow on one or more segments with caliber equal or greater than the previous level or the following level	1
	Emi empty block	When the time of the drainage flow detected by the Pulsed Doppler is longer than the stop flow on one or more segments of size much smaller than the previous level or the following level	1
	Morphological stenosis	Organic stenosis <3 mm^2	2
	Stenosis Hemodynamics	Flow velocity >150 cm/s	2
	Membrane	Hyperechoic area endovascular	1
	Septum	Abnormal valve leaflet	1
	Thickening	Valvular thickening	1
	Twist	Twisting of the vessel	1
	Vicarious	Flow vicarious >45 cm/s on vertebrals (V2) in clino and > 60 cm/s in orto - >100 cm/s on the Internal jugulars (J2) both in clino and ortostatic position	1
	Ectasia	Vessel diameter more than 20 mm	1
	Confluence	Thickening of the confluence of jugular to subclavian	1
	Thickening-dyspasia	Thickening (dysplasia) of the vessel wall	1
	Thrombosis	Thrombosed segment	2
	Recanalization	Recanalization with parietal residues	1
	White compression	The compression is defined white when the vein is completely compressed and we cannot detect any flow	2 x each white
	Frontal		
	Right lateral		
	Left lateral		
	Back protusion		
	Black compression	The compression is defined black when the caliber of the vessel is less than 6 mm^2 and shows a flow	1 x each black

	Frontal
	Right lateral
	Left lateral
	Antero protusion

In the upright position the symbol is green. Compressions can be detected through the head in the front and/or side position right and / or left lateral position

	Vase accessory	Collateral vessel visible but with physiological flow	1
	Net	reticular image into vessel lumen	0
	Reflux	Reverse, retrograde, anti physiological flow > 0.8 s	2
	Emi-Reflux	Bidirectional flow	1
	Hypoplasia	Vase with diameter of less than 6mm	2
	Ipovisibile	EDC hypo- visible flow with PRF 0.7	1
	Invisible	ECD not visible flow with PRF 0.7	2
	Vessel accessory pathological supine and Ortho	Collateral vessel with reverse, retrograde, anti physiological flow	2
D	double channel	EDC anechoic area	2
Functional stenosis	Equivalent to hemodynamic stenosis	Presence of morphological abnormalities and reflux or two-way flow or block on the same vein	2

SYMBOLS FOR MEASURES

	Caliber	Size in mmq
	Pressure	Measurement of pressure in mmHg
	Pressure	Measurement of pressure in cmH_2O
	Velocity	Measurement of velocity in cm / s
	Valsalva+	Valsalva Test positive
	Valsalva-	Valsalva Test negative
	Diameter	Measurement in mm

ADDITIONAL SYMBOLS

	Free text
	Thyroidectomy
	Nodules

RESPIRATORY HAEMODYNAMIC INDEX OF MANCONI

CSA in J2 inspiratory phase	Normally is reduced by at least 30% of expiratory CSA
CSA in subclavian inspiratory phase	Normally is reduced by at least 30% of expiratory CSA
Speed flow in J2 inspiratory phase	At least doubled compared to the previous inspiration speed
Speed flow in subclavian inspiratory phase	At least doubled compared to the previous inspiration

black when the caliber of the vessel is less than 6 sq. mm and shows a flow by ECD examination. Compressions can be detected through the head in the front and / or right and / or left lateral position. These types of compression can be find at different level of IJVs (J1, J2 and J3) or at V2 and V3 level of VVs were the veins are not visible by ECD.

Statistical analysis

All data were analyzed by SPSS software with a stratified data description for numeric and non-numeric variables. Statistical significance "between" and "within" groups was calculated on continuous variables by the analysis of variance (ANOVA) to test the equality of means. The Chi-square Yates corrected test was used for non-continuous variables by Statcalc and Analysis programs from Epi-Info. A p value <0.05 was considered significant, and 95% confidence intervals were also calculated.

Results

The analysis of the internal jugular veins showed: the block of the drainage by endovascular causes in 222 patients supine and in175 in the upright (54% of total). The block of the drainage by extrinsic compression in 116 patients supine and in 232 in the upright (48% of total). We found a significant increase of Internal Jugular Veins compressions on changing position from supine to orthostatic Table II.

When the patient turned the head to the right and left we found the compression of the IJVs (at J2) as shown in Table III. The complete compression of the jugular veins in the front position (48% of the sample) are equally distributed on the various segments assessed (J1-J2-J3). Bilateral compressions are present in 7% of sample Table IV. The passage from the supine to upright position shows a double increase of compressions. The homo-lateral head rotation to the investigated vessel shows a significant increase of the extrinsic compressions from 7 to 9 times compared to contralateral side rotation.

Discussion

Recently some case reports about the resection of the omohyoid muscle for the treatment of vein compression syndrome of the internal jugular veins have been published in the literature.[37, 38] This muscle crosses the deep layers on the middle part of the internal jugular veins. It lowers the hyoid bone. We think that it is not enough the simple resection of the omohyoid muscle for a decompression treatment of the internal jugular veins, but should be regarded as additional possibilities. The scalene muscle can be the cause for the compressions mainly the J1 terminal segment of the internal jugular vein. The sterno-mastoid muscle mainly interested in compressions at the level J3 of the internal jugular vein where it overlaps with the internal carotid artery and it can be pinched. The altered posture with dislocation of C1-C2 with or without associated rotation of the cervical vertebrae can act more distally:

1. tensing the middle fascia with compression of the vascular-nervous loggia of the neck;
2. blocking the discharge of the vertebral veins;
3. hindering the discharge of J3 after the jugular hole.[39]

To put a surgical indication for decompressive surgery it is necessary to identify which are the tests both with dynamic postural-ECD and during venography that allow us to identify, with sufficient certainty, which of the conditions outlined above is the cause of the vein compression syndrome.

The compression syndrome of the veins draining the brain, in our ECD data, can affect only a vessel that be bilateral. It can affect both the jugular and vertebral veins and be detectable either supine that in the standing position or in both positions. All of these variables make rather difficult to assess preoperative indication to the right decompression treatment.

Our preliminary results by manipulative treatments in patients with compressive syndromes of the internal jugular veins and/or vertebral veins associated with C1-C2 misalignment has been positive and encourages us to practice a upright TC scanner assessment of the first

Table II. – Shows the incidence of Internal Jugular Veins compressions in supine and orthostatic position at J1, J2 and J3 level.

	Right clino	Right orto	Left clino	Left orto
J3	25	65	28	80
J2	42	92	50	105
J1	16	39	7	34

Table III. – Shows the incidences of Internal Jugular Veins compressions during neck rotations.

	Right rotation	Left rotation
J2Dx	211	32
J2Sn	30	286

Table IV. – Shows the incidence of bilateral Internal Jugular Veins compressions in supine and orthostatic position.

	R+L clino+orto	R+L clino	R+L orto
J2	54		
J2		15	
J2			33

two cervical vertebrae in these patients with CCSVI. Our current effort is the identification of specific postural tests that allow us to put an right indications either physiotherapeutic that surgical in patients with venous compression syndromes of the veins draining the brain.

References

1. Compston A, Coles A. Multiple sclerosis. Lancet 2002;359: 1221-31.
2. Barnett MH, Sutton I. The pathology of multiple sclerosis: a paradigm shift. Curr Opin Neurol 2006;19:242-7.
3. Frohman EM. Multiple sclerosis - the plaque and its pathogenesis. N Engl J Med 2006;354:942-55.
4. Charcot J. Histologie de la sclerose en plaques. Gazette des Hopitaux, Paris 1868;41:554-5.
5. Kermode AG, Thompson AJ, Tofts PD *et al.* Breakdown of the blood brain barrier precedes symptoms and other MRI signs of new lesions in multiple sclerosis: pathogenetic and clinical implications. Brain 1990;113:1477-89.
6. Kidd D, Barkhof F, McConnell R *et al.* Cortical lesions in multiple sclerosis. Brain 1999;122:17-26.
7. Tan IL, van Schijndel RA, Pouwels PJ. MR venography of multiple sclerosis. Am J Neuroradiol 2000;21:1039-42.
8. Fog T. Vessel-plaque relationships and CSF and brain tissue changes in multiple sclerosis. Acta Neurol Scand 1964;40:9-15.
9. Fog T. The topography of plaques in multiple sclerosis with special reference to cerebral plaques. Acta Neurol Scand Suppl 1965;15:1-161.
10. Sayre LM, Moreira PI, Smith MA *et al.* Metal ions and oxidative protein modification in neurological disease. Ann Ist Super Sanita 2005;41:143-64.
11. Haacke EM, Cheng NYC, Michael JH *et al.* Imaging iron stores in the brain using magnetic resonance imaging. Mag Reson Imaging 2005;23:1-25.
12. Tjoia CW, Benedict RH, Weinstock-Guttman B *et al.* MRI T2 hypointensity of the dentate nucleus is related to ambulatory impairment in multiple sclerosis. J Neurol Sci 2005;234:17-24.
13. Sayre LM, Moreira PI, Smith MA *et al.* Metal ions and oxidative protein modification in neurological disease. Ann Ist Super Sanità 2005;41:143-64.
14. LeVine SM, Chakrabarty A. The role of iron in the pathogenesis of experimental allergic encephalomyelitis and multiple sclerosis. Ann N Y Acad Sci 2004;1012:252-66.
15. Reingold SC. Defining the clinical course of multiple sclerosis: results of an international survey. National Multiple Sclerosis Society (USA) Advisory Committee on Clinical Trials of New Agents in Multiple Sclerosis. Neurology 1996;46:907-11.
16. Compston A, Coles A. Multiple sclerosis. Lancet 2008;372: 1502-17.
17. Miller DH, Leary SM. Primary-progressive multiple sclerosis. Lancet Neurol 2007;6:903-12.
18. Trojano M, Paolicelli D. The differential diagnosis of multiple sclerosis: classification and clinical features of relapsing and progressive neurological symptoms. Neurol Sci 2001;22:98-102.
19. McDonald WI, Compston A, Edan G *et al.* Recommended diagnostic criteria for multiple sclerosis: guidelines from the International Panel on the diagnosis of multiple sclerosis. Ann Neurol 2001;50:121-7.
20. Polman CH, Reingold SC, Edan G *et al.* Diagnostic criteria for multiple sclerosis: 2005 revisions to the McDonald Criteria. Ann Neurol 2005;58: 840-6.
21. Rashid W, Miller DH. Recent advances in neuroimaging of multiple sclerosis. Semin Neurol 2008;28:46-55.
22. Ge Y, Zohrabian VM, Grossman RI. Seven-Tesla magnetic resonance imaging. New vision of microvascular abnormalities in multiple sclerosis. Arch Neurol 2008;65:812-16.
23. Link H, Huang YM. Oligoclonal bands in multiple sclerosis cerebrospinal fluid: an update on methodology and clinical usefulness. J Neuroimmunol 2006;180:17-28.
24. Gronseth GS, Ashman EJ. Practice parameter: the usefulness of evoked potentials in identifying clinically silent lesions in patients with suspected multiple sclerosis (an evidence-based review): Report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 2000;54:1720-5.
25. Hojnacki D, Zamboni P, Lopez-Soriano A *et al.* Use of neck magnetic resonance venography, Doppler sonography and selective venography for diagnosis of chronic cerebrospinal venous insufficiency: a pilot study in multiple sclerosis patients and healthy controls. Int Angiol 2010;29:127-39.
26. Geurts JJ, Bö L, Pouwels PJ *et al.* Cortical lesions in multiple sclerosis: combined postmortem MR imaging and histopathology Am J Neuroradiol 2005;26:572-7.
27. Zamboni P, Galeotti R, Menegatti E *et al.* Chronic cerebrospinal venous insufficiency in patients with multiple sclerosis. J Neurol Neurosurg Psychiatry 2009;80:392-9.
28. Zamboni P, Menegatti E. Doppler haemodynamics of vertebral venous return Curr Neurovasc Research 2008;5:260-5.
29. Zamboni P, Menegatti E, Galeotti R *et al.* The value of cerebral Doppler venous hemodynamics in the assessment of multiple sclerosis. J Neurol Sci 2009;282:21-7.
30. Zamboni P, Menegatti E, Bartolomei I *et al.* Intracranial venous hemodynamics in multiple sclerosis. Curr Neurovasc Res 2007;4:252-8.
31. Franceschi C. The unsolved puzzle of multiple sclerosis and venous function. J Neurol Neurosurg Psychiatry 2009;80:358.
32. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology 1983; 33:1444-52.
33. Zamboni P, Galeotti R, Menegatti E *et al.* A prospective open-label study of endovascular treatment of chronic cerebrospinal venous insufficiency. J Vasc Surg 2009;50:1348-58.
34. Simka M, Majewski M, Fortuna M *et al.* Internal jugular vein entrapment in a multiple sclerosis patient. Case Rep Surg 2012;2012:293568.
35. Zamboni P, Morovic S, Menegatti E *et al.* Screening for chronic cerebrospinal venous insufficiency (CCSVI) using ultrasound--recommendations for a protocol. 2011;30:571-92.
36. Mandolesi S, Ciciarello F, Marceca A *et al.* Data analysis of the chronic cerebro-spinal venous insufficiency in patients with multiple sclerosis: new disease classification. 72° Congresso Nazionale della Società Italiana di Cardiologia, Roma, 10-12 Dicembre 2011.
37. Simka M, Majewski M, Fortuna M *et al.* Internal jugular vein entrapment in a multiple sclerosis patient. Case Rep Surg 2012;2012:293568.
38. Gianesini S, Menegatti E, Mascoli F *et al.* The omohyoid muscle entrapment of the internal jugular vein. A still unclear pathogenetic mechanism. Phlebology 2013 May 16. [Epub ahead of print].
39. Seoane E, Rhoton AL Jr. Compression of the internal jugular vein by the transverse process of the atlas as the cause of cerebellar hemorrhage after supratentorial craniotomy. Surg Neurol 1999;51:500-5.

A rare case of hand ischemia caused by embolism from a large, unrecognized axillary artery aneurysm

E. Rescigno [1], Dr. G. Rosa [1], G. Dardano [2]
[1]S.S. Dipartimentale Chirurgia Vascolare, Ospedale Di Lavagna Asl 4 Chiavarese, Genova
[2]S.C. Chirurgia, Ospedale Di Lavagna Asl 4 Chiavarese, Genova

Aim

Axillary artery aneurysm is a rare disorder. Diagnosis of this type of aneurysm as a result of identification of peripheral embolism is even rarer.
We report a case of acute ischemia of the hand caused by embolism from a large, unrecognized axillary artery aneurysm.

Materials and methods

An 80-year-old man presented to the emergency room complaining of gradually worsening pain in his right hand, (sudden onset 3 days prior), associated with paresthesia and loss of motor function, which he had initially attributed to osteoarthtritis. He was an ex-smoker (30 pack years) with a history of well-controlled hypertension, hepatitis C virus infection, liver cirrhosis, diffuse osteoarthritis and surgery for a hernia of the cervical spine in 2000.
On admission his blood pressure was 150/90 mmHg and his heart rate 90 bpm. He appeared to be in good health.
On physical examination his right hand was pale, cool to the touch and tender, with hypoesthesia, hypostenia and bullae on the third finger. The coolness decreased in the middle third of the forearm. The brachial pulse was present but the radial and ulnar pulses were absent. A pulsatile mass, that had not been noticed by the patient, was found in the right armpit (Figure 1).
Since acute ischemia of the right hand was suspected a Doppler study was performed. It revealed embolic occlusion of the radial and ulnar arteries as well as an axillary artery aneurysm, 4.6cm in diameter, not complicated by rupture or thrombosis (Figure 2).
Emergency surgery was required. Under local anesthesia radial and ulnar embolectomy was performed with a Fogarty catheter. The angio-computered tomography scan performed after the procedure confirmed the Doppler finding of an atherosclerotic aneurysm of the right axillary artery. The aneurysm was 13 cm long and 43 mm wide with a proximal neck 15 mm in diameter (Figure 3). The distal part of the axillary artery and the proximal part of the subclavian artery were tortuous. The origin of the vertebral artery was normal. There was ectasia of the subclavian arteries and the abdominal aorta. The patient did not have thoracic outlet syndrome (TOS).
Seven days after embolectomy aneurysm repair was performed with a prosthetic graft via the right armpit. The aneurysm was carefully dissected off neighboring neurovascular structures (Figure 4), in particular the anterior and posterior branches of the median nerve. The aneurysm was then resected and the vessel repaired using a 3 cm long and 16mm wide Dacron graft and a T-T anastomosis was fashioned with 5/0 prolene (Figure 5).
Fifteen cm of the aneurysmatic tract were removed. There was extensive ulceration of the intima with tears that had led to dissection.
The patient's postoperative course was uneventful. Hand function was restored but though there was slight tissue damage on the third finger. The patient was discharged on postoperative day 8.
Follow-up at 4,8, and 12 months, consisting of clinical assessment and ultrasound examination, showed complete recovery of function in the hand with good blood flow in the bypass and the distal vessels.

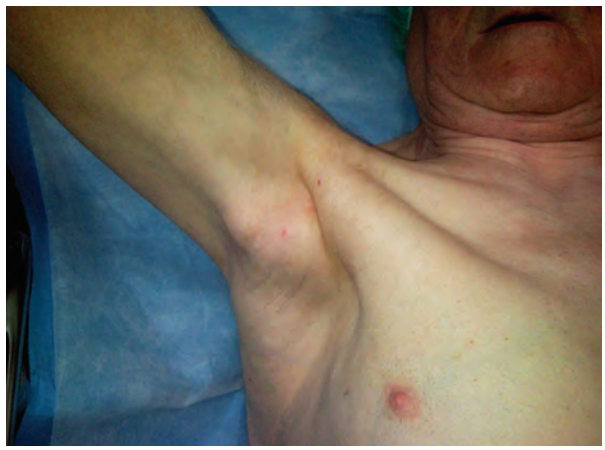

Figure 1.

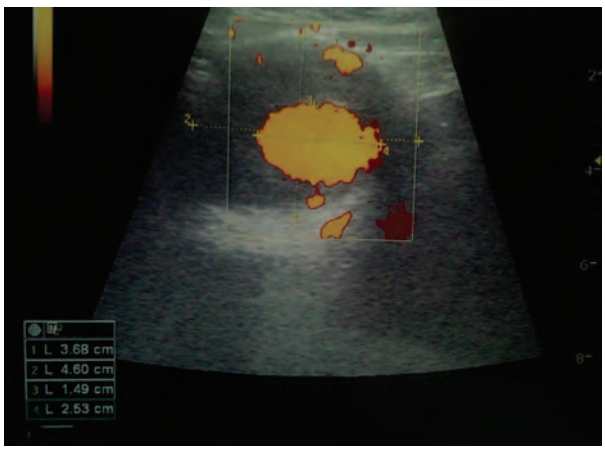

Figure 2.

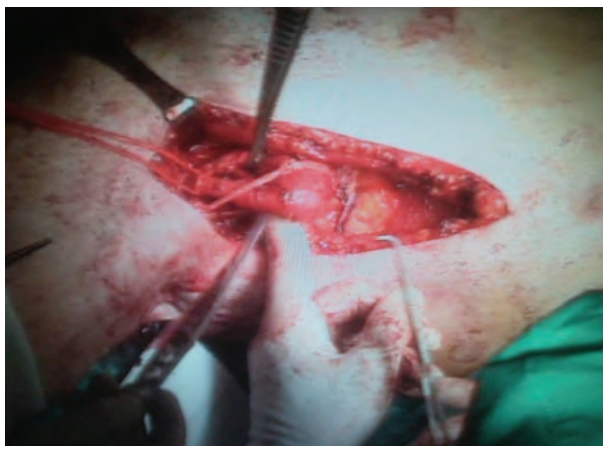

Figure 4.

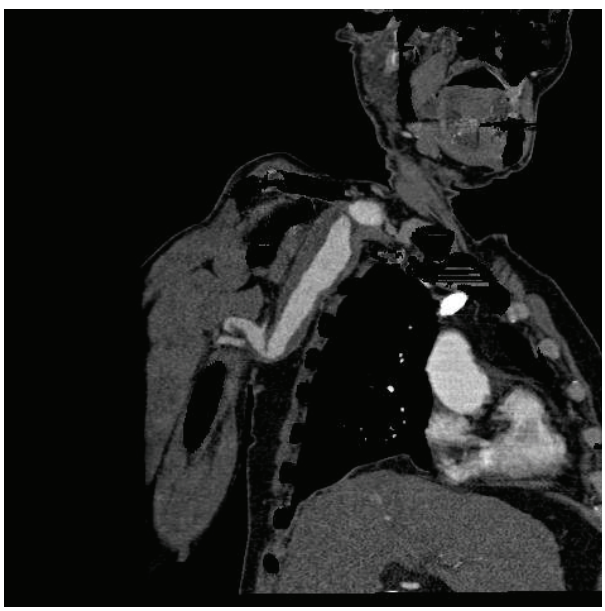

Figure 3.

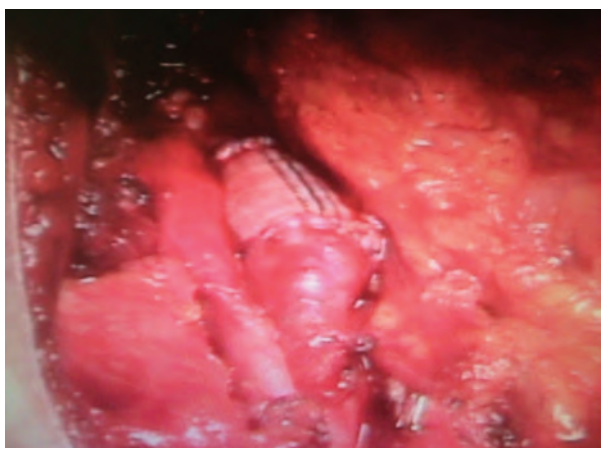

Figure 5.

Discussion

Acute embolic peripheral ischemia occurs less often in the arms (16%) than in the legs (75%). In 80% of cases the embolism is caused by arterial pathology due to TOS, acute penetrating or blunt chest trauma, atherosclerosis with ulcerating plaques, iatrogenic lesions, chronic direct trauma (use of cruthches) or indirect trauma (baseball player), mycosis, Takayasu syndrome, Behçet's syndrome, Marfan syndrome, cystic medial necrosis, and idiopathic lesions.[1]

The axillary-subclavian artery axis is only affected by atherosclerotic aneurysm in 0.13-1% of cases.[2] The first report of an axillary artery aneurysm, treated with ligation at the level of the subclavian artery, was published in 1836.[3] A review of the English language literature revealed that only 6 cases have been published since then.[4]

An aneurysm of the axillary artery can be managed with endovascular treatment. The advantages are preservation of the nerves and avoidance of surgical trauma, blood loss and wound or graft infection.[5] But often, when the aneurysm increases not only in diameter but also in length, as in our patient, the artery becomes so tortuous that catheterization or stenting is contraindicated. Aneurysm resection and artery replacement are then required and provide good results provided the brachial plexus is spared. Various approaches (supraclavicular, infraclavicular, axillary) and different types of grafts (autologous veins, prostheses) can be employed. The brachial or axillary veins have been used but there is a risk of aneurysmatic dilatation. The greater saphenous vein should be the graft of choice because of its long-term patency, but if it is not available because it has already been harvested for another purpose or its calibre is not sui-

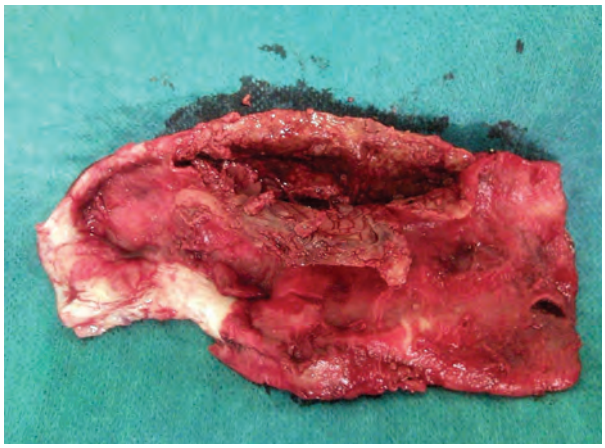

Figure 6.

table, a prosthesis made of polytetrafluoroethylene (PTFE), Dacron, or biological materials (Omniflex II) is indicated.[6]

Conclusion

Embolic ischemia caused by an axillary artery aneurysm is a very rare event which, however, requires rapid treatment of both the embolic occlusion and the aneurysm.

Our experience has confirmed that surgical treatment of such aneurysms, as already mentioned in the literature, is effective. Surgery makes it possible to prevent aneurysm rupture, dissection, or other events, that result from the large size often attained by these aneurysms, which are sometimes asymptomatic and unrecognized, and can cause the patient to lose the limb involved and/or their life.

References

1. Tetik O, Yilik L, Gurbuz A. Surgical treatment of axillary artery aneurysm. Tex Heart Inst J 2005;32:186-8.
2. Davidovic LB. Subclavian artery aneurysms. Asian J Surg 2003;26:7-12.
3. Godlee RS. A Case of Ligature of the Second Part of the Left Subclavian Artery for the Cure of an Axillary Aneurysm. Medico-Chirurgical Transactions 1892;75:275-83.
4. Rajarajan V, Vidyasagaran T. The Internat Journal of Surgery 2008;16.
5. He C, Wu X, Cao J. Endovascular management of spontaneous axillary artery aneurysm: a case report and review of the literature. Med Case Rep 2013;7:140.
6. Leroy S, Dölken W, Willeke F. J Mal Vasc 2008;33:225-8.

Worldwide experience on limb salvage according to the theory of angiosomes: 2013 update

E. Martelli [1], G. De Vivo [2]
[1]Department of Biomedicine and Prevention, University of Tor Vergata, Rome, Italy
[2]Division of Vascular Surgery, Tor Vergata Policlinic, Rome, Italy

Introduction

Critical limb ischemia (CLI) represents the deterioration of severe peripheral arterial disease, and infragenicular atherosclerosis is its most common cause. The natural prognosis of CLI is poor: around 30% of patients undergo a major amputation within one year from the diagnosis and 25% will die.[1] Revascularization is the optimal treatment for CLI to relieve ischaemic rest pain and avoid major amputations.

Management of CLI patients

At the moment, the techniques of revascularization for CLI are the endovascular (EV) procedures and open surgery (OS) by means of distal bypass grafts. Thanks to the newest EV materials and techniques, percutaneous transluminal angioplasty (PTA) is nowadays considered the first therapeutic option for patients affected by CLI; in fact, this option guarantees less invasivity and reduced hospital stay compared to OS. However, some pathological and functional factors (calcifications, length and grade of the stenosis or occlusions, poor run-off) negatively influence the outcome of the endovascular procedures. OS, although more invasive, allows revascularizations of very distal extremely calcified vessels, very long stenosis or occlusions and isolated arterial segments; the distal bypass grafts need the availability of adequate veins. There is still much confusion regarding which criteria to adopt in the selection of the best therapy for each CLI patient: neither the TASC II classification, nor the current guidelines give clear indications. Spinelli et al. showed that below the knee EV treatment should not be attempted as the first choice in every patient affected by CLI, because when the EV procedure fails or does not entail sufficient clinical benefit, the results of a subsequent distal bypass are significantly worse than in the previously untreated patients. These authors suggest an individualized approach for each patient rather than a particular intervention type.[2] Also the highest risk CLI patients have the most to gain from attempts at revascularization; even if end-stage renal disease is a risk factor for death after revascularization for CLI,[3] it should not preclude aggressive attempts at CLI revascularization as such treatment provides a survival benefit at all stages of renal failure over medical management alone.[4] Increasing age is another marker of poor outcomes in CLI patients in which the elderly were traditionally referred for conservative management; however, among octogenarians, a Swiss group reported significantly lower 30-day and 1-year mortality rates after revascularization compared to conservative management.[5] Bypass patency alone does not ensure clinical improvement.[6] On the other side, long-term limb salvage rates are substantially greater than patency rates, both in OS and EV. In fact, experience has shown that if wound healing is the primary objective of treatment in some patients with CLI, it may be sufficient to achieve only temporary patency until healing has taken place; after that, the blood flow can also diminish. Whereas limb salvage begins with revascularization, eventual wound healing requires a systemic team approach that includes wound perfusion assessment (ankle-brachial index, toe-brachial index, transcutaneous oximetry, skin perfusion pressure), aggressive medical management of atherosclerosis and related risk factors (aspirin, clopidogrel, diet control, statins, beta-blockers, angiotensin-converting enzyme inhibitors), protection of vulnerable tissue (coverage with appropriate footwear, recommendations for limb offloading, mechanical and enzymatic debridement, provisional antimicrobial therapy). Clinical progression of wound healing is critical to long-term success as those that fail to heal suffer high mortality rates.[7]

Effectiveness of angiosome theory

There seems to be an advantage to revascularizing the arterial territory directly associated with the area of tissue loss (Figure 1): more straight-line blood flow is restored to the pedal arteries, more clinical success is achieved.[8] Reports in the Literature support this evidence.[9, 10] A recent paper from a Japanese group has reformulated the concept from "one-angiosome direct revascularization" to "six-angiosomes direct revascularization". These authors have clinically demonstrated that in CLI, if any of the three vessels of the lower leg are blocked, the remaining vessel(s) can feed the periphery through arterial-arterial connections. Therefore, in the cases of patency of these connections, any

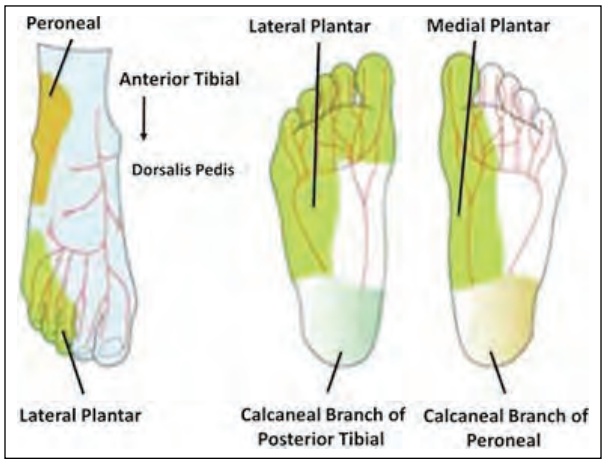

Figure 1. – Angiosomes of the foot and ankle.

of the three vessels in the lower leg can be targeted in EV treatment to achieve flow to the feeding artery in the foot area and potentially improve flow to the tissue loss.[11] Regarding this issue, however, a distinction between EV and OS treatment for limb salvage is essential. While the former earns the most benefits from the angiosome concept of wound-directed revascularization, actually for the latter is true the opposite. Two are the main reasons that explain this different behavior of the therapeutic options. First, distal grafts need a leg route as far as possible from contaminated skin areas, that is, they should be kept out from the "infected" angiosome; this is not the case for EV (percutaneous, remote) distal revascularizations for limb salvage, even in the presence of trophic lesions. Second, the angioplastied arteries of the leg achieve a blood flow just sufficient to feed the angiosome of tissue loss, hoping for tissue healing; on the other hand, distal bypasses carry high blood flows and can land even to blind segments of the leg vessels, forcing more and more the opening of new collaterals and choke vessels. These latter vessels demarcate the border of each angiosome and link neighboring angiosomes to one another; they represent important connections that allow a given angiosome to provide blood flow to an adjacent angiosome, if the latter's source artery is diseased. Even among diabetic patients with CLI, although there are numerous factors to consider (hyperglycemia and infection, peripheral neuropathy, atherosclerotic arterial insufficiency and microvascular injury, lipid disregulation), the angiosome model of reperfusion likely plays an important role.[12]

Conclusion

CLI revascularization is a complex clinical problem with significant variability among patients and reperfusion techniques. Conclusions about CLI reperfusion strategy are challenged by the heterogeneous and generally nonrandomized nature of available clinical studies. While these analyses have some limitations, they provide contemporary evidence of real-world limb revascularization that substantiate further clinical use and study of angiosome-directed limb reperfusion. A comprehensive approach to wound care is expected to propel CLI care further.

References

1. Norgren L, Hiatt WR, Dormandy JA *et al.* TASC II Working Group. Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). J Vasc Surg 2007;45 (Suppl S):S5-67.
2. Spinelli F, Stilo F, Benedetto F *et al*. Early and one-year results of infrainguinal bypass after failure of endovascular therapy. International Angiology 2011;30:156-63.
3. Kawarada O, Fujihara M, Higashimori A *et al.* Predictors of adverse clinical outcomes after successful infrapopliteal intervention. Catheter Cardiovasc Interv 2012;80:861-71.
4. Ortmann J, Gahl B, Diehm N *et al*. Survival benefits of revascularization in patients with critical limb ischemia and renal insufficiency. J Vasc Surg 2012;56:737-45.
5. Brosi P, Dick F, Do DD *et al*. Revascularization for chronic critical lower limb ischemia in octogenarians is worthwhile. J Vasc Surg 2007;46:1198-207.
6. Simons JP, Goodney PP, Nolan BW *et al.* Vascular Study Group of Northern New England. Failure to achieve clinical improvement despite graft patency in patients undergoing infrainguinal lower extremity bypass for critical limb ischemia. J Vasc Surg 2010;51:1419-24.
7. Chiriano J, Bianchi C, Teruya TH *et al.* Management of lower extremity wounds in patients with peripheral arterial disease: a stratified conservative approach. Ann Vasc Surg 2010;24:1110-6.
8. Tsetis D, Belli AM. The role of infrapopliteal angioplasty. Br J Radiol 2004;77:1007-15.
9. Neville RF, Attinger CE, Bulan EJ *et al.* Revascularization of a specific angiosome for limb salvage: does the target artery matter? Ann Vasc Surg 2009;23:367-73.
10. Iida O, Soga Y, Hirano K *et al*. Long-term results of direct and indirect endovascular revascularization based on the angiosome concept in patients with critical limb ischemia presenting with isolated below-the-knee lesions. J Vasc Surg 2012;55:363-70.
11. Osawa S, Terashi H, Tsuji Y *et al.* Importance of the six angiosomes concept through arterial-arterial connections in CLI. Int Angiol 2013;32:375-85.
12. Alexandrescu VA, Hubermont G, Philips Y *et al.* Selective primary angioplasty following an angiosome model of reperfusion in the treatment of Wagner 1-4 diabetic foot lesions: practice in a multidisciplinary diabetic limb service. J Endovasc Ther 2008;15:580-93.

Peripheral arterial disease increases the risk of perioperative complications

P. Poredoš, MK Ježovnik
University Medical Centre Ljubljana, Department of vascular disease, Ljubljana, Slovenia

Introduction

Peripheral arterial atherosclerotic disease of lower limbs represents one of the most frequent manifestations of atherosclerosis. In the age group over 65 years, the prevalence of the disease is 5-8%. From local point of view, the disease is relatively benign, but because of accompanied atherosclerotic diseases in other vascular beds: coronary heart disease (CHD) and cerebrovascular disease (CVD) it is related to worst prognosis. Mortality of PAD patients is particularly high in subjects with advanced PAD, like critical limb ischaemia. These patients are mostly dying because of CHD.[1, 2]

At least, 10% of patients with PAD have cerebrovascular disease and 28% coronary heart disease. Regardless whether symptoms are evident or not, PAD patients are 6-times more likely to die within 10 years than subjects without PAD.[2] The SPRINT study showed that in-hospital mortality of patients with acute myocardial infarction is associated with the presence of PAD. These patients exhibit more frequently cardiogenic shock, paroxysmal atrial fibrillation and, atrioventricular block than patients without PAD.[3] PAD is also closely related to carotid atherosclerosis. House with co-workers showed that patients with PAD are also at increased risk for stenosis of carotid arteries. In the study of 476 patients with PAD, stenosis of arterial carotid artery greater than 50% was identified in 35% of patients.[4] Similarly the SMART (Second Manifestation of ARTerial disease) showed that the prevalence of internal carotid artery stenosis increases to as much as 50% in patients who have PAD and additional risk factors, like age over 67 years, and pulse pressure above 74 mmHg.[5] Further, the prevalence of PAD is in high risk subjects and coronary or cerebro-vascular patients very high.[6]

Factor influencing high perioperative morbidity and mortality of patients with PAD

As PAD represents a wide-spread atherosclerotic disease, these patients are also at increased risk for perioperative morbidity and mortality. Particularly patients with PAD are accompanied by coronary artery disease which is present in 46-71% in this group of patients.[7] Therefore, perioperative mortality of vascular patients mostly depends on the presence of coronary heart disease which is responsible for 40% of deaths in first month after operative procedure.[8] One year mortality after operative vascular procedure accounts 6-7% and depends on the type of vascular procedures.[9] Further, in vascular patients risk factors are under-treated. In comparison to patients with coronary heart disease, much less patients with PAD are treated with statins or antiplatelet drugs, and hypertension is in this group of patients less well regulated than in patients with other atherosclerotic diseases. It was found out that antiplatelet drugs are prescribed in coronary patients twice more frequently than in PAD.[7]

Estimation of perioperative risk in patients with PAD

Reopening procedures on peripheral arteries (surgical or percutaneous) are accompanied with high risk for perioperative complications which account more than 5%. As these patients represent one of the more risk group for perioperative complications, careful examinations of perioperative risk is needed. However, we have to know what the effectiveness of these tests is. Surgical patients often undergo extensive preoperative diagnostics without a background of sound evidence that diagnostic benefit outweighs cost and potential harm. Some authors reported that, based on patient's history and physical examination 60-70% of laboratory tests ordered before general surgery are not required.[10] However, it seems reasonable to believe that preoperative testing may reduce adverse outcomes in patients undergoing elective non-cardiac surgical procedures, particularly in symptomatic subjects.

Preoperative investigation of patients with PAD should include assessment of the presence or absence of clinical predictors of increased risk for perioperative cardiovascular complications, and to determine patient's cardiac functional status. Physical examinations of cardiovascular system should include an assessment of vital signs (including measurement of

blood pressure in both arms), carotid pulse contour and bruits, auscultations of the lungs, precordial palpation and auscultation and examination of the extremities. The basic clinical evaluation obtained by history, physical examination and review of ECG usually provides sufficient data to estimate cardiac risk.[12] Functional status has been showed to be reliable for perioperative and long-term prediction of cardiovascular event.

Functional capacity can be expressed as metabolic equivalents (METs). Perioperative risks are increased in patients unable to meet a 4-MET demand.[11] Patients with functional capacity above 4 METs don't need additional investigations. Different scoring models and questionnaires are available for determinations of perioperative risk of cardiovascular complications. Most frequently Released Cardiac Risk Index (RCRI) and Vascular Study Group of New England Cardiac Risk Index (VSG-CRI) were introduced in every day clinical practice. Estimation of perioperative risk using above mentioned scores is based on risk factors which can be identified by clinical examination and if patient is in high risk group, additional examination of cardiovascular system are needed.[12] In patients with increased risk or patients undergoing high-risk surgery rest echocardiography assessment should be performed. In high risk patients also stress testing is recommended. Stress testing may be considered also in high risk patients with less than two clinical risk factors. Stress testing is not recommended in low-risk surgery. In high-risk patients also stress scintigraphy is indicated. If results of echocardiography and stress scintigraphy are negative, perioperative risk for cardiovascular complications is low. Basic biochemical tests which should be performed preoperatively include: haemoglobin, electrolytes, coagulation and liver tests. In patients with manifest heart failure, determination of BNP and NT-proBNP is indicated.

How to decrease risk for perioperative complications in patients with revascularization procedures on peripheral arteries?

As atherosclerosis is systemic disease, PAD patients frequently have also other atherosclerotic diseases which need intervention, particularly patients with accompanied heart disease. However, it was shown that preoperative revascularization of coronary arteries in patients with stable coronary disease does not improve prognosis of surgical procedures on peripheral arteries [12] with exception of subgroup of coronary patients with stenosis of main coronary trunk.[13] Operative risk could be reduced also with different drugs. Perioperative use of beta-blockers and statins significantly reduces mortality of patients who undergo surgical revascularization procedures on peripheral arteries. Particularly selective blocker of β1 receptors are indicated.[14] The aim is to decrease heart rate to 60-80/minute and to reach the systolic blood pressure between 120 mmHg and 140 mmHg. Further preoperative treatment with statins significantly (up to 59%) decreases perioperative morbidity and mortality in patients with revascularization procedures on peripheral arteries.[15] Treatment with statins should be introduced one month or at least one week before surgical procedure. Treatment with antiplatelet drugs significantly decreases perioperative complication and their withdrawal before operation is associated with 10% increase of perioperative complication rate. Antiplatelet drugs do not significantly increase major perioperative bleeding. Smoking increase the probability for perioperative complications, therefore abstinence of smoking 4-6 weeks before surgical procedure is suggested.[16]

Conclusion

Arterial atherosclerotic disease of lower limbs represent dangerous entity with wide spread atherosclerotic disease because of the presence of concomitant coronary or cerebrovascular disease. Therefore, PAD patients are also at increased risk for perioperative risk of morbidity and mortality. Before surgical revascularization procedure, the patient needs careful check-up of risk factors which increase perioperative complications and determination of cardiac functional status. Because of frequent simultaneous presentations of different atherosclerotic diseases, priorities of surgical procedures on different arterial beds should be checked. Operative risk could be reduced also with different drugs: beta-blockers, statins, and antiplatelets.

References

1. Vogt MT, Wolfson SK, Kuller LH. Lower extremity arterial disease and the aging process: a review. J Clin Epidemiol 1992;45:529-42.
2. Criqui MH, Langer RD, Fronek A *et al.* Mortality over a period of 10 years in patients with peripheral arterial disease. N Engl J Med 1992;326:381-6.
3. Secondary prevention reinfarction Israeli nifedipine trial (SPRINT). A randomized intervention trial of nifedipine in patients with acute myocardial infarction. The Israeli Sprint Study Group. Eur Heart J 1988;9:354-64.
4. House AK, Bell R, House J *et al.* Asymptomatic carotid artery stenosis associated with peripheral vascular disease: a prospective study. Cardiovasc Surg 1999;7:44-9.
5. Simons PC, Algra A, Eikelboom BC *et al.* Carotid artery stenosis in patients with peripheral arterial disease: the SMART study. SMART study group. J Vasc Surg 1999;30:519-25.
6. Poredos P, Jug B. The prevalence of peripheral arterial disease in high risk subjects and coronary or cerebrovascular patients. Angiology 2007;58:309-15.
7. McDermott MM, Mehta S, Ahn H *et al.* Atherosclerotic risk factors are less intensively treated in patients with peripheral

arterial disease than in patients with coronary artery disease. J Gen Intern Med 1997;12:209-15.
8. McFalls EO, Ward HB, Santilli S *et al*. The influence of perioperative myocardial infarction on long-term prognosis following elective vascular surgery. Chest 1998;113:681-6.
9. Welten GM, Schouten O, Hoeks SE *et al*. Long-term prognosis of patients with peripheral arterial disease: a comparison in patients with coronary artery disease. J Am Coll Cardiol 2008; 51:1588-96.
10. Johansson T, Fritsch G, Flamm M *et al.* Effectiveness of non-cardiac preoperative testing in non-cardiac elective surgery: a systematic review. Br J Anaesth 2013;110:926-39.
11. Reilly DF, McNeely MJ, Doerner D *et al.* Self-reported exercise tolerance and the risk of serious perioperative complications. Arch Intern Med 1999;159:2185-92.
12. Poldermans D, Bax JJ, Boersma E *et al*. Guidelines for preoperative cardiac risk assessment and perioperative cardiac management in non-cardiac surgery. Eur Heart J 2009;30: 2769-812.
13. Garcia S, Moritz TE, Ward HB *et al*. Usefulness of revascularization of patients with multivessel coronary artery disease before elective vascular surgery for abdominal aortic and peripheral occlusive disease. Am J Cardiol 2008;102:809-13.
14. London MJ, Zaugg M, Schaub MC *et al*. Perioperative beta-adrenergic receptor blockade: physiologic foundations and clinical controversies. Anesthesiology 2004;100:170-5.
15. Schouten O, Boersma E, Hoeks SE *et al.* Fluvastatin and perioperative events in patients undergoing vascular surgery. N Engl J Med 2009;361:980-9.
16. Mills E, Eyawo O, Lockhart I *et al.* Smoking cessation reduces postoperative complications: a systematic review and meta-analysis. Am J Med 2011;124:144-154.e148.

Peripheral artery disease and atrial fibrillation

R. Parisi [1], C. Bortoluzzi [1], A. Bonanome [2], G. Vescovo [3]
[1]UOSD of Angiology OC SS Giovanni e Paolo, Venice, Italy
[2]UOC of Internal Medicine OC SS Giovanni e Paolo, Venice, Italy
[3]UOC of Internal Medicine OC S. Bortolo, Vicenza, Italy

The term peripheral artery disease in the title is used to denote atherosclerotic stenosis or occlusion of the aorta and arteries supplying the lower extremities and abdominal aortic aneurysms.
Peripheral arterial disease (PAD), which is caused by atherosclerotic occlusion of the arteries of the lower limbs is an important manifestation of systemic atherosclerosis.[1] The prevalence of PAD varies among different populations and is often diagnosed when an ankle-brachial index (ABI) <0.9 is detected.
In the PARTNERS study the subjects aged ≥70 years PAD or aged 50-69 years with a risk factor for vascular disease (smoking, diabetes) screened for PAD were screened using the ABI. PAD was detected in 29% of the total population. The prevalence of PAD, in another study, ranged from 2.5% in the age group 50-59 years to 14.5% in subjects >70 years. At last in autopsies of unselected adults, 15% of men and 5% of women who were asymptomatic, had a 50% or greater stenosis of an artery to the leg.[2]
The classic symptom of PAD is intermittent claudication, i.e., leg pain with walking that improves with rest. However, most patients , more than 50% of patient with symptomatic peripheral artery disease, do not have intermittent claudication;[1] they have atypical leg symptoms or no symptoms at all.
Diabetes seems to be an important risk factor for patients with PAD. In a sub-analysis of the PANDORA study, which was carried out in Italian subjects presenting with moderate cardiovascular risk, in the absence of diabetes or overt vascular disease the 22.9% (95% CI 21.7-24.0) of subjects presented with asymptomatic PAD, and the mean age was 63.9 years.[3]
In the REACH survey of those patients identified with symptomatic PAD, 4.7% had concomitant CAD, 1.2% had concomitant cerebral artery disease and 1.6% had both. Thus in this survey, about 65% of patients with PAD had clinical evidence of other vascular disease. However, in one prospective study of 1886 patients aged 62 or over only 37% of subjects had no evidence of disease in any of the three territories.[2]
Diehm *et al.*, however, recently showed that the overall mortality at five years for patient with symptomatic PAD is 53.0 patients per 1000 patient-years and 41.7 for asymptomatic, and in patient without PAD is 19.5. Compared with patients without PAD, those with asymptomatic PAD or symptomatic PAD had a significantly increased risk of premature death.[4]
Patients with peripheral arterial disease, even in the absence of a history of myocardial infarction or ischemic stroke, are also known to carry approximately the same relative risk of death from cardiovascular causes as patients with a history of coronary or cerebrovascular disease.[1]
The correlation between PAD and STROKE is well demonstrated by The Edinburgh Artery Study and the ARIC (Atherosclerosis Risk in Communities) in witch the authors found an increased risk for stroke and transient ischemic attack in the population with increased PAD severity.
The combination of known coronary or cerebrovascular disease with PAD has been shown to increase mortality risk,[5] and this correlation is particularly high in patients with severe PAD. A strong trend for increasing risk of mortality was noted for decreasing ABI.[6]
The prevalence of atrial fibrillation (AF) in an European study, in subject's ≥55 years of age, was 5.5 percent in those aged 55 to 59 years and 17.8 percent for those ≥85 years.[7]
Observational studies consistently showed that most of the common risk factors for atherosclerosis such as age, hypertension, obesity and diabetes are also risk factors for AF.[8]
Some patients with paroxysmal or persistent AF have no underlying structural heart disease but most of the patients with AF are >65 years of age have many comorbidities, such as PAD, in particular, hypertension (37%), heart failure (23%), coronary artery disease (18%) and diabetes (15%). The data based on the REduction of Atherothrombosis for Continued Health (REACH) Registry demonstrated that the prevalence of AF in the PAD patient group was 10.4%. In this study patients with AF were significantly older; more often had a history of angina pectoris, MI, ischemic stroke, TIA, CHF, aortic valve stenosis, CVD, diabetes, hypertension and included a lower prevalence of smokers.
AF is furthermore a common condition in European patients with symptomatic PAD.[9]

If AF and PAD coexist, mortality increases. Indeed, long-term CV mortality occurred in 5.6% of patients with AF and in 1.6% of those without AF (P <0.001), demonstrating that AF is an independent predictor of long-term C mortality, with a 1.5-fold increase in patients with AF and PAD.[9] Also, the data of the REACH registry showed that the prevalence of AF was 12.5% in patients with coronary artery disease and 11.5% in patients with peripheral artery disease. In patients with atherosclerosis, the risk of cardiovascular events (including cardiovascular death, myocardial infarction, stroke, and hospitalization for an atherothrombotic event) was higher in patients with concomitant AF (17.9% *vs.* 12.1% at 1-year follow-up), and the risk associated with peripheral artery disease plus AF was higher than the risk associated with coronary artery disease plus AF (27.1% *vs* 19.7%). Furthermore in patients with PAD, AF was associated with a 2.5-fold increased risk of in-hospital death.[10]

In a large nationwide cohort study of non-anticoagulated patients with non-valvular atrial fibrillation, Bjerring Olesen showed that vascular disease was clearly a risk factor for stroke and thromboembolism, even after adjustment for CHADS2 score or baseline characteristics. Vascular disease increased the risk by approximately 10%, and the risk was similar to the risk associated with 2 established thromboembolic risk factors: hypertension and heart failure. Patients with peripheral artery disease were older, were more often female, and had a higher risk of thromboembolism (as assessed by the CHADS2 or CHA2DS2-VASc scores).

By adding vascular disease to the CHADS2 score the predictive power of the score was increased. This large study clearly shows that vascular disease needs to be incorporated into any risk prediction scheme, as proposed by the CHA2DS2-VASc score.[11]

Conclusion

Atrial fibrillation in the presence of peripheral artery disease increases the risk prediction of mortality for cardiovascular events, with the risk being higher in patients with severe PAD. Routine measurement of ankle brachial index in patients with atrial fibrillation could allow a more exhaustive estimation of cardiovascular risk. It remains to be established whether anticoagulant treatment in patients with atrial fibrillation could be beneficial also with respect to the progression of peripheral arterial disease. Asymptomatic PAD patients could have an atherosclerotic disease which is more important than showed so far. These patient need a special clinical and therapeutical attention.

Probably it is necessary to increase the use of ABI to identify asymptomatic patients for PAD in the group of patient with AF in order to identify those at higher risk of cardiovascolar mortality,

This test is at the moment underused in this group of patient.

References

1. Hiatt WR. Medical Treatment of Peripheral Arterial Disease And Claudication. N Engl J Med 2001;344:1608-21.
2. Norgren L, Hiatt WR, Dormandy JA *et al.* on behalf of the TASC II Working Group Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). J of Vasc Surg 2007:45/Suppl S):S5-67.
3. Sanna G, AlessoA, Mediati M *et al.* and the PANDORA study investigators. Prevalence of peripheral arterial disease in subjects with moderate cardiovascular risk: Italian results from the PANDORA study Data from PANDORA (Prevalence of peripheral Arterial disease in subjects with moderate CVD risk, with No overt vascular Diseases nor Diabetes mellitus. BMC Cardiovascular Disorders 2011;11:59.
4. Diehm C, Allenberg JR, Pittrow D *et al.* Mortality and Vascular Morbidity in Older Adults With Asymptomatic Versus Symptomatic Peripheral Artery Disease Circulation. 2009;120:2053-61.
5. Olin JW, Allie DE, Belkin M *et al.* ACCF/AHA/ACR/SCAI/SIR/SVM/SVN/SVS 2010 performance measures for adults with peripheral artery disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on performance measures, the American College of Radiology, the Society for Cardiac Angiography and Interventions, the Society for Interventional Radiology, the Society for Vascular Medicine, the Society for Vascular Nursing, and the Society for Vascular Surgery (Writing Committee to Develop Clinical Performance Measures for Peripheral Artery Disease). Circulation 2010;122:2583-618.
6. Criqui M. Peripheral arterial disease - epidemiological aspects. Vascular Medicine 2001;6(Suppl 1):3-7.
7. Chugh SS, Blackshear JL, Shen WK *et al.* Epidemiology and natural history of atrial fibrillation: clinical implications. J Am Coll Cardiol 2001;37:371-8.
8. Violi F, Lip GY, Basili S. Peripheral artery disease and atrial fibrillation: a potentially dangerous combination. Intern Emerg Med 2012;7:213-8.
9. Winkel TA, Hoeks SE, Schouten O. Prognosis of Atrial Fibrillation in Patients with Symptomatic Peripheral Arterial Disease: Data from the REduction of Atherothrombosis forContinued Health (REACH) Registry. Eur J Vasc Endovasc Surg 2010;40:9e16.
10. Bjerring Olesen J, Gislason GH, Torp-Pedersen C *et al.* Atrial Fibrillation and Vascular Disease - A Bad Combination. Clin Cardiol 2012;35(Suppl 1):15-20.
11. Bjerring Olesen J, Lip Gregory YH, Lane DA *et al.* Vascular Disease and Stroke Risk in Atrial Fibrillation: A Nationwide Cohort Study. Am J Med 2012;125:826.e13-23.

Factors influencing the recanalization rate of deep venous thrombosis

M.K. Ježovnik, P. Poredoš
University Medical Centre Ljubljana, Department of vascular disease, Ljubljana, Slovenia

Aim

Deep venous thrombosis (DVT) is a long-lasting and dynamic process including both thrombus formation and thrombolysis that occur after an acute episode of DVT. Complete recanalization of affected veins occurs in less than 50% of patients. Therefore, the disease is accompanied by different sequelae like post-thrombotic syndrome (PTS) and a high recurrence rate of the disease. The majority of patients with acute DVT will develop symptoms and signs of PTS secondary to chronic occlusion or valve incompetence of affected veins.[1] Resolution of thrombi depends on different factors; however, these factors that contribute to lyses of thrombi remain poorly understood. It is known that recanalization of affected veins progress with the duration of the disease and after one year more than 80% of occluded veins recanalize.[2] However, also later on, complete recanalization and normalization of blood flow occur in only about 50% of cases. It was shown that the rate and extent of recanalization is an important determinant of long-term outcome. Therefore, recently factors that contribute to lyses of thrombi were intensively investigated. It seems that mechanisms of intrinsic fibrinolysis are more important that extrinsic or the type of treatment.[3] So far, several markers of coagulation and fibrinolysis of blood milieu, in which thrombotic events occurred, were investigated. Recently, inflammation was shown to be related to activation of coagulation as well as in fibrinolytic resolution of thrombus.[4] Therefore, we investigated whether the levels of circulating inflammatory markers in the stable phases of DVT are associated with the rate of recanalization of occluded veins. Also other factors like extent of thrombotic occlusion were studied.

Materials and methods

Consecutive patients admitted to outpatient department between June 2006 and November 2008 with first idiopathic deep venous thrombosis of the lower limbs were included in the study. Patients with secondary deep venous thrombosis or symptomatic atherosclerosis and patients with renal disease and renal dysfunction (based on creatinine levels) were excluded. All patients included received treatment with single daily subcutaneous injections of low molecular weight heparin (LMWH) at therapeutic dose (dalteparin 200 IU/kg/d) along with vitamin K antagonist (warfarin) from the first treatment day. Initial treatment with LMWH was continued for at least 5 days and until an international normalised ratio (INR) was >2 for 48 hours. The treatment with warfarin was kept at an INR of about 2.5 (desirable range, 2.0-3.0). The therapy with warfarin lasted for six months.
Altogether, 49 patients were selected in the stable phase of the disease (four to six months after diagnosis). All patients were evaluated for the presence of risk factors of atherosclerosis. Demographic characteristics including age, sex, height, and body mass index (BMI) were recorded. The study was conducted according to the principles of the Declaration of Helsinki and approved by the State Ethics Committee. Written informed consent was obtained from all participants.

Results

Forty-nine consecutive patients with idiopathic venous thrombosis of the lower limbs were included. They were investigated four to six months after the acute phase of the disease. The mean age of patients was 52.3±14.3 years. There were 34 males (69.4%) and 15 (30.6%) females. The average BMI of the investigated patients was 27.4±3.6 kg/m^2, 14 (29.8%) of them had increased blood pressure, 11 (23.4%) dyslipidaemia and 6 (12.8%) diabetes mellitus. On average recanalization (partial or complete) was achieved in 38 (76%) out of 49 participants. The location of the venous occlusion and recanalization rate of proven venous segments is shown in Table I. Most frequently proximal deep vein segments were occluded. Complete recanalization occurred more frequently in distal segments (popliteal, calf) than in proximal venous thrombosis and the recanalization rate was lower in patients with more extended thrombosis. The recanalization rate was higher in females than in males: in 12 out of 15-87% *vs.* 25 out of 34-73% (P<0.05). Risk factors of atherosclerosis did not influence the recanalization of occluded deep veins. The influence of systemic inflammatory markers on recanalization rate was also studied and it was shown that recanalization is related to some circulating cytokines but not to high sensitive C-reactive protein

Table I. – Multivariate analysis, including inflammatory markers and adhesion molecules for recanalization of venous thrombosis (dependent variable).

	Unstandardized coefficients		Standardized coefficients *t*		P value
	B	SE	Beta		
Constant	34.27	16.02		2.16	0.037
IL-6 pg/mL	4.43	1.10	0.62	4.02	<0.001 *
IL-8 pg/mL	-0.14	0.358	-0.05	-0.38	0.71
IL-10 pg/mL	-1.35	1.08	-0.18	-1.25	0.22
hs-CRP mg/L	-0.31	0.35	-0.14	-0.89	0.38
P-selectin pg/mL	-0.94	0.33	-0.42	-2.86	0.007 *
TNF alpha pg/mL	-0.48	0.48	-0.14	-0.99	0.33
VCAM-1 ng/mL	-0.01	0.02	-0.06	-0.44	0.67

IL-6: interleukin-6; IL-8: interleukin-8; IL-10: interleukin-10; TNF-α: tumour necrosis factor alpha; VCAM-1: vascular cell adhesion molecule-1; * P<0.05 – significant difference; R2 =0.37 significance for the model: P<0.05.

(hsCRP) and to adhesion molecule - VCAM-1. The multivariate analysis including inflammatory markers and recanalization of occluded deep veins as dependent variables showed that IL-6 and P-selectin remained the only statistically significant independent predictors of recanalization of vein thrombosis.

Discussion

The results of our study show that in most patients lysis of thrombus starts early after an acute episode of DVT. However, complete thrombus resolution is after 6 months of period achieved in only of 1/3 of them. Complete recanalization was observed less frequently in patients with proximal extended DVT. It indicates that increased thrombus load is related to lower recanalization rate and probably after an acute episode a longer period is needed for thrombus resolution. Similarly, Markel with co-workers found that partial or complete recanalization of DVT after 6 months occur in 67% of patients, and in 4 years up to 100% recanalization is expected.[2] There is no definite answer whether exogenic activation of fibrinolysis with thrombolytic drugs significantly improves the recanalization rate.[5] Early elimination of thrombus is very important because it influence the long-term outcome. Otherwise, fibrotic transformation of the clot appears and results in chronic occlusion of the affected veins.

The precise mechanism of the recanalization process remains unclear. Recanalization is the process through which occluded thrombi undergo changes in size and structure, resulting in eventual re-establishment of the venous lumen.[6] At the beginning, the thrombus probably undergoes the process of fragmentation. In this process, peripheral parts of thrombus are broken up into small pieces separated by clefts.[7] The central parts of the thrombus soften and undergo lysis, which together with fragmentation result in thrombus elimination and recanalization. The crucial roles most probably have endothelial cells and their fibrinolytic and thrombotic activity. Endothelial cells produce thrombomodulin C, heparin and dermatan sulphate, tissue plasminogen activator, nitrogen oxide, and prostacyclin. However, in case of endothelial damage, the prothrombotic and pro-inflammatory sate is thrombus formation.

In our study, most of investigated fibrinolytic parameters were not significantly related to the recanalization rate with the exception of t-PA activity, which was significantly higher in patients with successful recanalization, and t-PA was shown to be an independent predictor of venous thrombosis.

The involvement of inflammatory process in thrombus formation and its resolution was confirmed in different studies. It was shown that inflammation increases tissue factor, platelet activity fibrinogen and inhibits fibrinolysis.[8] However, inflammation is also involved in thrombus resolution. Leukocytes invade in the thrombus during its transformation, and probably influence thrombus resolution by stimulation both fibrinolysis and collagenolysis.[9] Also monocyte chemotactic protein 1 (MCP-1) has also been shown to be associated with resolution of thrombus.[10]

This study is also the first to show that recanalization appears more frequently in females than in males. It is not clear why in our study the recanalization rate was higher in females. The age of both sexes was comparable, there were no differences in the extent of thrombosis (thrombus load), and levels of inflammatory markers and fibrinolytic parameters were comparable between the groups. Therefore, on the basis of the factors that were studied in this trial, it is not possible to explain the differences in the recanalization rate between males and females and other factors not included in this study, like differences in hormone status, most probably influenced the recanalization rate.

In our study of the circulating inflammatory markers only levels of IL-6 and P-selectin were related to recanalization rates of VT. These findings indicate that VT is related to the systemic inflammatory response and that inflammation is probably the basic mechanism through which different risk factors trigger thrombus formation.[11]

Conclusion

Deep venous thrombosis is a chronic process which includes both thrombus formation and thrombolysis. Recanalization of occluded veins is of utmost importance for long-term prognosis and sequelae. Results of our study show that recanalization of occluded deep veins depends on the extent of thrombus and is more frequently observed in females than in males, and is related to some circulating inflammatory markers.

References

1. Markel A. Origin and natural history of deep vein thrombosis of the legs. Semin Vasc Med 2005;5:65-74.
2. Markel A, Meissner M, Manzo RA *et al*. Deep venous thrombosis: rate of spontaneous lysis and thrombus extension. Int Angiol 2003;22:376-82.
3. Meissner MH, Zierler BK, Bergelin RO *et al*. Coagulation, fibrinolysis, and recanalization after acute deep venous thrombosis. J Vasc Surg 2002;35:278-85.
4. van Aken BE, Reitsma PH, Rosendaal FR. Interleukin 8 and venous thrombosis: evidence for a role of inflammation in thrombosis. Br J Haematol 2002;116:173-7.
5. Goldhaber SZ, Buring JE, Lipnick RJ *et al*. Pooled analyses of randomized trials of streptokinase and heparin in phlebographically documented acute deep venous thrombosis. Am J Med 1984;76:393-7.
6. Wakefield TW, Myers DD, Henke PK. Mechanisms of venous thrombosis and resolution. Arterioscler Thromb Vasc Biol 2008;28:387-91.
7. Sevitt S. The mechanisms of canalisation in deep vein thrombosis. J Pathol 1973;110:153-65.
8. Esmon CT. Inflammation and thrombosis. J Thromb Haemost 2003;1:1343-8.
9. Varma MR, Varga AJ, Knipp BS *et al*. Neutropenia impairs venous thrombosis resolution in the rat. J Vasc Surg 2003;38: 1090-8.
10. Humphries J, McGuinness CL, Smith A *et al*. Monocyte chemotactic protein-1 (MCP-1) accelerates the organization and resolution of venous thrombi. J Vasc Surg 1999;30:894-9.
11. Dosquet C, Weill D, Wautier JL. Cytokines and thrombosis. J Cardiovasc Pharmacol 1995;25 Suppl 2:S13-19.

SVHM Shared Venous hemodynamics Map: a common denominator for computerized comparison of the results of CVD treatment (chronic venous disease)

A.I. Galeandro [1], A. Zito [2], F. Cortese [2], M. Gesualdo [2], F. Ciciarello [3], D. Di Nunzio [2], G. Galgano [4], M.M. Ciccone [2], P. Scicchitano [2]

[1]*Department of Scientific-Technological Park of the University of Bari, Bari, Italy*

[2]*Cardiovascular Disease Section, Department of Emergency and Organ Transplantation, University of Bari, Bari, Italy*

[3]*Cardiac Department, La Sapienza University, Rome, Italy*

[4]*Cardiac Department, Miulli General Hospital, Acquaviva delle Fonti, Bari, Italy*

Varicose veins are not only an annoying problem of an aesthetic nature that undermines the vanity of those who want to show off toned legs with no blemishes, but they can hide a disorder concerning chronic venous insufficiency (CVI) of the lower limbs.[1]

There is no single solution to eliminate varicose veins. Each patient requires an individual approach, which involves the application of one method rather than another, or sometimes a combination of several methods.[2-4]

Up to now, specialists have preferred a therapeutic approach more in line with their own specific branch of medicine: in other words, often the phlebologist with a medical background prefers sclerotherapy,[5] the radiologist intravenous treatment and the surgeon traditional surgery, regardless of the specific clinical condition of each patient.[6, 7] Thus, the need for standardization of data and results, led to the MEVeC (Shared/CombinedHemodynamic VenousMap) creation, in order to solve the problems regarding the organization and comparability of data and results in the treatment of chronic lower limbs venous insufficiency.

MEVeC is an innovative diagnostic tool and represents the evolution of the old MEV (hemodynamic venous map), *i.e.* it is a graphic diagram of analysis which adopted the Doppler ultrasound evaluation to study both venous segments (as you normally would) and the entire hemodynamic of venous system. All the information acquired allows physicians to obtain an accurate "map" of the venous system, where all morphological (size of the veins, course, depth etc.) and functional (analysis of changes in venous flow in the various static positions and dynamics) characteristics are represented. The hemodynamic venous studies had been extensively validated over the last 20 years; furthermore, most of the literature that has been produced has not been fully exploited, due to the difficulty to easily access all the information gathered on the subject (despite the use of paper or computer data bases) mainly because it involves a lot of extra hard work (quite significant when dealing with such an elaborate process).

The MEVeC is a project which has been conceived and led by a specific task force that belongs to the School of Excellence in Phlebology. For the first time in the history of phlebology, MEVeC allows physicians to use multiple data and to compare all the different well-known ultrasound methods, reaching a final single, uniform and objective "control panel", where everything is connected. This will enforce the concept of "sharing information in a uniform way", becoming an instrument accessible to all those dealing with phlebology, no matter what the therapeutic approach (physician, surgery, rehabilitative, sclerotherapy, etc.) may be. Doctors will share the information gathered in the examination of the patients, accepting its absolute value in terms of credibility and thus recognizing it as a common diagnostic tool for standardized therapeutic solutions concerning CVI of the lower limbs with the possibility to reproduce a comparable clinical chart that goes beyond the technique used.

The core of this project lies in a software (MEVeC 3D) that reproduces a three-dimensional venous system of the lower limbs and it "guides" the operator in carrying out the diagnosis on the basis of an operational methodology scientifically validated in terms of accuracy, sensitivity and specificity (Figure 1).

This method of diagnosis performed with Doppler ultrasound has been developed by a task force coordinated by Aldo Innocente Galeandro, involving the Department of Cardiovascular and Respiratory Sciences of the University of Rome La Sapienza, Cardiology University of Bari and the Health Department of

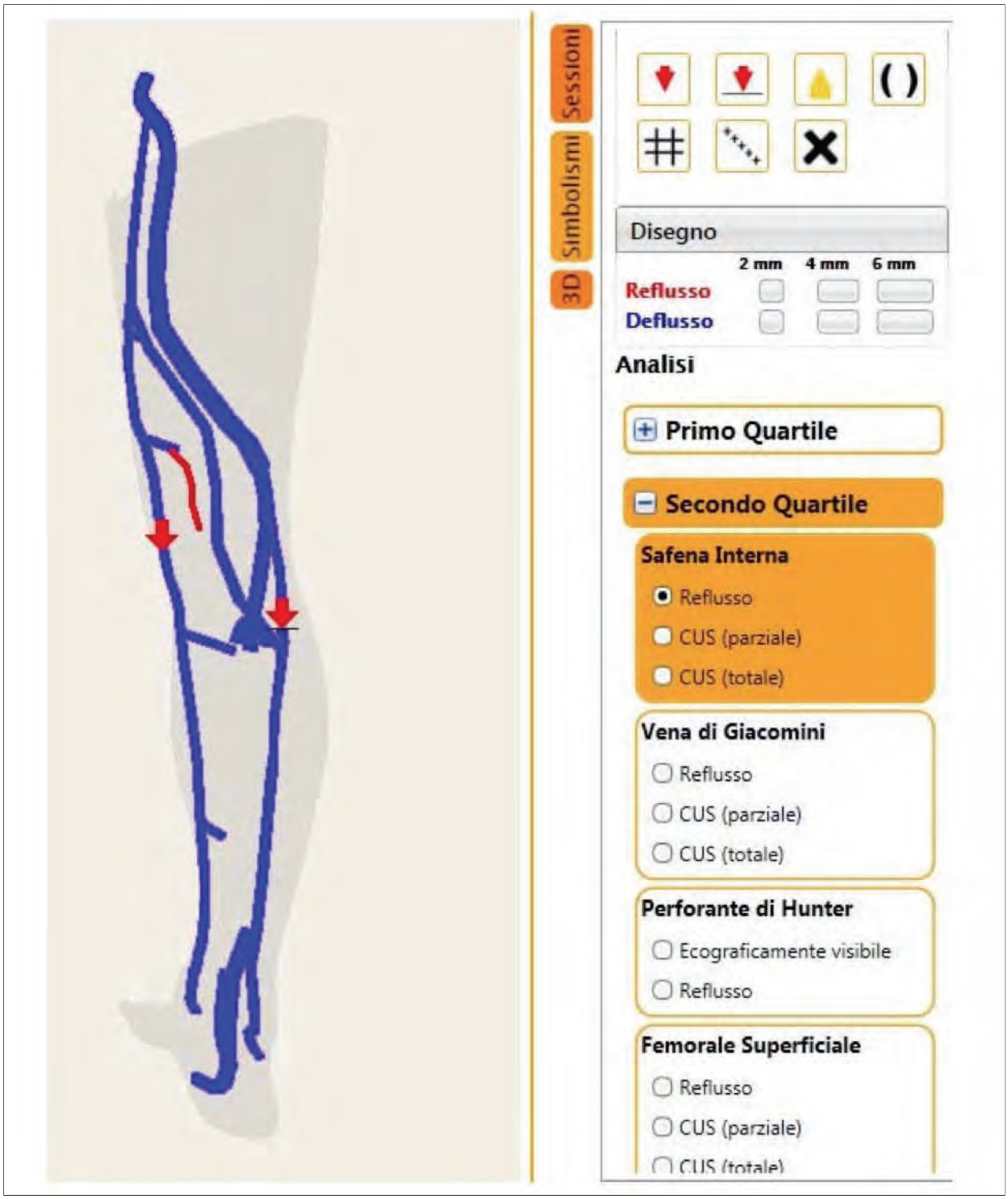

Figure 1. – MEVeC map example representation.

Scientific-Technological Park of the University of Bari. The first application and methodology was published in "the Vascular Health and Risk Management" in 2012 (Doppler ultrasound venous mapping of the lower limbs).[8]

The software was perfected at the Laboratory of Computational venous hemodynamics at the Technology Park and, as already mentioned, the doctor is literally "guided" through the process when it comes to creating a map with the information that is needed

to transpose the parts with a 3D representation, which is essential in order to understand the functional characteristics of a system, such as the venous system in a three-dimensional context.

Software features

The limb was divided into 4 parts (2 thighs and 2 legs) with the following topographic determinations:[8]

– 1st part: from the midpoint of the thigh to the inguinal ligament;
– 2nd part: from the kneecap to the midpoint of the thigh;
– 3rd part: from the midpoint of the calf to the kneecap;
– 4th part: from the heel to the midpoint of the leg.

List of veins that are examined for each part are gathered in table I.
In order to simplify the method, the MEVeC project was performed after extensive reviewing the anatomical representation and symbolism of the venous system, in order to give physicians the opportunity to represent a three-dimensional map of the limb not marked with the various old-fashioned and complicated venous segments (R1, R2, R3, R4).[9] This will simply the evaluation of the lower limb venous vasculature.

The concept of sharing information

Bearing in mind that the information to be transferred onto the map [10] varies according to different diagnostic and therapeutic needs, MEVeC is able to give important results and data to take into consideration in order to have an objective instrument available for all operators (*i.e.*, doctors, rehabilitation physicians, surgeons, etc.).

Furthermore, it is possible to obtain an Automatic 2D and 3D medical report, to be shared with the Data Processing Centre of the Technology Park. This will give physicians the chance to compare their findings and their performance with more colleagues. Such a purpose will ameliorate diagnosis of CVI and its treatment, thus it will create a common language and instrument for all phlebologists all over the world.

References

1. Robertson L, Evans C, Fowkes FGR. Epidemiology of chronic venous disease. Phlebology 2008;23:103-11.
2. Nüllen H, Noppeney T. Diagnosis and treatment of varicose veins : part 2: therapeutic procedures and results. Chirurg 2010;81:1125-38.
3. Davies AH, Magee TR, Jones DR *et al.* The value of duplex scanning with venous occlusion in the preoperative prediction of femoro-distal vein bypass graft diameter. Eur J Vasc Surg 1991;5:633-6.
4. Wittens CH, de Roos KP, van den Broek TA et al. Guideline "Diagnosis and treatment of varicose veins". Ned Tijdschr Geneeskd 2009;153:B71.
5. Gillet J, Lausecker M, Sica M *et al.* Is the treatment of the small saphenous veins with foam sclerotherapy at risk of deep vein thrombosis? Phlebology/Venous Forum of the Royal Society of Medicine. Phlebology 2013 Jul 17. [Epub ahead of print].
6. Labropoulos N, Tiongson J, Pryor L *et al.* Definition of venous reflux in lower-extremity veins. J Vasc Surg 2003;38:793-8.
7. Cina A, Pedicelli A, Di Stasi C *et al.* Color-Doppler sonography in chronic venous insufficiency: what the radiologist should know. Curr Probl Diagn Radiol 2005;34:51-6.
8. Galeandro AI, Quistelli G, Scicchitano P *et al.* Doppler ultrasound venous mapping of the lower limbs. Vasc Health Risk Manag 2012;8:59-64.
9. Franceschi C. So as to avoid any misunderstanding about Cure Conservatrice et Hemodynamique de l'Insuffisance Veineuse en Ambulatoire (CHIVA). Phlebology 2010;25:212.
10. Wong JK, Duncan JL, Nichols DM. Whole-leg duplex mapping for varicose veins: observations on patterns of reflux in recurrent and primary legs, with clinical correlation. Eur J Vasc Endovasc Surg 2003;25:267-75.

Liquid sclerotherapy

F. Mariani [1], M. Bucalossi [1], St. Mancini [2]
[1]Department of Vascular Surgery, Valdisieve Clinic, Pontassieve (Florence), Italy
[2]Department of Medical, Surgical Sciences and Neurosciences, University of Siena, Siena, Italy

To sclerose a vein means to inject in a vein lumen a chemical product which is able to induce an endothelial lesion, usually followed by a thrombus (sclerothrombus) formation; subsequently this process results in a varicose vein occlusion and finally vein fibrosis (vein "connettivisation") hopefully occurs. The injected substances typically involve only the diseased veins. Modern sclerosing substances act directly on the endothelium vein: three hours after the injection an endothelial swelling with desquamation is detected, after 15 hours a deposition of a mixed thrombus takes place and after about 24 hours it fixes to the vessel wall until its final connective organization; finally up to 60-90 days after the injection, fibrosis of the vein may occur (Mariani F. *et al.* 1996).

Indications

The indications of sclerotherapy in VCI are:
– incompetent saphenous veins;
– tributary varicose veins;
– incompetent perforating veins;
– reticular varicose veins;
– telangiectasias (spider veins);
– residual and recurrent varicose veins after previous interventions.

Liquid sclerotherapy is considered to be the method of choice for the treatment of CEAP 1 reticular varicose veins and telangiectasias. In the treatment of incompetent saphenous veins, thermal ablation or surgery are well established methods. Nevertheless, treatment of saphenous veins by sclerotherapy is also a good and cost effective treatment option. This applies in particular to foam sclerotherapy, as has been demonstrated by case control studies and prospective randomized controlled studies conducted in recent years.

Contraindications

The contraindications are:
absolute contraindications
– Known allergy to the sclerosant;
– Acute deep vein thrombosis (DVT) and/or pulmonary embolism;
– Local infection in the area of sclerotherapy or severe generalised infection;
– Long-lasting immobility and confinement to bed.
Relative contraindications
– pregnancy;
– severe peripheral arterial occlusive disease;
– strong predisposition to allergies;
– high thromboembolic risk (*e.g.* history of thromboembolic events, known severe thrombophilia, hypercoagulable state, active cancer);
– acute superficial venous thrombosis;
– anticoagulation treatment per se is not a contraindication to sclerotherapy.

Complications

If performed properly, sclerotherapy is an efficient treatment method with a low incidence of complications. The severe complications (very rare <0.01%) are anaphylaxis, visual disturbances, headache, migraine, tissue necrosis, stroke and TIA, DVT, pulmonary embolism and nerve injuries. The common benign complications are the residual superficial venous thrombosis (SVT), matting and residual pigmentation. The frequencies of SVT is between 0% and 45.8% with a mean value of 4.7%. The definition of phlebitis after sclerotherapy in the literature is controversial: an inflammatory reaction in the injected part of the vein should not be interpreted as phlebitis, whereas superficial vein thrombosis in a non-injected vein would fulfil this definition. Skin pigmentation has been reported with frequencies ranging from 0.3% to 30% in the short term but in general, this phenomenon resolves slowly in weeks or months. The more effective method to prevent pigmentation is to remove intravascular clots by stab incision or direct puncture by a needle. In addition, post-sclerotherapy UV exposition should be avoided for the first period after sclerotherapy.
Matting is a new occurrence of fine telangiectasias in the area of a sclerosed vein or telangiectasias. Inadequate or no treatment of the underlying reflux is the cause in many cases of matting. High initial concentrations or large volumes of sclerosant can also result in inflammation or excessive vein obstruction with subsequent angiogenesis. Treatment of matting should concentrate on the underlying reflux.
Other general or local transient reactions after sclerotherapy include vaso-vagal reactions, nausea, metallic taste, intravascular coagula, haematomas, ecchymoses at the injection site, pain at the injection site, indurations, wheals, blisters and erythema.

Sclerosing solutions

Currently used sclerosing substances have different mechanisms of action and aggression on vein walls,

but basically they are all osmotically active and as overall their action on the endothelium may be just irritative, necrotizing or colliquative.
Factors which influence the sclerosing power are:
a) dose and concentration of medication;
b) physical-chemical variables (pH, liquid or foam) of the agents and of the blood;
c) physical-hemodynamic reasons inherent to local flow conditions;
d) injection technique;
3) variability of the factors related to thrombosis and fibrosis of the treated vessels.

All sclerosant drugs have a different mechanism of action, but by changing (usually increasing) the pH of a drug, this becomes a more powerful sclerosant. Different sclerosing solutions have been used to treat varicose veins in recent decades, depending on national regulations, national traditions, and the size of the veins to be treated.
Sclerosing substances are grouped, depending on the power, in three main groups:
major sclerosants: iodine solutions and Sodium tetradecyl sulphate STS;
medium sclerosants: Polidocanol POL, sodium salicylate SS;
minor sclerosants: chromated glycerin CG, dextrose-sodium chloride DCS, hypertonic saline solution 23.4%.
Polidocanol (lauromacrogol 400) is available in different concentrations, for example 0.25, 0.5, 1, 2 and 3% (this corresponds to 5 mg, 10 mg, 20 mg, 40 mg, 60 mg respectively in a 2 mL-ampoule). Polidocanol is a non-ionic detergent and a local anaesthetic. The dose of 2 mg polidocanol per kg body weight and per day should not be exceeded (German Summary of Product Chracteristics/Package Insert for Aethoxysklerol-Kreussler 2012).
For a patient weighing 70 kg – independently of the medically indicated amount – a total of up to 140 mg polidocanol (lauromacrogol 400) per kg body weight per day should not be exceeded. 140 mg polidocanol are contained in:

polidocanol-solution 0.25%	56 mL injection solution
polidocanol-solution 0.5%	28 mL injection solution
polidocanol-solution 1%	14 mL injection solution
polidocanol-solution 2%	7 mL injection solution
polidocanol-solution 3%	4.6 mL injection solution

Sodium tetradecyl sulphate is an anionic detergent sclerosant drug. It is supplied in concentrations of 0.2%, 0.5%, 1% and 3% (2 mg/mL, 5 mg/mL, 10/mL and 30 mg/mL respectively (*e.g.* Prescribing Information Fibrovein, UK STD 2012). Excessive doses of STS may lead to haemolysis of red blood cells and therefore the manufacturers recommend limiting the dose of STS to not more than 4 mL of 3% solution and not more than 10 mL of all other concentrations per session of treatment.

Indications	Concentration % POL	Concentration % STS
Telangiectasias (spider veins)	0.25-0.5	0.1-0.2
Reticular varicose veins	0.5-1	up to 0.5
Small varicose veins	1	1
Medium-sized varicose veins	2-3	1-3
Large varicose veins	3	3

Chromated Glycerin or glycerol is a glycol (bivalent alcohol) used as an osmotic diuretic and it is a sclerosant liquid, when combined with chrome alum, which has strong coagulating properties. Today a bluish coloured and oily sterile solution of chromated glycerin is commonly used, and it is composed of 72% of glycerin and of 1,11% of chrome alum; alternatively in a few countries the single glycerin or glycerol is used as a compound drug. Thanks to Kern's recent studies CG has re-gained some popularity in the scientific community, as it proved to achieve good results in the treatment of telangiectasias, over the use of POL, STS or sclerosant foam. CG has an irritating chemical action on the endothelium, and it is a weak, viscous sclerosant which may result in some minor local side effects such as pigmentation, peri-venous inflammation (rarely necrosis), skin redness and/or short lasting pain in the surrounding area. Systemic reactions are those common to all sclerosant agents (allergies, etc.) plus a dark colored urine emission in rare cases. Generally CG dose per session and per injection never overcomes 10 mL and 3 mL respectively (usually few drops per injections in telangiectasias) and this "weak" drug is used for telangiectasias and reticular varices only.
Salycilates (Sodium Salicylates and Potassium Salicylate) an ancient remedy known to Hippocrates and Galen and also in the Middle Ages, exist in nature such as salicylic and methyl salicylate. Firstly used in 1876 in rheumatic fever, then basic components of acetylsalicylic acid (ASA) 20 years later, salicylates were introduced by Jean Sicard in 1919 in France (sodium salicylate, SS) in sclerotherapy of varicose veins. SS has been widely used worldwide (mainly in France, Italy, Canada and Argentina) in the last 60 years, basically for minor varicosities only, more frequently under the form of compound drug.
SS is usually used at 10-20% concentration, with xylocaine included to compensate the hyperalgesia which SS may generate in the first seconds after the injection. More recently Mariani and Izzo introduced Potassium Salicylate (PS) to potentiate salicylate ion activity on endothelial cells, using an alkaline ph formulation; this also resulted in a lower pigmentation rate in the authors' experience. SS and PS have also shown a beneficial effect on venous symptoms such as cramps and heaviness though a short-lasting painful injection is associated with higher concentrations. Side effects are skin necrosis (if extra-venously injected), rarely pigmentation. Allergy to ASA and deaf-

ness are common contraindications to usage of SS or PS. 10 mL of SS 20% is the recommended maximum dose per session, while 0,1-0,5 mL of SS or SP are commonly used per injection.
Hypertonic Saline solution (HSS) (23,4%) damages endothelial wall and induces a thrombus within one hour after injection, while the sclerosis is completed in 2-4 weeks. Addition of heparin to HSS resulted in some more "matting", probably due to the angiogenesis action of heparin, without any improvement of the outcomes.
Local side effects are similar to those of salicylates, while the lack of selectivity of action of HSS on the diseased vessel walls may explain the higher incidence of deep vein thrombosis (DVT)/pulmonary embolism (EP) in literature. Finally caution in hypertensive patients is recommended if large amounts are injected. Generally 15 mL is the suggested highest dose per session, and 1 to 3 mL of HSS is the dose per injection, while few drops are used in telangiectasias.
Dextrose+Sodium Chloride (DSC) is composed of a mixture of: Dextrose 250 mg/mL, NaCl 100 mg/mL, Phenethylic alcohol 8 mg/mL, propylene Glycol 100 mg/mL, water up to 10 mL. This hypertonic solution with 5.9 pH value causes dehydration and necrosis of endothelial cells, after 3 minutes from injection. The deposition of fibrin and thrombus formation occurs because of a change of electrostatic charges in the endothelium under esfoliation. Local side effects of DSC may include pigmentation, rare skin necrosis, while, like HSS, a lack of the selectivity of action may rise the risk of DVT/PE if large amounts are injected (total volume of 10 mL per session is recommended). Again from few drops to 3 mL is the dosage per injection and DSC is mostly recommended in telangiectasias and reticular varices only.

Physics of the sclerosing injection

Experimental studies carried out by Stemmer R. show that blood and sclerosant liquid always move towards the area of lowest pressure according to a pressure gradient. Through compression you can canalise the liquid towards a segment (*e.g.* perforator) or increase the contact time with the endothelium; also it was demonstrated that the manner in which the sclerosant substance is distributed also depends on the size of the vessel.
The so called "air block" technique (which has been proposed for small varices) consists in an injection of a quantity of air before the liquid sclerosant, to displace some blood from the injected segment, obtaining a better contact between the substance and the endothelium, as shown in Stemmer's studies.
In Stemmer's and our own experimental studies, the caliber of the needle affects the dynamics of the injection: at the same injection speed rate and with the same amount of time, the quantity of substances that touches the wall, increases or decreases according to the dimensions of the needle.
While Stemmer's experience demonstrates that the injection rate does not affect the sclerosis effect, Zelikovski A. demonstrated that the rapid injection of labeled iodine solution 4% results in a longer contact time with the vein wall compared to a slow technique. It is somehow finally agreed that the bending of the needle is completely irrelevant as to liquid injection dynamics.
Chemical and physical constants of blood and of sclerosant agents interact in due course of sclerosing action. An endothelial injury may be caused by alteration of the electrical charge, of blood pH, of osmolality and of the surface tension. The lowering of surface tension induced by detergent agents and the osmotic variations of hypertonic solutions determine significant changes in the endothelium. The viscosity of the sclerosant agent does not influence the effect, but a strong viscosity slows the progression of the product along the venous route (which is the case, for example for CG). Density is important in the distribution of the liquid in the vessel: if the specific weight of sclerosant agent considerably differs from that of blood (mean 1.050) it will tend to float or sediment (depending on whether it is lighter or heavier, respectively), which affects the necrotizing effect on the endothelium.
Factors related to thrombosis and fibrosis of venous vessels may be different from those ones in Virchow's triad: the thrombus is poor of fibrin and there is a reduced participation of coagulation mechanisms. The slowdown of blood flow and hypercoagulability do not play an important role in the formation of post-sclerotherapy fibrosis and for example no decrease of the sclerosing POL activity has been reported in anticoagulated patients, as the endothelial injury is the key-mechanism that provokes the localized sclero-thrombosis.
Several physical variables may positively or negatively interfere with the sclerosis process and the volume of the target vein is probably one of the most important. When injecting a sclerosant agent into the vein, the blood dilution plays a major role, due to the interaction of blood components (primarily proteins) with the sclerosant drugs. Intuitively the larger the vein, the higher the blood/protein content, the higher the negative interference with the sclerosant drug action on the blood content itself and finally on the vein walls.
Vein calibre reduction, prior to any injection is hence suggested in liquid or foam sclerotherapy, to maximise the sclerosant effect on the vein walls. This simple statement brings most sclerotherapists to inject patients only in supine position; in this position vein size decreases by about 50% from standing position and the dilution of the sclerosant drug at 5 cm from the injected site is about three times lower. The possibility of raising the limb before any sclerosing treatment commences, may lead to a further reduction of the dilution of the sclerosant drug 5 cm far from the

Table I. – Compression therapy during sclerotherapy

Varicose veins	Concentric compression	Duration	Eccentric compression	Duration
Greater saphenous vein Collateral varicose veins	Non-elastic or short-stretch bandages. MCS(*) at least 2nd class or Sigvaris® postoperative stocking	7-21 days	Obligatory, better if in non compressible material	Fixed or removable 4-7 days
Short saphenous vein Collateral varicose veins	Non-elastic or short-stretch bandages. MCS(*) at least 2nd class	7-21 days	Optional Obligatory for large varicosities	Fixed or removable 4-7 days
Non-saphenous varicose veins	Non-elastic or short-stretch bandages. MCS at least 1st class	7-21 days	Optional, not necessary for veins with a diameter <2 mm	–

(*) It can be recommend the use of two superimposed elastic stockings, removing one of them at night.

injected point (8 times higher concentration in comparison with a standing position); similarly with 30°-50° elevated limb a 60-80% calibre reduction is expected in the saphenous and tributary veins. To overcome the possible difficulty to cannulate a vein in a raised limb many physicians prefer to raise the limb after entering the vein in supine position and after fixing the needle/catheter to the skin. Limb elevation does not necessarily attain to sclerotherapy of minor varicosities, as the latter reduce in size much less (or not at all) due to their location in the dermal space and to the minor changes of the inner pressure with postural changes. For reticular varices and telangiectasias a possible option to improve the blood reduction/clearing effect in the treated segment. could be to inject and retrieve the sclerosant drug within the vessel a few times In our empirical experience this procedure seems to reduce clot retention, while increasing the sclerosing power, even of low concentration drugs (*e.g.* POL 0,25%, STS 0,1%, SS 12%).
As vein calibre and blood content are strictly regulated by the transmural pressure (external pressure *vs.* inner vein pressure) it is possible to increase external pressure through stockings or bandages (with or without pads to increase local pressure according to Laplace's law), which is more easily achievable for varicose tributaries or for subcutaneous veins in general.
Some of the considerations and data mentioned above may not necessarily be pertinent to the injections of sclerosant foam. In fact foam dynamics significantly differ from liquid dynamics, both in supine and raised limbs. A potentiated action of foam over liquid drug has been proved in different studies, which can be referred to the prolonged contact between drug and vein wall, to the great multiplication of the active surface of the drug over the microbubble surface, to the reduced blood content in the injected segment and to many other factors which intervene in foam activity and which are still under investigation.

Compression

Compression therapy is the cornerstone of sclerotherapy. It involves the use of bandages during active treatment in order to reduce the lumen of the treated vein, to reduce the clots and the inflammatory reaction of the vein walls to sclerosing agents. Local eccentric compression significantly increases local pressure in the sclerosed area and improves the efficacy of sclerotherapy. The use of elastic stockings (MCS) is recommended with the aim of ensuring adequate compression to consolidate the venous fibrosis. The duration and methods of compression vary according to the specialists and sclerotherapy techniques. Some studies show equal efficacy in the therapeutic outcome of bandages maintained for a few hours to six weeks, as a significant fall in the pressure exerted by the bandages 6-8 hours following application has been shown. Compression combined with mobilisation of the patient is, however, fully justified after sclerosis of varicose veins, especially if they are large in size and located in the lower leg. This cannot be standardised but must be assessed from case to case. In general, a rigid bandage with the aid of "eccentric" compression is applied after sclerotherapy of medium to large varicose veins, and this is replaced after about a week by a MCS 1st or 2nd class. Compression therapy in brief controls extension of the thrombus resulting from the endothelial lesion produced by the sclerosing agent, approximates the vein walls and limits periphlebitic reactions, thus improving the final result and the incidence of pigmentation decreases significantly.
The use of MCS after sclerotherapy of reticular varices and telangiectasias is controversial since the pressures necessary to exert an effective action on small veins are too high (about 80 mmHg); it is advisable to prescribe support of a compression class suitable for the degree of venous insufficiency that is present. A study by Kern P. et al. shows the necessity of a MCS 2nd class (Sigvaris® 702) worn for three weeks to improve the results of sclerotherapy carried out with

liquid drug in 100 cases with C1, Ep, As1, Pn. The table below gives suggestions for application of compression during sclerotherapy. Compression treatment with bandage and medical compression stockings may improve the results of sclerotherapy for varicose and spider veins (Table I).

References

1. Agus GB, Allegra C, Arpaia G *et al.* Linee Guida per la Diagnosi e il Trattamento delle Malattie delle Vene e dei Linfatici. Collegio Italiano di Flebologia, aggiornamento 2013. Torino: Edizioni Minerva Medica;2013.
2. Alos J, Carreno P, Lopez JA *et al.* Efficacy and safety of sclerotherapy using Polidocanol foam: A controlled clinical trial. Eur J Vasc Endovasc Surg 2006;31:101-7.
3. Blaise S, Bosson JL, Diamand JM. Ultrasound-guided sclerotherapy of the great saphenous vein with 1 % *vs.* 3 % Polidocanol foam: a multicentre double-blind randomised trial with 3-year follow-up. Eur J Vasc Endovasc Surg 2010;39:779-86.
4. Blaise S, Charavin-Cocuzza M, Riom H *et al.* Treatment of Low-flow Vascular Malformations by Ultrasound-guided Sclerotherapy with Polidocanol Foam: 24 Cases and Literature Review. Eur J Vasc Endovasc Surg 2011;41:412-7.
5. Bullens-Goessens YIJM, Mentink LF, Nelemans PJ *et al.* Ultrasound-guided sclerotherapy of the insufficient short saphenous vein. Phlebologie Germany 2004;33:89-91.
6. Busch RG, Derrick M, Manjoney D. Major neurological events following foam sclerotherapy. Phlebology 2008; 23:189-92.
7. Deichman B, Blum G. Cerebrovascular accident after sclerotherapy. Phlebologie 1995;24:148-52.
8. De Maeseneer M, Pichot O, Cavezzi A *et al.* Duplex ultrasound investigation of the veins of the lower limbs after treatment for varicose veins - UIP consensus document. Eur J Vasc Endovasc Surg 2011;42:89-102.
9. Gillet JL, Guedes JM, Guex JJ *et al.* Side effects and complications of foam sclerotherapy of the great and small saphenous veins: a controlled multicentre prospective study including 1025 patients. Phlebology 2009;24:131-8.
10. Gillet JL, Donnet A, Lausecker M *et al.* Pathophysiology of visual disturbances occurring after foam sclerotherapy. Phlebology 2010;25:261-6.
11. Gillet JL. Neurological complications of foam sclerotherapy: fears and reality. Phlebology 2011;26:277-9.
12. Guex JJ, Allaert F-A, Gillet J-L. Immediate and midterm complications of sclerotherapy: Report of a prospective multicenter registry of 12,173 sclerotherapy sessions. Dermatol Surg 2005;31:123-8.
13. Guex JJ. Complications of sclerotherapy: an update. Dermatol Surg 2010;36:1056-63.
14. Kern P, Ramelet AA, Wütschert R *et al.* Compression after sclerotherapy for telangiectasiastelangiectasias and reticular leg veins. A randomized controlled study. J Vasc Surg 2007;45: 1212-6.
15. Izzo M, Amitrano M, Bacci PA *et al.* Pigmentation post-sclérothérapie: physiopathologie et traitment. Phlébologie 2001;54:273-77.
16. Lee BB, Do YS, Byun HS *et al.* Advanced management of venous malformation with ethanol sclerotherapy: mid-term results. J Vasc Surg 2003;37:533-8.
17. Mancini S, Mariani F, De Sando D *et al.* La sclérose de la grande saphene. Histologie et microscopie electronique des alterations chez l'homme. In: Davy A, Stemmer R (Editors). Phlébologie '89, 10° Congrés Mondial Union Internationale de Phlébologie. Montrouge: John Libbey Eurotext Ltd. 1989. p. 769-71.
18. Mariani F. Compression. Consensus Document based on Scientific Evidence and Clinical Experiences. Torino: Edizioni Minerva Medica; 2009.
19. Mariani F, Bianchi V, Mancini St *et a*l. Telangiectases in Venous Insufficiency: Point of Reflux and Treatment Strategy. Phlebology 2000;15:38-42.
20. Mariani F, Binaghi F, Pitzus F. Scleroterapia-Testo Atlante. Torino: Edizioni Minerva Medica; 1996.
21. Mariani F, Mancini S. Scleroterapia. Torino: Edizioni Minerva Medica; 2006.
22. Mariani F, Trapassi S, Mancini St *et al*. Telangiectases in Venous Insufficiency. Investigation of Refluxes and Sclerotherapy. Acta Phlebologica 2000;1:33-8.
23. Nootheti PK, Cadag KM, Magpantay A *et al.* Efficacy of graduated compression stockings for an additional 3 weeks after sclerotherapy treatment of reticular and telangiectatic leg veins. Dermatol Surg 2009;35:53-8.
24. Partsch H, Flour M, Coleridge Smith P *et al.* Indications for compression therapy in venous and lymphatic disease. Consensus based on experimental data and scientific evidence. Under the auspice of the IUP. Int Angiol 2008;27:193-219.
25. Peterson JD, Goldman MP, Weiss RA *et al.* Treatment of Reticular and Telangiectatic Leg Veins: Double-Blind, Prospective Comparative Trial of Polidocanol and Hypertonic Saline. Dermatol Surg 2012;38:1-9.
26. Ramelet A-A. Phlébologie esthétique. Télangiectasies : possibilités thérapeutiques. Cosmétologie et Dermatologie esthétique. Paris: EMC (Elsevier Masson SAS, Paris); 2010.
27. Rabe E, Pannier-Fischer F, Gerlach H *et al.* Guidelines for sclerotherapy of varicose veins. Dermatol Surg 2004;30:687-93.
28. Rabe E, Schliephake D, Otto J *et al*. Sclerotherapy of telangiectasias and reticular veins: a double-blind, randomized, comparative clinical trial of polidocanol, sodium tetradecyl sulphate and isotonic saline (EASI study). Phlebology 2010;25:124-31.

PRINTED BY
MINERVA MEDICA
DECEMBER 2013
SALUZZO (ITALY)
CORSO IV NOVEMBRE 29-31