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Editors

P.L. Antignani, C. Allegra, S. Novo

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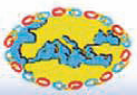

Mediterranean League of Angiology and Vascular Surgery

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Foreword

This volume contains a small, but representative, part of papers presented at the 18th EUROCHAP Congress (European Chapter of the International Union of Angiology) jointly organized with the XIX MLAVS Annual Meeting of the Mediterranean League of Angiology and Vascular Surgery. The congress has held between the 24th and 27th of October 2009 at the Hotel Park Florio and Magaggiari of Cinisi (Palermo, Italy).

It has had a four-day core structure (that consisted of daily sessions, state-of-the-art lectures, keynote lectures, symposia, oral communications and poster sessions) covering many topics in the spectrum of Cardiology, Vascular Medicine and Angiology.

The scientific program aimed at presenting and debating with world academic experts and all the participants (ie young clinicians, students and trainees) the most recent researches and advances in these fields of interest. Our aim and the great enthusiasm that has led us in the congress working are well reflected in this volume. It is, then, our hope that it will be appreciated as an opportunity to update clinical knowledge. With these auspices, we would like to thanks the authors for submitting their works and the Medimond Publisher for putting this valuable volume together.

Prof. Pier Luigi Antignani
Prof. Claudio Allegra
Prof. Salvatore Novo
Chairmen of the Congress

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Screening of aaa

Aluigi L.

General, Interventional and Vascular Ultrasound Center – Complex Unit of Medical Care - Department of Medicine - Major Hospital - Bologna - Italy

Summary

Abdominal aortic aneurysm (AAA) is defined as a dilation of the abdominal aorta to a size 50% greater than the proximal normal segment or to a maximum aortic diameter greater than 3 cm. AAA is found in 5% to 10% of men aged 65 to 79 years. The four leading risk factors for development of AAA include increasing age, smoking, male gender, and family history.[14] Abdominal aortic aneurysms are often asymptomatic but a rupture is a surgical emergency and often leads to death. The mortality after rupture is high, 80% for patients reaching hospital and 50% for those undergoing surgery for emergency repair.[12] There is interest in population screening to detect, monitor and repair abdominal aortic aneurysms before rupture. The most important objectives concerning AAA screening are to identify subjects at risk and to reduce mortality rate due to rupture moving from the issue that elective surgical repair is recommended to prevent rupture for aneurysms discovered to be larger than 5.5 cm.

Introduction

Very important persons (VIP) of the very past like as George William Frederick, King of the United Kingdom "George the third" (1760), the great Italian musician Niccolò Paganini (1840), the American explorer Christopher "Kit" Carson (1868) and more recently the great physicist Albert Einstein 1955, the French President Charles De Gaulle (1970) and the great Italian pianist Arturo Benedetti Michelangeli (1995) died for rupture of an aortic abdominal aneurysm. Of course many and many other "normal" persons died in the same way because the pathology was poor known and/or not at all investigated. Surely today the problem is better well known and VIP like as the actor Richard Gere or the Ferrari's President Luca Cordero from Montezemolo or the USA President Barack Obama, but "normal" persons too, are likely less exposed to the risk to die for the same disease. And this just because in the west population everyone easily undergo ultrasound abdominal scan for some reason (Liver, Pancreas, Kidney disease for example) during his own life and more and more frequently to directly exclude abdominal aortic aneurysm too.

Table 1

1.	The disease should be an important health problem
2.	A generally acceptable method of treatment must be available
3.	The policy for treatment must be clear
4.	Provision for diagnosis and treatment must be available
5.	The disease must have a detectable latent stage
6.	A suitable screening method must be available
7.	The screening method must be accepted by the target population
8.	The natural course of the disease must be known
9.	The program must be cost-effective
10.	The treatment of the disease should favour the prognosis of the patients

Surprisingly, over the past 20 years despite advances in diagnostic imaging and in general medical care of patients, there has been essentially no change in the number of patients seen in US hospitals with ruptured AAA.[13] Every year Approximately 15,000 persons die of ruptured AAA and dissections[17] and it is estimated that about 300,000 persons per year die suddenly without receiving medical care.[18] Furthermore, studies have shown that the incidence of ruptured AAA in cases of sudden death ranges from 4% to 5%. The yearly death rate from ruptured AAA in US could be therefore as high as 30,000. This is comparable to a yearly mortality of 32,000 for prostate cancer and 42,000 for breast cancer.[17] The presence of an asymptomatic phase with the opportunity of a relatively low risk treatment compared to the symptomatic phase raised the question of whether screening for AAA would be effective. If seriously considered, all the criteria for screening formulated by WHO and the Council of Europe would need to be fulfilled.[8,31] (Table 1)

The WHO ten criteria for screening (Table 1).

EPIDEMIOLOGY, CLINICAL PRESENTATION AND NATURAL HISTORY

An aortic abdominal aneurysm (AAA) is defined as a dilation of the abdominal aorta to a size 50% greater than the proximal normal segment or to a maximum aortic diameter greater than 3 cm. The epidemiology of AAA is derived mainly from population based ultrasound (US) screening studies and autopsy studies.[3,5,11,19,20] AAA is primarily a disease of elderly white men, with white males being two to three times more likely develop AAA than black males. There is an inverse relationship between Diabetes (DM) and development of AAA. Patients with DM where two times less likely to develop AAA than those without DM.[14] The four leading risk factors for development of AAA include increasing age, smoking, male gender, and family history.[14] Secondary risk factors include other cardiovascular risk factors (eg, hypertension and hyperlipidemia) and established cardiovascular disease. The frequency of aneurysms increases steadily in men older than 55 yrs, reaching a peak of 6% at 80 to 85 yrs. In women peak of 4.5% at older than 90 yrs. Male : Female ratio is 4:1 to 5:1 in the 60 to 70 year age group, but beyond age of 80 it approaches 1:1. Several population-based studies [24,26] have shown increasing prevalence of AAA with increasing age. Smoking is associated with 78% of AAAs and the prevalence of AAA is also signi-

Table 2

- **YEARLY GROWTH RATES:**

0.19 cm for	**AAA**	**2.8 to 3.9 cm**
0.27 cm for	**AAA**	**4.0 to 4.5 cm**
0.35 cm for	**AAA**	**4.6 to 8.5 cm**

- **RUPTURE RATE AT 5 YEARS:**

AAA > 6 cm 43% vs. 20% for smaller AAA

- **ESTIMATED RISK OF RUPTURE:**

0	**AAA**	**less than 4.0 cm**
0.5 to 5% for	**AAA**	**4.0 to 4.9 cm**
3 to 15% for	**AAA**	**5.0 to 5.9 cm**
10 to 20% for	**AAA**	**6.0 to 6.9 cm**
20 to 40% for	**AAA**	**7.0 to 7.9 cm**
30 to 50% for	**AAA**	**8.0 cm**

ficantly greater among smokers (5.1%) than in nonsmokers (1.5%), with some studies demonstrating a more than fivefold increased risk of AAA.[14] The natural course of AAA is to gradually expand, to form mural thrombus and eventually to rupture or give complications as thromboembolism or compression or erosion of adjacent structures. Most AAA are quiescent until rupture; rarely abdominal pain or back pain is present. New pain and tenderness may indicate recent expansion and therefore more intensive surveillance is required. Thromboembolism to lower extremities is the more frequent complication of the AAA with mural thrombus, but may occur in absence of mural thrombus too because of the presence of some ulcer's wall.[27] Triad of abdominal or back pain, hypotension, and pulsing abdominal mass may reveal a "rupturing" AAA. After rupture of an AAA, only half of patients arrive at the hospital alive: 50% reach the hospital alive, 7% died before surgery, 17% died during the operation, 37% died within 30 days of the operation for an overall mortality rate for open surgical repair of 45% .[2,28] The average expansion pattern is exponential rather than linear, estimated to about 10% annually.[6] However, individual variations are considerable. It is also notable that about 1/3 of the very small AAAs (<3.5 cm), do not expand at all.[16,30,9] In addition to the initial diameter, rapid expansion is associated with age, smoking and hypertension.[9,10,22] Unfortunately the pathophysiological mechanism responsible for aneurysm expansion is not known, and besides smoking cessation and treatment of hypertension, no specific therapy to prevent or reduce expansion exists today.

Natural history of AAA [29] (Table 2)

Less than 20% of all AAAs eventually rupture. The risk of rupture is in proportion to the aneurysm size. Small AAAs, less than 5.0 cm, have a very low rupture rate, whereas the rate of rupture is approximately 5 e 10% per year for AAAs between 5.0 to 6.0 cm and more than 10% for AAAs larger than 6.0 mm.[7,29] (Table 2) At a size of

Table 3

Overview of Randomized Controlled Trials of AAA Screening [4,15,18,23]

Study	Sex	Age (y)	No. of Pts. Randomized	Invited for Screening	Screened	AAA-related Mortality
[4]MASS	Men only	65–74	67,800	33,839	27,147 (80%)	0.58 (0.42–0.78)
[23]Scott et al	Men and Women	65–80	15,775 (6,433 men, 9,342 women)	7,887 (3,205 men, 4,682 women)	2,342 men (73%) 3,052 women (65%)	0.59 (0.27–1.29)
[15]Lindholt et al	Men only	65–73	12,658	6,333	4,852 (77%)	0.33 (0.16–0.71)
[18]Norman et al	Men only	65–83	38,704	19,352	12,203 (63%)	0.61 (0.33–1.11)* 0.19 (0.04–0.89) in men aged 65–74 y

* Age-standardized mortality rate ratio.

5 and 5.5 cm in diameter or >0.5 cm expansion within 6 months most surgeons therefore agree that OR or EVAR is indicated, in the absence of contraindications. [1,25]

MAIN CLINICAL TRIALS AND METHODS OF SCREENING

The benefit of AAA screening has been clearly demonstrated in several studies [4,15,18,23], with a remarkable reduction in incidence of ruptured AAA (from 45 to 49%) and in aneurysm related deaths decrease (from 21% to 68%.) (Table 3) Moreover in the largest one,[4] 70,495 men screened, aged 65 to 74 years, a 42% reduction in deaths at 4 years was found and the mortality curves for screened and unscreened patients in this trial continue to diverge after 4 years.

(Table 3)

This four main studies involving 127,891 men and 9342 women (only one study included women[23]) randomly assigned to aortic aneurysm screening using ultrasound or no screening were included in the Cochrane Database of Systematic Reviwes[12] and revealed some important issues: there is evidence of a significant reduction in mortality from AAA in men aged 65 to 79 years who undergo ultrasound screening; there is insufficient evidence to demonstrate benefit in women; the cost effectiveness may be acceptable, but needs further expert analysis. Men who had been screened underwent of course more surgery for abdominal aortic aneurysm: this is an important point of view concerning total screening economical evaluation to be considered. Duplex US is the most common diagnostic modality used for detection of AAA, with high sensitivity (95%) and specificity (100 %) to detect aneurysms greater than 3.0 cm[28]; it is safe, cheap and quite simple and gives a lot of information concerning morphological and hemodynamic evaluations useful for aneurysm characterization and surveillance programs. Although large aneurysms may be detected with routine physical examination alone, abdominal palpation cannot be considered useful for AAA screening because of its wide sensitivity rates too ranging from 22% to 96 % in different studies. Computed tomography (CT) and magnetic resonance (MR) imaging

allow better definition of AAA shape and of other vascular structures visible together with any other abdominal pathology but are not recommended for screening purposes, given the increased cost and risks of contrast agent and radiation exposure.[21]

CONCLUSIONS

AAA are more common in men than in women and mainly in those with cardiovascular risk factors, including family history, smoking, hypertension, and established vascular disease. A suitable age in the male population when screening should be considered seems to be somewhere around 65 years. However, even if the optimal age has not yet been established there is evidence of a significant reduction in mortality from AAA in men aged 65 to 79 years who undergo ultrasound screening. There is insufficient evidence to demonstrate benefit in women. White males seem to be more exposed than black males. Diabetes seem to be a protecting condition. Imaging can effectively, and at reasonable cost, identify asymptomatic individuals at risk for AAA related death and US are the best instrumental method to perform AAA screening. When detected AAA_s require periodic surveillance and careful follow-up: AAA_s < 4.0 cm annual US; AAA_s 4 - 5.4 cm biannual US. Intervention may be considered when AAA_s > 5.5 cm or > 0.5 mm expansion within 6 months occurs or also when increasing abdominal/back pain or tenderness or embolism modify the clinical course. Although current knowledge on the natural course of AAA is sufficient to fulfil the WHO criteria, several important aspects need further research, mainly the pathophysiological processes behind expansion and rupture. The cost effectiveness of a nationwide program to detect AAA_s may be acceptable, but needs further expert analysis.

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Venous thromboembolism in elderly hospitalized patients

Avram J.[1], Avram R.[2], Pasztori M.[1], Parv F.[2], Ciocarlie T.[2], Avram I.O.[1]

[1] *1st Surgery Clinic, County Hospital Timisoara, Romania*
[2] *Cardiology Clinic, County Hospital Timisoara, Romania*

Summary

Background. The elderly seem to be vulnerable to venous thromboembolism (VTE) and the associated pathologies may increase diagnostic difficulty. **Objectives.** The management and particularities of TEV in elderly hospitalized in different clinical departments. **Methods.** We studied the demographic and clinical data, risk factors, co morbidities, risk classification and the correlation to ultrasonography in patients over 65 years old hospitalized in two different clinical departments. **Results**. Elderly develop pulmonary embolism (PE) more frequently, especially men (72% men vs. 28% women). The most frequent risk factors in the Cardiology Department are cardiac failure (50%), deep venous thrombosis (DVT) (37%) and obesity (75%) and in the Surgical Department (75% DVT, 60% obesity, 55% venous insufficiency, 20% cancer, 15% surgery). Dyspnoea (84%) and anxiety (93%) are the most frequent symptoms. Ultrasonography can change the risk group, increasing the diagnostic probability in 9 cases (28%).Conclusions. Elderly are vulnerable to severe forms of venous thromboembolism (VTE), with scarce symptoms. Cardiac failure, DVT, surgery, and cancer are frequent, and that justifies appropriate prophylaxis. Ultrasonography is an important diagnostic tool, complementary to clinical signs.

Introduction

Although the incidence of deep venous DVT has increased, possible through more accurate diagnostic technology, PE still remains a frequent and a relatively constant pathology. (1)

The elderly constitute a risk group for VTE. For this reason, we aim to evaluate the clinical and the management particularities for this patient category that are hospitalized in 2 different clinical profile departments - medical and surgical.

Table 1. Gender and clinical form of PE

	High risk	Non-high risk
Man (15)	10 (66%)	5 (33%)
Women (17)	8 (47%)	9% (53)

Table 2. Risk factors and clinical forms of PE

	High risk 18	Non-high risk 14
	Cardiology	Cardiology
Heart failure	9 (50%)	7 (50%)
Deep venous thrombosis	7 (38%)	5 (35%)
History of pulmonary embolism	5 (27%)	3 (21%)
Obesity	11 (61%)	13 (92%)
Chronic venous insufficiency	7 (38%)	11 (78%)
Cancer	5 (27%)	2 (14%)
Surgery	1 (5%)	6 (42%)

Matherials and methods

We recorded demographical characteristics, clinical manifestations and management of the elderly over 65 years old hospitalized in the Cardiology Clinic and the 1st Surgery Clinic of the County Hospital Timisoara between 2007-2009.

The clinical diagnosis was based on the Wells Score which considers predisposing factors, clinical signs and symptoms, clinical judgment and the Geneva Score which is limited to predisposing factors, clinical signs and symptoms, both of which classify in low, moderate or high probability.

We used, according to the guidelines [2], compression Doppler ultrasonography, D-dimers and computed tomography angiography to diagnose the high risk and without the high risk PE.

Results

From a total of 50 patients hospitalized with or which have developed PE in the Cardiology Cardiology, 32 were over 65 years old.

Regarding gender, there were 17 (53%) women and 15 (47%) men (Table 1.).

The dominant risk factors in the medical cases were DVT and cardiac failure (Table 2.).

Men are more frequently obese, with cardiac failure, while women have DVT, are obese and have pelvic malignant pathology.

Regarding symptoms – 27 (84%) patients had dyspnoea, 30 (93%) anxiety, 11 (34%) had thoracic pain and 15 (47%) palpitations.

Table 3. Classification in Wells and Wicki clinical scores and correlation to the ultrasonographic exam.

	High probability 17	Moderate probability 11	Low probability 4
Ultrasonography – positive compression	6	2	2
Ultrasonography – intraluminal clots	9	2	0
Tumor compression thrombosis	0	0	3
Wide flow	3	4	0

In patients with high risk PE we found ultrasongraphic anomalies and positive compression ultrasonography. (Table 3)

2 oral anticoagulated patients developed high risk pulmonary embolism.

In the First Surgical Clinic Timisoara in the period 2005-2008 were hospitalized 9257 patients. A special lot is the great saphena vein thrombosis, registered at 42 patients in this period. 29,7% were over 65 years old, and predominantly women (27 women vs 15 men). Except this superficial vein thrombosis, we found 2% of DVT in the post-operative period, in patients without previous DVT and under anticoagulant prophylaxis.

Discussion

From the incidence point of view, it is certain that the elderly are more vulnerable clearly with a higher incidence and with a predisposition for the female gender, which is in agreement with the literature.[3] The clinical forms of PE are predominantly with high risk.

In the medical department, the dominant risk factors are cardiac failure (50%), DVT (37%) and obesity (75%).

It is noticeable that the relapse of PE was present in 40% of patients, possible suggesting an inefficient management and the necessity for anticoagulation. According to Arnoud [4] relapses are 8.7% after 6 months. Cancer is less frequent in the Medical Department (7 cases).

Ultrasonography increases the risk in the clinical classification in 5 cases considered with low probability and 4 with moderate probability, becoming a useful complementary diagnostic tool ([5] [6]).

Dyspnea and anxiety are the most frequent symptoms. Cancer is frequent in the surgical department and may suggest the need for anticoagulation. [7, 8]

The prevalence of DVT in elderly surgical patients is higher than in adults because the malignancy is "more often operated and the comorbidities, especially the cardiac, obesity, diabetes are associated with difficult postoperatory mobilization and risk of anticoagulation[9].

Sylvia Haas (2004) mentioned that 3-4% of patients dying in hospitals with PE

had no recent surgery. If the older are more exposed to DVT and PE, an operation increases the risk.

Because the risk of DVT and PE is high, in the elderly patients operated in the First Surgical Clinic Timisoara we used LMWH in all the cases without contraindication and without major risk factors for haemorrhage. In this situation we had no lethal DVT and PE in our patients with prophylactic treatment. We also used in all patients associated prophylactic measures like early mobilization, correct parenteral hydratation and compression stockings [10].

In conclusion, hospitalized elderly patients, regardless of department, have a high susceptibility for VTE. Female gender, cardiac failure, DVT, cancer are factors of high risk. Clinical particularities consisting of scarce symptoms, the presence of associated pathology, make diagnosis difficult. In the form with moderate clinical probability, the ultrasonography may increase both the negative and positive predictive value, may allow diagnostic reinstatement and the adoption of an appropriate treatment. The prophylaxis with anticoagulant, associated with other methods can be recommended in this group of patients.

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Carotid endarterectomy versus stenting in patients with contralateral carotid artery occlusion

Bracale UM[2], Porcellini M[1], Dinoto E[2], Amabile GP[1], Pecoraro F[2], del Guercio L[1], Bajardi G[2], Bracale G[1]

Vascular and Endovascular Surgery, Federico II University of Naples, Naples, Italy[1]
Vascular and Endovascular Surgery, University of Palermo, Palermo, Italy[2]

Summery

Objective. The aim of this prospective study was to compare outcomes after CEA and CAS in patients with contralateral carotid artery occlusion.

Materials and Methods. Between 2004 and 2009, 527 consecutive patients underwent CEA (n= 281) or CAS (n= 246) for severe stenosis of internal carotid artery (ICA).

Of them, 85 (16.1%) were identified with contralateral carotid artery occlusion. CEA was performed in 31(36.4%) patients with contralateral ICA occlusion, and 15 (48.4%) were symptomatic. Intraoperative shunts were placed in 12% versus 41.9% (P<0.05) patients with patent (n= 250) or occluded contralateral ICA (n= 31). 54 (63.5%) patients with contralateral ICA occlusion underwent CAS with distal protection, and 38 (70.4 %) were symptomatic.

Results. The ICA occlusion time during CEA was 27.9 ± 2 min, and 5 ± 1 s during

balloon inflations in CAS (P < 0.001). The perioperative rate of adverse neurologic events was not significantly higher in patients with contralateral ICA occlusion after both CEA (3.22% vs 1.20%) and CAS (1.85% vs 1.04%). Also the incidence of the 30-d total stroke/mortality rate was not significantly different (CEA: 6.45% vs 1.60%; CAS: 3.70% vs 1.56%).

Conclusions. CAS is a safe and efficacious alternative for the treatment of carotid artery stenosis in patients with contralateral occlusion. The avoidance of general anesthesia and other CEA-related factors, and a significantly shorter period of ICA occlusion during balloon inflation can be the reasons for a 1.7-fold decreased risk after CAS.

Table I. Patients characteristics

Characteristics	Contralateral occlusion *(85pts)*	Contralateral patency *(442pts)*	*P*
Male	69 (81.2%)	253 (57.2%)	0.02
Female	16 (18.8%)	187 (42.3%)	0.02
Smoking history	71 (83.5%)	285 (64.4%)	0.01
Hypertension	52 (61.1%)	179 (40.5%)	0.4
Diabetes	27 (31.8%)	85 (19.2%)	0.1
Coronary artery disease	12 (14.1%)	86 (19.4%)	0.1
Hyperlipidemia	19 (22.3%)	91 (20.6%)	0.5

Introduction

The benefits of carotid endarterectomy (CEA) for stroke prevention have been demonstrated from several randomized controlled trials (RCTs) in both symptomatic patients and asymptomatic patients with carotid stenosis[1-3]. Perioperative outcomes of CEA have been shown to be related to patient risk factors[4,5], so carotid artery stenting (CAS) has been proposed as an alternative to CEA in high-risk patients[6,7]. Despite of continuous technological progress and advance clinical expertise in endovascular procedures, no population based study[8] or RCTs[9-12] have found superiority of CAS to CEA.

Patients with contralateral carotid occlusion represent a higher risk subgroup, and the results of published series of CEA[13,14] or CAS[15-16] in these patients remain controversial.

At the present no studies nor RCTs have compared CEA versus CAS in the treatment of patients with contralateral internal carotid (ICA) occlusion. The aim of the present study was to compare 30-day outcomes after elective CEA and CAS in patients with and patients without contralateral ICA occlusion.

Patients and Methods

A retrospective analysis of a joint institution, prospectively mantained database including 527 patients submitted to CEA or CAS from January 2004 to present was conducted. This report discusses 30-day outcomes, but study patients continue to be monitored through 3 years of follow-up. Eighty-five patients with contralateral ICA occlusion (group 1) were compared with 442 patients with no contralateral occlusion (

Table II. Neurological status prior to CEA

Preoperative status	Contralateral occlusion	Contralateral patency	*P*
	(31 pts)	*(250 pts)*	
Asymptomatic	16 (51,6%)	151 (60,4%)	0.4
Symptomatic	15 (48.4%)	99 (39.6%)	0.4

group 2). The percentage of contralateral ICA occlusion was greater in men (81.2% vs 18.8%, $P = 0.002$). Risk factors were more prevalent in patients in group 1 compared with group 2: smoking history (83.5% vs 64.4%, $P=0.01$), hypertension (61.1% vs 40.5%, $P=0.4$), diabetes (31.8% vs 19.2%, $P=0.1$) (Table I).

The diagnosis of carotid stenosis with or without contralateral ICA occlusion was made on the basis of preoperative color-flow duplex scanning (DUS) and computed tomography angiography (CTA). Degree of stenosis was assessed by mean of the ECST method[3]. All patients presented symptomatic or asymptomatic high-grade internal carotid stenosis (≥ 70%) and received preoperative neurological evaluation. Patients with recurrent carotid artery stenosis were excluded from analysis. Patients were selected for CAS based on criteria that placed them an increased risk for standard CEA surgery. Transcranial Doppler (TCD) monitoring during CEA and CAS was used in all patients, except in 7.6% of cases because of missing a temporal bone window.

Cea

Two hundred eighty-one patients underwent conventional CEA for a symptomatic (n=114) or asymptomatic (n=167) ICA stenosis. For 31 patients (11%) there was a contralateral carotid occlusion. No significant difference between the patients with and without contralateral occlusion regarding preoperative neurological status was found (Table II). All patients with contralateral occlusion underwent CEA under general anesthesia. Patients without contralateral occlusion were operated under general anesthesia in 68.4% of cases, and under cervical block in 31.6 % of cases. A single dose of heparin (3500 IU) was administered intravenously before carotid clamping. There were 13 patients (41.9%) with contralateral occlusion who needed shunting versus only 12% of patients without contralateral occlusion ($P<0.05$).

Bovine pericardium patch (Vascu-Guard, Synovis, St Paul, Mn) angioplasty followed CEA in 72.9% of cases. All patients received clopidrogel (75 mg), aspirin (100 mg) or ticlopidine (500 mg) postoperatively indefinitely. Surveillance DUS was performed at yearly interval after the procedure.

Cas

Two hundred forty-six patients underwent CAS procedures. These patients were also more likely to have a history of severe comorbidities, ipsilateral neck irradiation or dissection for cancer treatment. 54 (22%) had contralateral carotid occlusion and

Table III. Neurological status prior to CAS

Preoperative status	Contralateral occlusion (54 pts)	Contralateral patency (192 pts)	*P*
Asymptomatic	16 (29.6%)	115 (59.9%)	0.01
Symptomatic	38 (70.4%)	77 (40.1%)	0.01

198 (78%) had contralateral carotid patency. Patients with contralateral carotid artery occlusion were significantly more symptomatic than patients without (70.4% vs 40.1%, *P*=0.01) (Table III). During the preoperative CTA evaluation, anatomic and lesion criteria, including bovine arch and excessive ICA tortuosity, were assessed to determine if patients were at high risk for CAS. Patients were excluded from CAS if they had inadequate femoral arterial access, unfavourable aortic arch anatomy, severely calcified arch or carotid lesions, presence of a fresh thrombus, or ICA stenosis > 99%. Any patient with a contrast dye allergy or severe renal insufficiency (creatinine > 2.5 mg/dL) was not offered CAS. All CAS procedures were performed by vascular surgeons in an operating suite with a mobile C-arm fluoroscopy unit (9800 OEC, General Electric).

All patients were taking aspirin 100 mg/day and clopidogrel 75 mg/day beginning at least 3 days before the procedure. Local anesthetic was used before obtaining percutaneous femoral artery access in all cases. An intravenous bolus of 5,000 U of heparin was given immediately before CAS procedure. Atropine 0.5-1 mg was administered before balloon angioplasty of the ICA. Angiography of the supra-aortic trunks and both extra- and intracranial carotid and vertebral arteries was performed in all patients. A 6F or 7F long sheath introducer (Cook Inc., Bloomington, Ind) was positioned in the common carotid artery at the site of the stenosis. Cerebral protection devices were used in all but three cases (98.7%). These devices included Spider (EV3 Inc,, Plymouth, MN) in 70% of cases and FilterWire (Boston Scientific, Natick, Ma) in 30% of cases. Self-expanding stents were used in all patients: Carotid Wallstent (Boston Scientific Corp) in 52% of cases, Protégé (EV3) in 31%, Precise (Cordis Corporation, Miami Lakes, Fla) in 27%, Vivexx (Bard Inc.,Tempe, Az) in 4.4% and Cristallo Ideale (Invatec, Bs, Italy) in 1.6% of cases. When indicated, predilation was achieved with a 2.5 or 3.5 mm low profile balloon, and final full dilatation was achieved with a 5- to 6-mm balloon (Sterling monorail balloon dilatation catheter, Boston Scientific Corp). Completion angiography was performed to evaluate the stented artery and the intracranial circulation. (Figs. 1-4). Postoperative antiplatelet medication consisted in clopidrogel (75 mg) plus aspirin (100 mg) for a month. Aspirin was continued for life. DUS was performed in the immediate postoperative period, at 1- and 3-month intervals for the first year and then yearly thereafter.

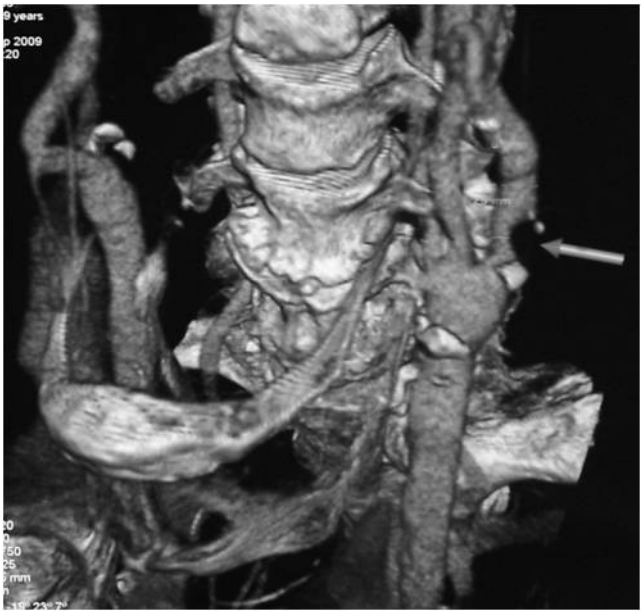

Fig.1. Pre-operative contrast-enhanced CT scan showing left internal carotid stenosis (arrow) and right internal carotid occlusion.

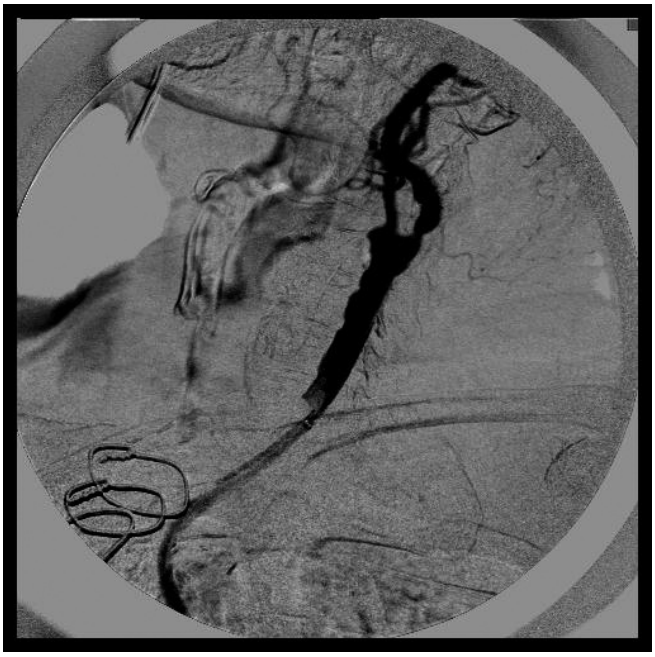

Fig.2. Intra-operative angiogram showing left internal carotid stenosis.

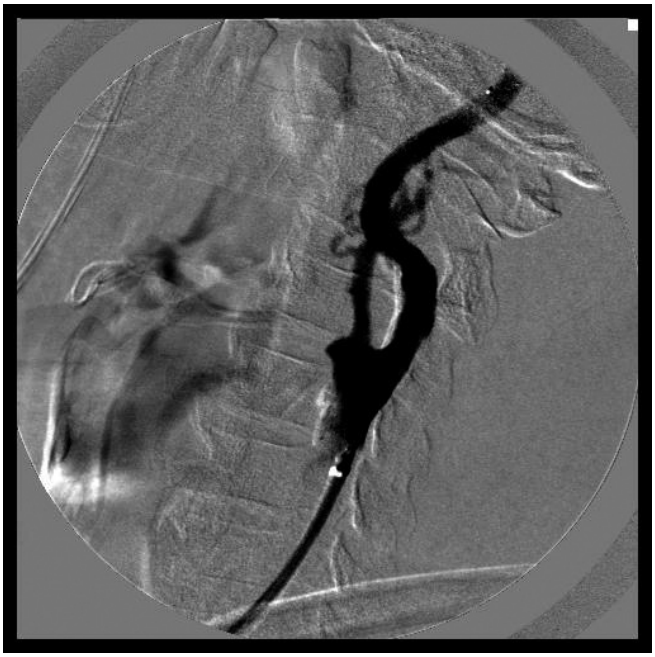

Fig.3. Post-stenting angiogram showing good result of the procedure.

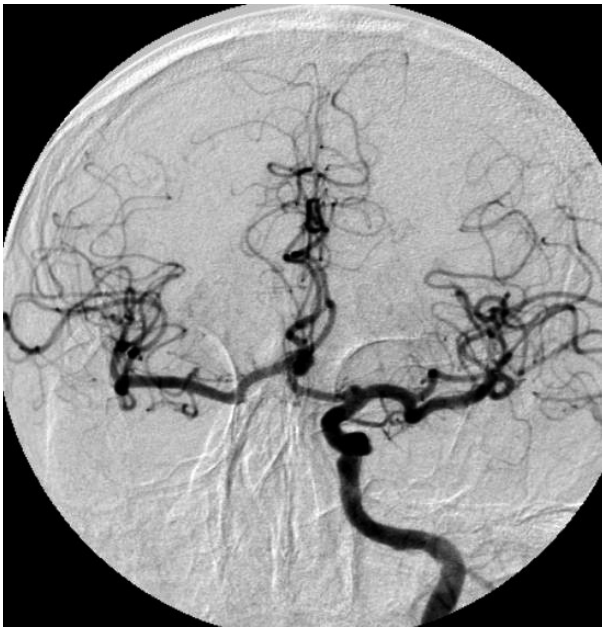

Fig.4. Post-stenting angiogram of the intracranial circulation through the sheath positioned in left common carotid artery.

Follow-Up

Patients were evaluated clinically and by duplex ultrasonography (DUS) in the immediate postoperative period, and at 1 month interval. If neurologic events were suspected, a neurologist was asked to evaluate the patient.

Statistical Analysis

Student *t* test was used to compare the patient demographics and the χ^2 test (or the Fisher exact test when appropriate) was used to compare the perioperative and 30-day neurologic adverse events and death rate in patients who underwent CEA or CAS. A *P* value of ≤ 0.05 was considered statistically significant.

Results

A significant difference in mean age was not observed between patients treated with CEA and CAS (71±7.2 vs 67± 12.3, *P*=NS). Preoperative percentage stenosis did not differ between patients treated with CEA and CAS (83.1%±12.2 vs 78.1%±16.2%, *P*=NS). The ICA occlusion time during CEA was 27.9± 2 min, and 5± 1 s during balloon inflations in CAS ($P < 0.001$).

Additionally, significant differences were not noted in early outcomes between patients who underwent CEA and CAS: 30-day ipsilateral neurologic adverse events (1.42 vs 1.21, P=NS), and mortality (0.71% vs 0.81%, *P*=NS).

Surgical site complications in patients treated with CEA included eight (2.84%) transient cranial nerve palsies, 5 (1.77%) neck hematoma, three (1.06%) of which required operative evacuation, and two wound infection (0.71%) that resolved with antibiotic therapy. Vascular access site complications for patients treated with CAS included five (2.03%) groin hematomas that resolved spontaneously and one (0.40%) common femoral artery pseudoaneurysm that was treated with ultrasound-guided manual compression. In one patient after CAS, reintervention with surgical stent removal was necessary due to acute stent occlusion and major ipsilateral stroke.

Perioperative neurologic adverse events rates were similar in patients with contralateral occlusion compared with patients without who underwent CEA (3.22% vs 1.20%, *P*=NS) and CAS (1.85% vs 1.04%, *P*=NS). Combined 30-d stroke/death rates were also comparable between patients with and without contralateral occlusion after CEA (6.45% vs 1.60%, *P*=NS) and CAS (3.70% vs 1.56%, *P*=NS).

Discussion

Although CEA is currently considered as the *gold standard* treatment for patients with severe carotid stenosis, contralateral carotid occlusion has often been considered to be a predictor of poor ouctcome.

In patients with carotid stenosis and contralateral occlusion treated with medical therapy alone the risk of neurologic adverse events resulted of 69.4% at 2 years in symptomatic patients enrolled in the NASCET[17] and of 3.5% at 5 years in asymptomatic patients in the ACAS[18].

On the contrary, AbuRahma et al[19] reported a 33% risk of major stroke and 60%

risk of TIA or stroke in asymptomatic patients with carotid stenosis >60% and contralateral occlusion who were treated conservatively.

As CEA reduced the risk of an ipsilateral stroke at 2 years to 22% (47.3% absolute risk reduction), it was recommended in this subgroup of patients[20].

Conversely, in a meta-analysis of 14 studies, Rothwell et al[21] reported a significant increase in the risk of perioperative stroke and death after CEA in patients with contralateral ICA occlusion.

More recents studies showed no differences in 30-d cumulative stroke and death rates in patients with contralateral carotid occlusion versus patients without contralateral carotid occlusion[13,14,22-24], while a meta-analysis, based on 19 studies, showed in 13,438 CEAs a significantly higher perioperative stroke rate of 3.7% compared to 2.4% (P= 0.002) in the presence of a contralateral carotid occlusion[25].

Although the incidence of contralateral carotid occlusion has been reported to be lower in women than in men (3.9% vs 6.9%, P<.001), women with contralateral carotid occlusion have a significant higher risk for 30-day stroke rate after CEA (6.6% vs 0.5%, P < 0.001)[26], also if asymptomatic[23].

This gender-specific risk increase may limit the indication to CEA in female patients with contralateral occlusion[27] or could represent an indication for CAS, but also conservative treatment.

Our patients with contralateral carotid occlusion were significantly more likely to be male and symptomatic, to be treated with CAS than CEA (63.5% vs 36.5%, *P*=0.05), to undergo operation with general anesthesia (68.6%), and to need a shunt (41.9% vs 12%, *P*<0.05) than patients without carotid occlusion.

Routine use of intraoperative shunt may appear a better choice in patients with contralateral carotid occlusion, but in one series, patients with occluded and non occluded contralateral occlusion treated with CEA under general anesthesia and without use of shunt presented similar early outcomes[28].

In another series, the rate of shunting in patients with or without contralateral carotid occlusion (10.% vs 9.1%) was not significantly different, but stroke rate was higher in carotid occlusion group (3.6% vs 0.5%)[29].

On the contrary, a significantly higher shunt insertion rate in patients with contralateral carotid occlusion was reported by Dorigo et al[26] , both in males (29% vs 6.2%, *P* <0.001) and in females (20% vs 8.5% , *P*=0.007).

Some investigators[15,16,30,31] have evaluated the role of CAS in patients with contralateral carotid occlusion. The designs of these studies varied widely, and included symptomatic and asymptomatic patients with contralateral carotid occlusion and stenosis, with or without the use of protection devices, mostly without a comparison group, and with an early incidence of death varying from 0% to 1.5%, major stroke from 0% to 2.1%, and minor stroke from 0% to 3.8% .

Sayeed et al[32] identified three main factors associated with 30-day stroke complicating CAS: age ≥80, ostial lesions, and lesion length >15 mm. The presence of contralateral occlusion was non significantly associated with periprocedural adverse events.

Among 191 patients with and 2946 patients without contralateral carotid occlusion who underwent CAS (German ALKK-CAS Registry), the incidence of in-hospital adverse events was low and was not significantly different between those with and without contralateral occlusion. A combined stroke and death rate (3.3%) occurred in symptomatic patients, with no events in asymptomatic patients[33].

Based on these results, CAS seems to be an attractive option for the treatment of this cohort of patients.

Accordingly, in a recent series of 678 patients undergoing CEA or CAS, patients with a contralateral occlusion were preferentially treated with CAS (12.1% vs 1.1%, $P<0.001$). Perioperative outcomes did not differ between patients treated with CAS and CEA, but no evaluation was made with respect to that risk factor[34].

The RCTs comparing CEA to CAS did not evaluate the status of contralateral carotid artery[9], or included only patients with contralateral stenosis[12] or a mixture of patients with contralateral carotid stenosis and occlusion[10,11].

For the first time, to our knowledge, our study presents early results of patients with severe carotid stenosis and contralateral occlusion treated in a prospective study comparing CEA to CAS. We found a low rate of periprocedural and 30-day adverse events in both the groups. We hypothesize that the routine monitoring of cerebral blood flow changes with transcranial Doppler during clamping to select patients for shunting and the use of pericardial patch angioplasty in 72.9% of cases possibly has reduced the incidence of post-CEA neurologic deficit rate. However, perioperative neurologic adverse event rate was 2.6-fold greater in the contralateral occlusion group undergoing CEA and 1.7-fold greater after CAS. Similarly, combined 30-d stroke/death rate was 3.9–fold greater in patients with contralateral occlusion treated with CEA and 2.3-fold greater in patients treated with CAS. None of the comparisons reached statistical significance because of the small number of events. The avoidance of general anesthesia and other CEA-related factors, and a significantly lower ICA occlusion time ($P < 0.001$) between CAS and CEA can be the reasons for a 1.7-fold decreased risk after CAS in our patients. Although the significance of the results is limited because of the low number of patients, this prospective study supports the use of CAS for patients with contralateral carotid occlusion.

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Hypertension in Patients with Peripheral Artery Disease: status 2010

Clement Denis L.

Ghent University, Ghent, Belgium
University of Ghent
Belgium

Introduction

Peripheral artery disease (PAD) is one of the most underdiagnosed and undertreated areas in the cardiovascular system. Although, intermittent claudication of the lower limbs is the most common symptomatic manifestation of PAD , it has become clear last years, that the majority of patients are asymtomatic. The issue has come into a new dimension since it has been documented that PAD not only can invalidate quality of life but that it also carries a very high risk for cardiovascular morbidity and mortality. These messages will be further elaborated on in the present short review. For a more detailed review, the reader is referred to previously published documents (1,2)

Prevalence and risk

Hypertension is a risk factor for vascular disorders, including PAD. Of hypertensives at presentation, about 2-5% have intermittent claudication, with increasing prevalence with age (3). Conversely, 35-55% of patients with PAD at presentation also show hypertension and this is particularly the case in elderly patients.(4). As mentioned above, at least half to two-thirds of individuals with PAD are asymptomatic or have symptoms; this may further increase the figures on prevalence that were published the last years.

The new approach to PAD has become to consider it much more as a risk factor of cardiovascular death, increasing it by three-fold, and increasing all-cause mortality by two-to-five fold. Data from the Framingham study (3) have shown convincing evidence that mortality linked to PAD is surprisingly high; approximately 40% of the patients with intermittent claudication (IC) died within the 10 years following diagnosis! Also, patients who suffer from hypertension and PAD have a further strongly increased risk of myocardial infarction and stroke. In the REACH registry (5,6), it was shown that the CV risk of PAD patients is at least as high as patients who have gone through a coronary event; therefore, PAD is seen more and more as a “coronary

like" syndrome in terms of risk as well as in terms of costs to the society. It should be remembered that this increased risk is present no matter whether the patient is symptomatic are not; in the landmark paper of Criqui et al. (7) it can clearly be seen how sharply survival is decreased in asymptomatic PAD patients and and that this is quite similar to symptomatic patients.

Ankle-Brachial artery pressure Index (ABI)

All vascular physicians presently know very well that measuring the pressure gradient (ABI) existing between the foot arteries and the brachial artery with the Doppler instrument is an extremely useful tool to detect PAD. It is simple, cheap, painless and totally non invasive. However, it is not only a diagnostic tool; it also helps in estimating cardiovascular risk in PAD patients. The risk for cardiovascular events increases stepwise with decreasing levels of ABI and this has been confirmed by several recent studies. A detailed review on this issue can be found elsewhere (2,8). In a recent meta analysis (9) it was demonstrated that the prognostic value of ABI remains strong even after adjusting for all regular risk factors and in particular the Framingham risk profile. It is a great pity that measurement of ABI is still not introduced enough in the daily use as it offers at a glance, information on diagnosis and risk evaluation.. The indications for measuring ABI were recently summarized in the TASCII document (1,2,8); (see table 1). Several indications are applicable to hypertensive patients. It is not surprising therefore, that in the last ESC-ESH guidelines (10), ABI was suggested as one the useful test to be performed in hypertensive patients.

Table 1. Indications to perform and ankle-brachial artery pressure index (ABI) 1,2,8)

ABI should be performed in all patients:

With exertional symptoms in the legs

Between the age of 50 and 69 years, who have a cardiovascular risk factor (particularly diabetes or smoking)

Aged 70 years or more, irrespective of risk factor status

Who have a Framingham (or SCORE) risk score between 10 and 20%

Management of Hypertension in PAD patients

Definition of blood pressure and Target blood pressure

It is very essential to have a correct measurement of blood pressure in PAD patients. Often, they also have vascular problems in the upper limbs making blood pressure figure erroneous. Repeated measurements at both arms should be done to certify the values to be used for further treatment and follow up.

Also ambulatory blood pressure monitoring is very useful in this context as it has been shown that ambulatory blood pressure monitoring correlates significantly better with long term prognosis than regular office readings **(**11**).** Home pressure recordings are an excellent alternative although lacking night pressure readings **(**12**).**

It still is unclear onto which level blood pressure should be decreased in hypertensive PAD patients. Guidelines (10) have proposed in general that all hypertensive patients (with or without PAD) should have their blood pressure control to 140/90 mm Hg. or lower; however, when total cardiovascular risk is very high like in diabetes

or renal dysfunction, a lower target value of 130/80 mm Hg. has been suggested. It is not sure yet to what extent this lower target is applicable to hypertension in PAD; moreover, there an uncertainty in general has arisen about the lower values as explained in detail in the recent "Reappraisal' paper (13).

Life Style adaptation

Both for hypertension as for PAD, the first step in the management should be to focus on life style. Adapting food intake with special attention to salt and calories, is often a neglected but essential first step in the management of elevated blood pressure. Walking distance will in many patients improve quite significantly by stop smoking and adapted exercise (training) programs, preferably in supervised conditions. Physicians should regularly check on the compliance to lifestyle adaptation as they often are accepted well at the start of the treatment but quickly forgotten later on.

*Antihypertensive drugs_*

Which antihypertensive drug is to be preferred in hypertensive PAD patients? There is no convincing proof that any of the antihypertensive drugs can control blood pressure better than the other drugs in this class. Conversely, there is no antihypertensive drug contra-indicated because of the presence of PAD. The most essential point is to control blood pressure "per se" rather than to focus on one or another antihypertensive class. Moreover, as the risk is so high in hypertension associated to PAD, combination treatment will be necessary. A detailed analysis on the data available so far is given in a recent review (1,2); most important practical information is summarised below.

ACE inhibitors.

There are arguments that ACE inhibitors may perform slightly better in this class of patients than the other antihypertensive drugs. There is an increase in muscle blood flow with ACE inhibitors (Sonecha et al. (14) that could correspond to a small but significant increase in walking distance (Novo et al. (15). On top of these, comes the positive effect of ACE inhibition on total cardiovascular risk as demonstrated in the Heart Outcomes Prevention Evaluation (HOPE) trial (16) in all large group of patients with increased total risk; among these, a large cohort of patients with PAD.

Calcium antagonists

Calcium antagonists could also be good candidates for decreasing blood pressure in PAD patients because of the local vasodilator effect; (17); there also is an anti-atherosclerotic action (ELSA trial, 18). Moreover, the data of the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT-BPLA) (19) demonstrated that combination treatment with "newer" antihypertensive drugs (amlodipine with or without perindopril) performed better than treatment with "older drugs" (beta blockers + diuretics); also there was a reduction of the relative risk of PAD by 35% and an indication that the onset of PAD could be delayed.

However, there are no convincing studies of a beneficial effect with calcium antagonists on local symptoms like claudication distance. Therefore, although very

convincing data in hypertension in general, one can hardly find solid clinical arguments that calcium antagonists would perform better in hypertensive PAD patients than the other classes of antihypertensive drugs.

Beta Blocking Agents

Contrary to the common belief of many physicians, mainly in the 90's, beta blocking agents are not contraindicated in patients with intermittent claudication. (8). Several studies and a meta-analysis have convincingly shown that beta blockers do not decrease walking distance in PAD patients (20,21). Moreover, newer beta blocking agents also possess vasodilator capacities. Finally, in case of associated angina pectoris or coronary artery disease, which often is the case in PAD patients, beta blocking agents can be indicated.

Centrally acting antihypertensive agents

Interesting features are coming up in the class of centrally acting antihypertensive agents with the newer drugs acting on the imidazoline receptors like rilmenidine and moxonidine; these drugs act more selectively on imidazoline I-1 receptors than on the central alpha-2 receptors what seems to avoid or at least diminish the many disturbing side effects as seen with the older drugs. On top of the antihypertensive effect, there seems to be with moxonidine treatment an increase in insulin sensitivity (22) which is an appealing property as diabetes or an abnormal glucose tolerance is seen in many PAD patients. But, as for calcium antagonists, there are no studies showing an increase in walking distance.

Diuretics

There are no large outcome studies specifically addressing treatment with (low-dose) diuretics in PAD with hypertension; but there is no doubt that diuretics are effective antihypertensive agents both for BP lowering as for reduction of cardiovascular morbidity and mortality in uncomplicated hypertension (1).

Angiotensin II receptor blockers

The angiotensin II receptor blockers have, of course, convincingly proven their capacity to decrease blood pressure in general; they are an alternative in patients intolerant to ACE inhibitors and their efficacy is not inferior to ACE inhibitors, as shown by a recent study (ONTARGET, 23). Unfortunately, there are no specific studies focused on the approach of hypertension in PAD patients and on evolution of walking distance in those patients.

Direct renin inhibitors

Many patients with peripheral artery disease exhibit renal artery involvement as well. Such is accompanied in many cases by strong renin stimulation. Therefore, direct renin inhibition may be an interesting approach to hypertension in PAD patients.

Aliskiren has been shown to cause effective 24-hour blood pressure decrease with a tolerability similar to that of placebo. Again, studies specifically focusing on PAD patients and their walking distance are lacking so far.

Control of total cardiovascular risk

From the information given above, it can be derived that besides blood pressure control, all efforts should be made to decrease total cardiovascular risk. This can be achieved as well known in the prevention and treatment of all cardiovascular diseases, by acting on each individual risk factor. On top of this, in hypertensive patients with peripheral artery disease, benefit can be derived from using antiplatelets drugs (8) like aspirin or Clopidogrel, on top of ACE inhibitors and statins. In Recommendation 6 of the TASC II guidelines on PAD (8), it is mentioned that "all symptomatic PAD patients, with or without a history of other cardiovascular disease should be prescribed an antiplatelet agent (level A)". The CAPRIE study (24) has shown that Clopidogrel significantly decreased the number of cardiovascular events as compared to placebo in symptomatic PAD patients. As far as statins are concerned, information coming from very large groups of patients at increased risk (HPS Study) has convincingly shown that statins are capable of improving long term prognosis even when lipid levels seem not to be especially elevated (25).

Obviously like for any pharmacological treatment, before administration, all contraindications should be taken into account as possible side effects.

Conclusions and Summary

In patients with peripheral artery disease (PAD) and hypertension, the total cardiovascular CV risk is substantially increased. Blood pressure should be decreased to at least 140/90 mm Hg. This can be achieved by life style adaptation and by all antihypertensive drugs; ACE inhibitors seem to have a better profile as they possess an effect combined on the local circulation, claudication distance and total cardiovascular risk. However, most of the benefit is derived from blood pressure decrease "per se" rather than what can be derived from any individual antihypertensive drug. The most important measure will be to decrease total CV risk. This can be done by adding antiplatelet drugs, ACE inhibitors and statins to the specific antihypertensive treatment. Thus, treatment of hypertension associated to PAD is by definition consisting of a multiple drug combination; all efforts should therefore be made to improve patient compliance to such treatment regime; cost calculations also should be made to unravel whether the costs for drug treatment do outweigh the costs necessary to treat the cardiovascular events.

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Are venous thrombotic and arterial atherosclerotic disease interrelated?

Jezovnik M. K., M.D., Poredoš P., M.D., PhD.

Department of Vascular Diseases, University Medical Centre Ljubljana, Zaloska 7, SI-1000 Ljubljana, Slovenia

Summary

In recent decades studies have indicated that there is an association between atherosclerotic and venous thrombembolic disease. This presumption is supported by similar or identical risk factors and common pathogenetic mechanisms. Some studies have also shown that patients with venous thrombosis (VT) are at increased risk of atherosclerotic thrombembolic events.

We investigated whether the prevalence of preclinical indicators of atherosclerosis (increased intima-media thickness (IMT) and the number of atherosclerotic plaques) is higher in patients with idiopathic VT than in healthy subjects. Further, we studied the flow mediated endothelium dependent (FMD) vasodilatory response of the brachial artery in both groups. Forty-nine patients with idiopathic VT of both sexes (mean age 52.3 ± 14.3) and 48 age-matched healthy controls were studied. Using ultrasound, bifurcations of the carotid and femoral arteries were investigated and IMT, as well as the presence of atherosclerotic plaques and their thickness, were determined. The flow mediated vasodilatory response was studied by determination of changes of the diameter of the brachial artery during reactive hyperaemia. Biochemical analyses of circulatory markers of inflammation and endothelial damage were performed.

The intima-media was on average and in all investigated beds significantly thicker in patients than in controls. The prevalence of atherosclerotic plaques was higher in patients. Furthermore, the number of plaques per individual, the number of arterial segments involved and total plaque thickness, were all significantly higher in patients than in controls. Compared to the control group FMD was significantly reduced in the group of patients. Patients with VT also had a significantly reduced endothelium independent dilation capability of the brachial artery. Functional and morphological deterioration of the arterial wall were interrelated. Furthermore, FMD was related to circulating indicators of endothelial dysfunction.

The findings of our study show a close interrelationship between the presence of the idiopathic VT and preclinical atherosclerotic deterioration of the peripheral arte-

ries. This means that patients with VT probably have simultaneous deterioration of the arterial and venous wall and that there is a close relationship in the development of both diseases.

Introduction

Traditionally, the pathophysiology of thrombosis has been separated into venous and arterial thrombosis. The formation of arterial and venous thrombi has been explained by two distinct mechanisms influenced by different risk factors. Over the last few decades, however, this notion has been partially challenged by the accumulation of evidence suggesting an association between arterial atherothrombotic disease and venous thrombosis (VT) (1). Studies have indicated that patients with atherosclerosis may be at increased risk of venous thromboembolism and that thrombogenic factors are involved in the development of atherosclerosis (2-4). Further, recent basic and pathomorphological studies suggest similar aetiopathogenetic mechanisms and risk factors for the two diseases (5-7).

Further, investigation of the pathogenesis of venous and arterial thrombosis showed similarities in the development of thrombi in the arterial and venous systems (8). Both venous and arterial thrombi occur on the damaged endothelial surface which may profoundly influence the thrombotic process. Therefore, it is expected that endothelial dysfunction or damage of endothelial cells may represent the common pathogenetic background of venous thromboembolism and arterial atherothrombosis. Similarly, deteriorated vessel wall function (venous or arterial) could promote thrombus formation.

A clear link has been established between inflammation and the development of atherothrombosis. It was shown that plasma markers of inflammation are predictive of future myocardial infarction and stroke (9). However, recent studies showed that inflammation may also play a role in venous thromboembolism (VTE) (10). Inflammation may be a common mechanism through which different risk factors trigger thrombus formation in veins and in the pathogenesis of VTE (11). The findings also showed that inflammation and haemostasis are coupled by common activation pathways and feedback regulation systems.

Similarities in aetiopathogenetic mechanisms are also indicated by a resemblance in the appearance of atherosclerotic disease and venous thromboembolism. Grady and colleagues found the risk of venous thromboembolism in women with myocardial infarction to be 2.1-fold higher over the entire course of the follow-up, but more than 5-fold higher during the first 90 days (12). Further, a case control study revealed an association between venous thromboembolic disorder and arterial disease of the lower limbs (13).

To test the hypothesis that a relationship exists between arterial and venous thrombosis in patients with idiopathic venous thrombosis, and that patients with preclinical atherosclerosis are at increased risk of idiopathic (spontaneous) venous thrombosis, we investigated the association between venous thrombosis and preclinical markers of atherosclerotic disease, namely intima-media thickness, and the presence of atherosclerotic plaques in the carotid and femoral arteries. Further, we studied the extent of preclinical deterioration of the arterial wall in different beds of the arterial system, considered the strongest predictors of VT among markers of atherosclerosis, as well

Table 1. Demographic and clinical characteristics of the study population

Variables	Patients (n= 49)	Controls (n= 48)	p
Age (in years)	52.3 ± 14.3	52.4 ± 12.3	0.91
Sex (males: n (%))	33 (70.2%)	19 (43.2%)	0.01
Height (in cm)	172.6 ± 9.1	171.1 ± 10.1	0.41
BMI (in kg/m^2)	27.4 ± 3.6	25.2 ± 5.0	0.004
Hypertension (yes: n (%))	14 (29.8%)	11 (24.4%)	0.65
Smoking, (yes: n (%))	11 (23.4%)	3 (6.8%)	0.04
Dyslipidaemia, (yes: n (%))	11 (23.4%)	9 (20.5%)	0.80
Diabetes mellitus, (yes: n (%))	6 (12.8%)	1 (2.3%)	0.11

All values are mean ± standard deviation for continuous variables and number of patients with the characteristics for categorical variables (n (%)).
Abbreviation: BMI – Body Mass Index.

as evaluating the endothelium dependent and independent vasodilatory capability of the brachial artery. In addition the serological markers of inflammation and endothelial dysfunction were followed.

Materials and methods

In all participants with idiopathic venous thrombosis and healthy subjects the prevalence of preclinical indicators of atherosclerosis was studied. Using ultrasound, intima media thickness and the presence of atherosclerotic plaques were analysed in the bifurcation of the carotid and femoral arteries. All participants also underwent investigation of the endothelium dependent and independent dilation capability of the brachial artery by a non-invasive assessment using B-mode ultrasonography. The diameter of the brachial artery was measured at rest, during reactive hyperaemia provoked by forearm occlusion and the endothelium independent dilatory response was studied by application of glyceryl trinitrate.

Using biochemical analysis systemic circulating markers of inflammation (high sensitive C reactive protein (hsCRP) and interleukins (IL)), adhesion molecules, tumour necrosis factor alpha (TNF-α) and indicators of endothelium hyperactivity/ damage were studied.

Results

Study Population

Forty nine consecutive patients with idiopathic venous thrombosis of the lower limbs were studied. During the study period, 48 eligible healthy subjects gave their informed consent and were enrolled. The controls were selected from volunteers and were age matched. The clinical and demographic characteristics of patients and controls are shown in Table 1.

The group of patients with idiopathic venous thrombosis was similar to the controls with regard to the prevalence of risk factors of atherosclerosis, with the exception of body mass index (BMI) which was higher in patients (p=0.004) and smoking (more frequent for patients). There were 8 (16.3 %) patients with ilio - femoral, 22 (44.9

Table 2. Concentrations of plasma makers of inflammation in patients with VT (patients) and healthy subjects (controls) (values are expressed as medians and interquartile range)

Parameter	Patients	Controls	P value
hs - CRP (mg/L)	2.58 (1.37-6.61)	1.67 (0.97 - 3.24)	**0.044**
IL 6 (pg/mL)	2.37 (1.59-4.10)	2.03 (1.45 – 2.59)	**0.025**
IL 8 (pg/mL)	3.53 (2.94-5.3)	2.25 (1.77 - 2.90)	**< 0.0001**
P-selectin (pg/L)	39.0 (34.0 - 40.6)	34.8 (32.5 - 38.6)	**0.009**
vWf (g/L)	150.0 (121.0-195.0)	91.5 (70.5 - 104.0)	**< 0.0001**
TNF-α (mg/L)	1.65 (1.13-3.2)	1.30 (0.85-1.93)	0.068
VCAM-1 (ng/L)	395 (343-482)	422 (353-474)	0.85

Abbreviations: vWF: von Willebrand factor, hs CRP: high sensitive C - reactive protein, IL - 6: Interleukin 6, IL - 8: Interleukin 8, TNF-α: tumour necrosis factor alpha; VCAM-1: vascular cell adhesion molecule-1

%), patients with femoro - popliteal, 12 (24.5%) with popliteal, and 7 (14.3%) with isolated calf venous thrombosis of the lower limbs.

The intima-media was on average and in all beds investigated significantly thicker in patients than in controls (0.94 mm ± 0.29 vs. 0.71 mm ±0.15, $p<0.001$). The prevalence of atherosclerotic plaques was higher in patients (33/47 vs. 15/44, $p<0.001$). Furthermore, the number of plaques per individual, the number of arterial segments involved, and total plaque thickness were significantly higher in patients than in controls.

In patients with idiopathic venous thrombosis significantly higher levels of circulating inflammatory markers were found (Table 2).

Compared to the control group FMD was significantly reduced in the group of patients with idiopathic VT - 4.9% (95% CI 1.1 - 8.7%) vs. 12.7% (95% CI 7.8 - 17.6%), $P<0.001$. Patients also had a significantly reduced NMD of the brachial artery - 12.5% (95% CI 9.9 - 15.6%) vs. 18.6% (95% CI 16.1 - 24.1%), $P<0.0001$. Levels of the von Willebrand factor (vWF) in plasma were significantly higher in patients with VT than in controls (150.0 g/L (95% CI 121.0 – 195.0) vs. 91.5 g/L (95% CI 70.5 – 104.0)), as well as P-selectin levels (39.0 pg/L (95% CI 34.0 – 40.6) vs. 34.8 pg/L (95% CI 32.4 – 38.6)). FMD was significantly correlated with vWF ($R=-0.437$, $P<0.0001$). Moreover FMD was correlated with P-selectin ($R=-0.237$, $P=0.019$). Similar relationships were found for NMD with vWF ($R=-0.252$, $P=0.013$), but not with P-selectin ($R=-0151$, $P=0.141$).

Discussion and Conclusions

The results of our study showed that different interrelationships exist between arterial atherosclerotic and venous thrombotic disease. Similarly as in arterial atherosclerotic disease, in our study patients with idiopathic venous thrombosis also had increased levels of inflammatory markers. As increased circulating markers were detected in the chronic phase of the disease, this could indicate that inflammation is involved in the aetiopathogenesis of idiopathic venous thrombosis. In patients

the presence of venous thrombosis was also associated with impaired endothelium dependent and independent dilation capability of the brachial artery. The functional incapability of the peripheral arteries was closely related to the increased systemic inflammatory response. Therefore, the inflammatory process could be involved in the aetiopathogenesis of venous thrombosis through deterioration of endothelial function. It may also suggest that endothelial dysfunction and functional deterioration of the vessel wall is directly involved in the development of VT and indicates a relationship between VT and atherothrombosis.

In our study also a close interrelationship between idiopathic venous thrombosis and preclinical atherosclerotic changes in different arterial territories was shown. This indicates that patients with primary arterial or venous disease have simultaneous deterioration of both the arterial and venous vessel wall and that common local or systemic factors influence the clinical appearance of venous, arterial or both diseases.

Our findings support evidence of the association between arterial atherosclerotic and venous thrombotic disease and that these two diseases may represent different aspects of the same disease entity.

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Thrombolytic treatment of peripheral arterial occlusion

Kozak M

University Medical Centre Ljubljana, Department for vascular diseases, Zaloška 7, 1000 Ljubljana, Slovenia

Summary

In the occluded peripheral artery due to thrombosis or embolism blood flow could be restored by thrombolytic treatment applied through intra-arterial catheter. There are several catheter-directed thrombolytic techniques, and several thrombolytic drugs, but there are no big differences between different therapeutic regimes. Thrombolysis (T) is effective in blood flow restoration in about 80% of treated patients with acute arterial occlusions, and in about 70% of patients with chronic occlusions. The rate of adverse events is low – the most feared – intracranial bleeding happens in about 1% of patients. T is not suitable for patients with serious neurosensorical or motorical deficit. T is as effective as surgery in limb salvation with the same mortality. The advantage of T is lower morbidity and better outcome when serious disability of patients due to concomitant diseases is present.

Introduction

Occlusion of a peripheral artery or a bypass graft could be of thrombotic or embolic origin. Clinical manifestations are usually correlated to the rapidity of the onset and to the extent of the occlusion. When patient disability is severe the need for blood flow restoration is obvious. T could be treatment of choice. First reports on T were published in the sixties. The technique developed later and nowadays catheter-directed intra-arterial T is a well established treatment option (1).

Thrombolysis – principle, techniques

In local intra-arterial T exogenous plasminogen activator, which activates endogenous plasmin is used as a thrombolytic and is administered into the occlusive thrombus via an intra-arterial catheter. There are several infusion methods. When stepwise infusion fixed dose of lytic agent is infused in a short period of time (minutes). As thrombus dissolves, the catheter is advanced and the process is repeated until all of the thrombus has dissolved. This technique requires the patient to be confined to the

angiography suite during the entire treatment and it is labor extensive, but relatively fast (2). In continuous infusion technique the lytic agent is infused with a constant flow over several hours, and the effect of the treatment is assessed by angiography every 6 to 24 hours. At that time catheter is advanced into the thrombus again, if at least partial success has been achieved. This is the most common way of treatment used in big clinical trials (3, 4). The treatment is relatively slow and lasts up to 48 hours. It is probably not suitable for the patient who need faster blood flow restoration. The technique is also cumbersome for the patients because of prolonged bed immobilization. In forced periodic (e.g. pulse-spray) infusion technique lytic agent is forcefully injected through specially designed multihole catheters into the thrombus to fragment it and to increase the surface area available for enzymatic action of the drug. When this technique is used, more distal embolisations are expected (5). The treatment is probably more expensive, too. However, when compared, different techniques showed no real advantages (6).

Thrombolytic agents

At least 30 different doses of different drugs have been used in clinical practice till now (6). Most commonly described treatment regimens are shown in Table 1. There are only few studies comparing different agents or treatment regimes. No absolute recommendations on drugs and doses to be preferred are possible on the basis of available data (6).

Indications for thrombolysis

T can be used as a part of a recanalisation treatment strategy in a patient with viable or threatened limb (Rutherford class I and II) due to acute arterial occlusion of thrombotic or embolic origin. It could be used before PTA (to shorten the occlusion), before or during surgery (to open the distal vessels). Patients with irreversible leg ischemia (Rutherford class III) are usually not candidates for T, although some encouraging results were reported. In those patients primary amputation is preferred (6).

In patients with chronic occlusions indications for T are less clear. T is discouraged according to TASC II consensus document (7) due to only one prospective study (STILE) where surgery was better than T in patients with occlusions older than 14 days (3). The differences were nevertheless minor and not significant. Some participating (surgical) centers were probably not experienced to T due to low volume of treated patients, as was reflected in nearly 25% of unsuccessful placement of the catheters (3). Maybe we can predict the outcome of T in patients with chronical occlusions with some noninvasive test like magnetic resonance imaging (9) %%In our opinion T should be considered in seriously disabled chronic patients, when surgical or endovascular therapy are not available or appropriate. However, because of its potential risks, T is not suitable for patients with no significant impairment of lifestyle.

Contraindications

Patients at risk of hemorrhagic complications established cerebrovascular event or neurosurgical procedure in last two months should not be treated with T (6). In

Table 1. Most commonly used doses of thrombolytic agents in local thrombolytic therapy for peripheral arterial occlusions.

Thrombolytic	Dose	Application
Streptokinase	5000 IU/h	continuous up to 48 h
	1000-3000 IU	stepwise every 2-15 min
Urokinase	4000 IU/min for 4 h, than 2000 IU/min	continuous up to 48 h
	3000 - 4000 IU	stepwise every 3-5 min
	25000 IU/ml, 0.2 l/bolus	pulse-spray, every 30s for 20 min every 60 s thereafter
t-PA	0.5-1.0 mg/h	continuous up to 48 h
	0.5 mg/ml; 0.2 ml/bolus	pulse-spray, every 30 s for 20 min every 60 s thereafter

IU - international unit

patients with already present neurosensory deficit low dose T is relatively contraindicated as this often takes to long to be effective (1). We believe that at least relative contraindication exists also in patients - usually older, who are not fully compliant with this long-lasting procedure.

Results

T is successful in limb salvage in about 80% of treated patients (1, 3, 6) with acute or subacute arterial occlusion. In recent metaanalysis authors concluded that there is no overall difference in limb salvage or death at one year between initial surgery and initial T (10). The main hazard of T is bleeding – about 1% of hemorrhagic stroke and about 5% of major and 14% of minor hemorrhages (1). The results of T of chronic occlusions are worse than for the acute ones, but reported recanalisation rate from observational studies is about 75% and longterm success is about 50-60% (6).

Adjunctive treatment

Angioplasty, aspiration thrombectomy and sometimes surgery are procedures, which can be used after T to improve the outcome of treatment.

After completed T anticoagulants (especially when occlusion was due to embolism) or antiplatelet agents should be used (1, 6).

Conclusions

Catheter-directed T could be used in patients with acute, subacute and chronic arterial occlusions due to thrombosis or embolisation. It is as effective as surgery, when indications and contraindications are strictly followed. Serious intracranial bleeding in 1 % of treated patients is the main risk. Close cooperation between interventional radiologists, internist and vascular surgeons is needed to obtain the best results.

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Metabolic Syndrome and Obesity in Peripheral Arterial Disease

Mattioli A.V. MD, PhD, FESC, FACC; Farinetti A. MD*

*Department of Biomedical Science, Istituto Nazionale di Ricerche Cardiovascolari, U.O. of Cardiology and angiology and *department of surgery and surgical specialties. University of Modena and Reggio Emilia (Modena, Italy)*

The metabolic syndrome (MetS) is a complex of interrelated risk factors for cardiovascular disease (CVD) and diabetes (1). These factors include dysglycemia, raised blood pressure, elevated triglyceride levels, low high-density lipoprotein cholesterol levels, and obesity particularly abdominal adiposity. Abdominal obesity plays an important role in the insulin resistance associated with MetS.

Defining thresholds for abdominal obesity is complicated, in part because of differences in the relation of abdominal obesity to other metabolic risk factors. In addition, predictive values for various levels of abdominal obesity for CVD and diabetes may differ, and it is clear that there are and will continue to be differences between sexes and ethnic groups. There is also the problem of generating cut points for continuous variables.

A recent statement paper (1) focused on definition of Met S. Although there is general agreement that obesity and its medical complications, including the metabolic syndrome, deserve greater attention, there has been considerable disagreement over the definition and diagnostic criteria of MetS. Several clinical definitions of the metabolic syndrome have been proposed. The first controversy is about whether the metabolic syndrome is a true syndrome or a mixture of unrelated phenotypes. A syndrome is a clustering of factors that occur together more often than by chance alone and for which the cause is often uncertain. The metabolic syndrome fulfils these criteria.

The metabolic syndrome arises largely out of abdominal obesity. With aging and increasing obesity, metabolic risk factors worsen. Many persons with the metabolic syndrome develop type 2 diabetes. As the syndrome advances, risk for CV disease and its complications increase. Once diabetes develops, diabetic complications other than CV disease often develop. The metabolic syndrome encompasses each stage in the development of risk factors and type 2 diabetes. (2)

Factors involved in the evolution from metabolic syndrome risk factors and diabetes is adiponectin. The adipose tissue is now considered an endocrine organ, actively regulating energy balance and many other physiological functions. Adiponectin is one of

a number of proteins secreted by adipose cells that might couple regulation of insulin sensitivity with energy metabolism and serve to link obesity with insulin resistance. Adiponectin stimulates production of NO, reduces expression of adhesion molecules in endothelial cells, and decreases cytokine production. Plasma levels of adiponectin are negatively correlated with adiposity, and decreased plasma adiponectin levels are observed in patients with obesity and type II diabetes. Several studies show that elevated biomarker levels are associated with increased cardiovascular event rates and mortality in people with PAD. Moreover, elevated levels of inflammatory biomarkers have been found to be associated with greater functional impairment and faster functional decline in people with PAD. Among people with and without PAD, those with high levels of 3 or more inflammatory biomarkers or D-dimer had a greater decline in 6-min walk performance and other functional performance measures at 3-year follow-up compared with those with uniformly low levels of these biomarkers at baseline. (3).

The question has been raised as to whether the risk for ASCVD associated with the metabolic syndrome is greater than the sum of its risk factors (2). The answer is the affirmative. First, epidemiological studies strongly suggest that multiple risk factors raise risk more than the sum of accompanying single risk factors; risk rises geometrically instead of linearly. This phenomenon is called *multiplicative risk*. Second, several metabolic risk factors are not included in standard risk algorithms; but all of them seemingly impart independent risk for cardiovascular events. These are a prothrombotic state, a proinflammatory state, and elevated triglyceride (2). This additional risk exceeds that which can be explained by standard risk factors.

The metabolic syndrome is not an absolute risk indicator, because it does not contain many of the factors that determine absolute risk, for example, age, sex, and low-density lipoprotein cholesterol levels. Nonetheless, patients with the metabolic syndrome are at twice the risk of developing CVD over the next 5 to 10 years as individuals without the syndrome. Furthermore, the metabolic syndrome confers a 5-fold increase in risk for type 2 diabetes mellitus.

Much less information is available on the relationship between MetS and PAD, a condition affecting 8 million men and women in the U.S. and nearly 30% of patients in primary care practice settings who are either age 70 years and older or age 50 to 69 years with risk factors for PAD (3,4).

Recent analyses suggested that patients with PAD had a prevalence of MetS greater than 50% (5,6,7,8). A prospective evaluations suggested that MetS is a predictor of end-stage PAD (lower-extremity amputation or revascularization) but that this risk increase is largely attributable to the impact of diabetes alone (9). Moreover, patients with PAD and Met S had a higher prevalence of myocardial infarction and a lower ankle/brachial index, which are negative prognostic indicators in PAD (9).

Many important findings come from a recent study assessing the relationships between MetS, inflammation, and future symptomatic PAD, defined as intermittent claudication or lower-extremity artery revascularization, in women included in the Women Health Study. (10)

In this prospective study on initially healthy, middle-aged women the MetS was associated with a moderate increase in risk of future symptomatic PAD. Women with MetS had a 62% increased risk of future PAD (hazard ratio 1.62, 95% confidence interval 1.10 to 2.38). After multivariable adjustment, MetS remained significantly associated with PAD (adjusted hazard ratio 1.48, 95% confidence interval 1.01 to

2.18), with a 21% risk increase per additional MetS-defining trait (adjusted hazard ratio 1.21, 95% CI 1.06 to 1.39).

In this population, the risk appeared to be mediated largely by the effects of inflammation and endothelial activation.

In the previous NHANES study, MetS was linked to a high likelihood of prevalent PAD (OR 4.8, 95% CI 2.2 to 34.0), and the presence of PAD increased with increasing levels of C-reactive protein. (11)

Data from the Women Health Study confirm that markers of inflammation and endothelial activation are strongly related with MetS. An increase in plasma levels of hsCRP and sICAM-1 per additional MetS-defining trait such that women with MetS had substantially higher plasma levels than those without MetS. Furthermore, the addition of either hsCRP or sICAM-1 individually to multivariable models substantially attenuated the effect of MetS on subsequent PAD, whereas inclusion of both markers virtually abolished this association. These findings suggested that in relatively healthy population of women, inflammation and endothelial activation may be potential mediators of the heightened PAD risk conferred by this risk factor cluster.

Men and women with PAD have higher levels of circulating inflammatory biomarkers compared with people without PAD (12,13).

Understanding the significance of elevated inflammatory biomarker levels in PAD can identify prognostic indicators of risk in PAD and improve understanding of adverse outcomes in people with PAD. At least 2 mechanisms by which inflammation may contribute to functional decline in people with PAD were hypothesized. The first hypothesize support the idea that inflammation may contribute to the progression of lower extremity atherosclerosis, thereby promoting ischemia of lower extremity skeletal muscle and impairing lower extremity functional performance.

A second mechanism could be related to the action of chronic inflammation on lower extremity skeletal muscle in PAD, independently on ischemia.

Elevated levels of inflammatory biomarkers are also associated with greater functional impairment and faster functional decline in people with PAD. Among patients with PAD, higher levels of IL-6, D-dimer, sVCAM-1, CRP, and homocysteine are associated with a shorter distances achieved in the 6-min walk test (14)

On the basis of these observations, 2 trials have been published evaluating the effects of statins on PAD. Statin medications reduce inflammation and CRP levels. Therefore, statins may mitigate against the association of elevated levels of inflammatory biomarkers with functional impairment and decline in PAD. The 2 clinical randomized controlled trials showed that statin therapy improves treadmill walking performance in people with PAD supporting the hypothesis of a key role of inflammation in peripheral arterial diseases (15,16).

Moreover a number of studies have suggested that different statins, similarly to ACE-inhibitor and antiplatelet drugs, reduce cardiovascular morbidity and mortality in PAD (17,18).

A recent study from Maksimovic found that the degree of peripheral arterial disease clinical manifestations was not related to metabolic syndrome score, whereas gangrene was significantly positively associated with increased fasting glucose, high-sensitivity C-reactive protein, and lower education (19). This cross-sectional study involved 388 consecutive patients with verified PAD. Metabolic syndrome was present in 60% of the patients with peripheral arterial disease.

Moreover increasing fasting glucose was present in 44% of patients with MetS and only in 9% of those without MetS. The mean glucose level increased with increasing MetS score, and gangrene was significantly related to high fasting glucose level.

Similarly Vleck and coworkers in study evaluating 461 patients with symptomatic PAOD found that the MetS was associated with an increased risk of vascular events (HR 1.51; 1.01-2.30, age- and gender-adjusted). Weight control reduced metabolic syndrome incidence and increased metabolic syndrome resolution during follow-up (20).

On contrary the Edinburgh Artery study found that the metabolic syndrome phenotype may have a differential impact on atherosclerosis in the cerebrovascular and the peripheral arterial circulations and that metabolic syndrome is a risk factor for cerebrovascular disease independently of conventional cardiovascular risk factors and the measured haemostatic and inflammatory factors whereas they found no evidence of a significant association between metabolic syndrome and PAD (21).

An interesting point of view was evaluated by Brevetti and coworkers, they compared 2 different criteria for MetS definition: the IDF and the APT III. 173 patients with intermittent claudication and ABI <0.90, in whom MetS was defined using the criteria of both Adults Treatment Panel III (rATP III) and International Diabetes Federation (IDF). IDF-MetS was independently associated with increased cardiovascular risk (HR 1.91, 95% CI 1.03-3.51, p=0.038).

They found that IDF-MEtS, but not rATP III-MetS, is an independent predictor of cardiovascular events. IDF-MEtS combined with an ABI<0.73 identifies a subgroup of claudicants at very high risk (8) IDF-MetS significantly improves risk stratification provided by ABI alone, which, to date, is considered the most powerful prognostic indicator in PAD. IDF-MetS, when added to ABI, could be used to identify PAD patients for further diagnostic evaluations, more frequent follow-up visits, and more aggressive and specific therapy.

Considering the high absolute risk of vascular morbidity and mortality in PAD patients, the high prevalence of the metabolic syndrome in this population, as well as the increased vascular risk associated with the metabolic syndrome, might be an important condition in patients with PAD.

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Endothelial Dysfunction: Prognostic and Clinical Application

Poredoš P.

Department of Vascular Disease, University Medical Centre Ljubljana, Slovenia

Abstract

Healthy endothelium plays a central role in cardiovascular control. Therefore, endothelial dysfunction (ED) may have a particularly significant role in the pathogenesis of atherosclerosis. ED is a consequence of the harmful effects of risk factors of atherosclerosis on the vessel wall and is closely related to the number of risk factors, to their intensity and their duration.

ED promotes progression of atherosclerosis and probably plays an important role in the development of thrombotic complications in the late stages of the disease. Endothelial dysfunction may trigger and potentiate mechanisms of myocardial ischemia. As ED is a key underlying factor in the atherosclerotic process, markers of endothelial abnormalities have been sought, particularly those involving disturbed endothelium-dependent vasomotion or related cellular products – circulating markers. Using these tests it is possible to follow the dose – response of harmful effects of risk factors, and the effects of preventive procedures on vessel wall function. Determination of ED also has important clinical implications. It was shown that ED is significantly and directly correlated with the occurrence of cardiac events and that cardiac events increased as ED worsens.

Introduction

The vascular endothelium is an important regulatory organ in maintaining of cardiovascular homeostasis. Normal endothelial function includes control over thrombosis and thrombolysis, platelets and leukocyte interaction with the vessel wall, and regulation of vascular tone and smooth muscle cell proliferation.

Because healthy endothelium plays a central role in cardiovascular control, it follows that endothelial damage may contribute to disease states characterized by vasoconstriction, inflammation, excessive thrombus formation, leukocyte adhesion to vessel walls, and atherosclerosis (1).

Endothelial dysfunction is characterized by an imbalance between relaxing and

contracting factors, between anticoagulant and procoagulant mediators, or between growth-inhibiting and promoting factors. Such dysfunction can result from mechanical or biochemical injury to the endothelium. Physical damage of the endothelium is mostly caused by hypertension; several other risk factors like hypercholesterolemia, diabetes, and smoking probably cause injury to the endothelium through biochemical mechanisms. Therefore, vessel wall damage may result in endothelial dysfunction and can be clinically manifested as thrombosis and atherosclerosis (2).

Involvement of endothelial dysfunction in atherogenesis

Endothelial dysfunction has been demonstrated in subjects with different risk factors of atherosclerosis, such as hypercholesterolemia, diabetes (3), hypertension (4), smoking (3), and in patients with atherosclerotic disease (coronary, peripheral arterial) (6). We demonstrated that endothelial dysfunction progresses with the duration of hypertension, diabetes, or smoking and that a close relationship exists between the intensity of an individual risk factor or the number of presented risk factors and endothelial function. Furthermore, treatment of risk factors results in improvement of endothelial dysfunction. It has been shown that treatment of hypercholesterolemia with statins improves endothelial function (7). Regression of endothelial dysfunction was observed during treatment of arterial hypertension with various drugs (8) and during physical training of patients with cardiac insufficiency and polymetabolic syndrome (9). We also observed improvement of endothelial dysfunction during growth hormone replacement in growth hormone-deficient patients (10). Therefore, a dose-response relation exists between risk factors of atherosclerosis and endothelial dysfunction.

The mechanisms whereby risk factors cause endothelial dysfunction are largely unknown; a common denominator for all these conditions is probably increased oxidative stress, which has therefore been suggested as an important cause of endothelial dysfunction. Most known risk factors cause excessive production of superoxide anions, with consequent degradation of NO before it can reach target tissues. Decreased biovailability of NO in the presence of risk factors is most probably also caused by decreased expression of nitrogen oxide synthase activity. Because NO acts as a vasodilator and inhibits platelet adherence and aggregation, smooth muscle proliferation, and endothelial cell-leukocyte interaction, decreased NO activity may contribute importantly to the initiation and progression of atherosclerotic lesions. The consequences of mechanical or chemical damage of the endothelium by different risk factors are also several cellular processes, such as inflammation and lipoprotein oxidation, that maintain endothelial dysfunction and promote atheroslerosis.

Endothelial dysfunction is most probably a consequence of the harmful effects of risk factors of atherosclerosis on the vessel wall. However, recent observations favor the hypothesis that endothelial dysfunction could also be a primary, directly inherited defect. Thus, some observations showed that dysfunctional endothelial NO synthase gene polymorphism is associated with some risk factors (e.g., hypertension) and is therefore not a consequence, but rather a primary abnormality. This assumption is also supported by the demonstration of endothelial dysfunction in normotensive siblings of parents with essential hypertension in one of our studies (4).

Endothelial dysfunction probably promotes atherogenesis through different mechanisms, such as increased adherence of monocytes and enhanced permeability of the

endothelial layer to monocytes/macrophages and lipo-proteins, which then accumulate in the vessel wall. It was indicated that endothelial dysfunction is also related to increased platelet adherence and smooth muscle cell migration and proliferation, both of which are involved in atherogenesis. Because one of the earliest events in atherogenesis is the adherence of circulating monocytes to intact endothelial cells, in some cases atherosclerosis behaves as a chronic inflammatory process. However, this presumption does not preclude involvement of endothelial dysfunction, which most probably initiates different pathologic processes, including inflammation.

Furthermore, it has been shown that endothelial dysfunction that precedes the early morphologic atherosclerotic changes in the arterial wall plays an important role in the development and growth of atherosclerotic lesions, and in the development of ischemia and thrombosis in the late stages of the disease (11).

Because the endothelial vasodilator function of the microvessels is an important determinant of tissue perfusion, microvascular endothelial dysfunction may play a particularly significant role in the pathogenesis of tissue ischemia.

Indicators of endothelial dysfunction

After the recognition that atherosclerosis develops over decades and therefore has a long preclinical (silent) phase before the onset of clinical symptoms, and that in this early phase changes of the arterial wall are mostly reversible and preventable, there has been considerable interest in developing diagnostic tools for detecting and monitoring early vascular changes in asymptomatic subjects. Because endothelial dysfunction is a key underlying factor in the atherosclerotic process, marker of endothelial abnormalities have been sought, particularly those involving disturbed endothelium-dependent vasomotion or related cellular products (12). Because endothelium has different functions, different tests would be needed to measure several different aspects of endothelial dysfunction. Areas of potential interest for detection of endothelial function include circulating markers of endothelium-dependent vasomotion. Endothelial injury may result in the release of various factors that can be detected in circulation and can be potentially used as markers of endothelial dysfunction.

Endothelial function may also be tested noninvasively in the peripheral conduit arteries using high-resolution external vascular ultrasonography. In this noninvasive method, arterial diameter is measured in response to an increase in shear stress, which causes endothelium-dependent dilatation in response to sublingual nitroglycerin. The brachial arterial dilator response to increased blood flow during reactive hyperemia has been shown to be mainly caused by endothelial release of NO, and to correlate significantly with coronary endothelial function and with the extent and severity of coronary atherosclerosis (13).

Noninvasive ultrasonography has been applied widely to asymptomatic subject groups. These studies have provided information on the effects of various risk factors on early atherogenesis. Because these techniques are accurate and relatively reproducible, serial studies may be performed including trials of reversibility of endothelial dysfunction in asymptomatic subjects at high risk of arterial atherosclerotic disease.

Endothelial dysfunction and cardiovascular disease

Because of endothelia dysfunction in atherosclerotic human coronary arteries endothelium-mediated relaxation is impaired and shifting the balance in favour of vasoconstriction in response to a variety of stimuli as exercise, mental stress, and cold exposure. Subsequent clinical studies demonstrated that abnormal constrictor responses to acetylcholine were not only observed in angiographically diseased epicardial arteries, but also in subjects with entirely smooth epicardial arteries and the presence of risk factors for coronary artery disese (14).

Atherosclerotically changed epicardial arteries are exhibiting abnormal constrictor responses also to a variety of common daily life stimuli like exercise, mental stress, or exposure to cold. Thus, endothelial vasodilator dysfunction appears to render the atherosclerotic vessels more sensitive to the constrictive effects of catehoamines and results in the pathogenesis of inappropriate vasoconstriction, which represents the fundamental functional disturbance in the vascular biology of atherosclerosis (15).

A defective endothelium-mediated vasodilator function may therefore potentiate known trigger mechanisms of myocardial ischemia and thereby induce a mismatch between myocardial oxygen supply and demand. Even through the changes in luminal diameter produced by inappropriate vasoconstriction of the epicardial vessel in response to sympathetic activation are usually less than 30%, such an increase in the arterial tone might be enough to convert a subcritical stenosis into a critical one with an ensuing decrease in blood flow and impaired FMD of the resistance vessels will further reduce coronary flow reserve.

Endothelial dysfunction might also be related to circadian variation in transient ischemic episodes, being most frequent in the morning hours. Indeed, endothelium-dependent vascular resistance has been shown to be elevated in the morning hours.

In unstable angina pectoris, which is mostly caused by plaque rupture, a number of vasoactive substances are released into the coronary circulation, most notably serotonin and thrombin. Both substances have been shown to exert potent vasoconstrictor effects in the presence of dysfunctional endothelium. Thus, endothelial dysfunction may cause a constrictor response and importantly magnify the ischemic response in the distal vascular bed and whatever the mechanism of acute myocardial infarction, inappropriate dilation of resistance vessels distal to the site of coronary thrombosis could influence the size of myocardial necrosis. This is one of reasons that acute events and consequences are not related only to stenosis severity. Further in the vascular bed of the non-infarct related arteries in the presence of endothelial dysfunction, there are also enhanced response of resistance vessels to systemic and local neurohormonal constrictor stimuli, which could increase the extent of the ischemia at the periphery of the infracted area and reduce collateral flow to the infarct-related arterial bed, thus contributing to the acute impairment of ventricular function and the extension of necrosis (16).

Endothelial dysfunction could also be responsible for the no-reflow phenomenon. Endothelial cells are at least as susceptible as myocytes to acute ischemic injury and reperfusion damage. This is evident from the profound loss of capacity of myocardium to be reperfused following severe ischemia which is known as the no-reflow phenomenon. However, this inability to perfuse dead tissue compromises also perfusion of the immediately adjacent viable tissue, which is a region of “low flow” in which, despite their dilation, many capillaries are incompetent.

There also exists interrelationship between endothelial dysfunction and microvascular angina syndrome (syndrome X). This clinical setting is characterized by angina-like pain and abnormal exercise ECG changes in the presence of a normal coronary angiogram. The role of endothelial dysfunction in this setting is controversial. It has been shown that patients with microvascular angina have endothelial dysfunction in the resistance vessels, possibly as a result of diminished formation of NO.

Therefore, endothelial dysfunction has different clinical implications. Its importance was also confirmed by study of Schächinger who found close relationship between endothelial dysfunction and the occurrence of coronary events (16).

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Management of superficial thrombophlebitis - use of low molecular weight heparin

Poredoš P., Jezovnik M. K.

Department of Vascular Diseases, University Medical Centre, Ljubljana, Slovenia

Abstract

Traditionally superficial thrombophlebitis (ST) has been considered a benign disease. In recent years as a result of systemic ultrasound investigations it was shown that ST is often related to deep venous thrombosis and to serious thromboembolic events (VTE). Therefore treatment of ST should be orientated not only to treatment of local symptoms, but also to prevention of VTE.

The treatment of ST should improve local symptoms and prevent the development of complications such as venous thromboembolism (VTE). The most effective approach to ST seem to be represented by low molecular weight heparin (LMWH) which has been shown to prevent extension and/or recurrence of ST and most probably diminishes VTE events. In addition, the administration of LMWH does not seem to carry a high risk of bleeding. Although the data are still too preliminary to make any recommendation, an intermediate dose of LMWH for at least 4 or 6 weeks might be appropriate. Non-steroidal anti-inflammatory drugs may be helpful in reducing symptoms of the disease, whereas there are not enough data to support surgery or topical treatment as options.

Introduction

The term superficial thrombophlebitis (ST), also known as superficial venous thrombosis, refers to a pathological state characterized by an inflammatory-thrombotic process in a superficial vein. Clinical findings include pain and a reddened, warm, tender cord extending along the vein. The surrounding area may show signs of erythema (reddening of the skin) and edema (1).

Superficial thrombophlebitis is a relatively common disease and although its incidence has never been properly determined, it is estimated to be higher than that of deep vein thrombosis (DVT), which is about 1 per 1000 cases (2). The incidence of ST could be around 400 cases in 100,000 person–years according to UK estimates (3). It is dependent on the age of the population, the entity of the problem (mostly

treated at the general practitioner level) and the level of patient's complaint. The prevalence of ST is largely associated with the presence of varicose veins, the incidence increasing with working age and in old age. Two kinds of ST can be defined: one is "causal", which is associated with an identifiable cause (immobilization, varicose vein, trauma, etc.). The second one, "noncausal" ST, occurs without identifiable causes and may be an early sign of an unknown (or known) neoplastic disorder or other systemic disease.

Risk factors

Predisposing risk factors for ST and venous thromboembolism (VTE) are similar and include varicose veins, immobilization, trauma, postoperative states, pregnancy, the puerperium, active malignancies, auto immune diseases, use of oral contraceptives or hormonal replacement therapy, advanced age, obesity, and a history of previous VTE (4). Varicose veins account for some 65% to 80% of cases and this event usually follows moderate or minor trauma. Intravenous catheters represent another frequent cause of ST. This mainly occurs when the infused solution and drugs are hyperosmolar. Solid and blood malignancies (pancreas, lung, gastrointestinal, ovary, prostate) are also associated with ST. In these cases the events often migrate and recur, lasting for some days, and are often present even in areas without varicose veins. Haematological disorders (thrombocythaemia, polycythaemia vera, leukaemia, lymphomas) are often associated with ST. Systemic and immunological disorders such as Buerger's disease, Bechet's disease, systemic lupus, and collagen diseases are associated with ST too, (5).

The role of primary hypercoagulable states (thrombophylia) is unclear and probably associated only with a limited number of cases of ST. Temporary thrombophylic states (such as those associated with neoplastic disorders) seem to be more important.

Clinical manifestation

According to different aetiopathogenetic mechanisms, clinical manifestations of the disease differ to some extent. Superficial vein thrombosis is characterized by clotting of superficial veins. Superficial thrombophlebitis is a nonthrombotic or minimally thrombotic pathological process of the superficial veins associated with vein wall inflammatory changes or vein infection (6).

Symptoms/signs often occur relatively suddenly. A painful cord-like mass along the course of a vein is observed. The overlying skin becomes erythematous and hot. The associated pain may be severe, and it may extend along the full length of the veins involved. Chills, high fever, and leucocytosis indicate septic ST. Serious complications such as deep venous thrombosis and pulmonary embolism may accompany ST.

Superficial thrombophlebitis – risk of VTE

Traditionally ST has been considered a relatively benign and self-limiting disease or sign a of chronic venous insufficiency, but several studies have described an association between ST and VTE. In recent years as a result of systematic ultrasound investigations of the venous system a large number of deep venous thromboses con-

comitant with ST have been revealed. Using ultrasound it is possible to determine the extent of the thrombus in superficial veins and its protrusion in deep veins. The thrombus may continue to the deep venous system through perforating veins and/or *via* sapheno-femoral or sapheno-popliteal junctions. Therefore, for proper evaluation of the disease and its progress ultrasound investigation is essential. Thus ST is not a banal condition and some physicians consider ST an integral part of venous thromboembolism, together with deep venous thrombosis (DVT) and pulmonary embolism (PE). Deep vein thrombosis rarely precedes ST; more often it follows VT because of reduced mobility caused by the pain.

Superficial thrombophlebitis located in the saphenous main trunk and with an above knee extension seems to have the strongest association with VTE (11, 12).

In a recent, prospective, observational study on 602 patients with acute isolated symptomatic ST of the legs at least 5 cm long on compression ultrasonography, after three month PE occurred in 0.3% of the patients, symptomatic DVT in 2.5%, symptomatic extension of ST in 1.8%, and recurrence of ST in 1.6% of the patients investigated (10). The variations in estimates of the incidence of VT in patients with ST reported in the literature are probably due to the retrospective character of most studies and the small number of participants included.

While the prevalence of VTE in patients with ST is relatively high, those managing ST should consider the prevention of this scarring complication beyond the resolution of local symptoms (13) and some authors recommend treating ST in the same way as DVT (14) Conservative management, mainly focusing on the painful symptoms of disease, might therefore be insufficient.

Treatment of superficial thrombophlebitis

There is no consensus on the optimal treatment of ST in clinical practice. Several therapies have been proposed in the literature, including surgical therapy (ligation or stripping of the affected veins), elastic stockings, non-steroidal anti-inflammatory drugs (NSAIDs) which aim to reduce pain and inflammation, and different anticoagulant agents for prevention of DVT.

Compression and mobilization

The main therapeutic procedure in all types of ST is compression and mobilization. Everyday experience shows that compression of the thrombosed vein relieves the symptoms and speeds up healing. There have been no randomized studies demonstrating the effectiveness of compression in preventing complications, although this approach is considered by all experts to be essential. Fix compression bandages used as the only treatment improved or eliminated the symptoms in 92.5% of patients (15).

In patients with limited ST in a varicose collateral vein local treatment and mobilization with elastic compression might be sufficient (16).

Anti-inflammatory drugs

Non-steroidal anti-inflammatory drugs (NSAID) may be given, either systematically

or locally. They reduce painful symptoms and perivenous inflammation. But there is no evidence that they reduce the incidence of thromboembolic events.

Different studies included a NSAIDs group (17) or compared NSAIDs with placebo (18), and two with LMWH (17, 18). It was reported that NSAIDs significantly reduced the risk of ST extension and/or recurrence by 67% compared with placebo. However, there were no differences in the incidence of VTE or in the resolution of local symptoms and signs, while no major bleeding episodes were recorded in any NSAIDs or placebo groups.

Surgery

In patients with chronic venous insufficiency and ST different surgical procedures are used, most frequently stripping or ligation. One study compared surgery (saphenofemoral disconnection) with LMWH (19). In the remaining two studies, surgery combined with elastic stockings was compared with elastic stockings alone. In the first trial, thrombectomy plus elastic stockings with or without venoruton lead to an improvement of the local clinical signs and a greater reduction in the number of veins with ST, compared with an elastic compression bandage alone (19). There were no cases of DVT in either study group. In the second trial, ligation of the vein plus elastic stockings was associated with a non-significant reduction in VTE events and ST recurrence and/or extension, relative to control treatment (20). Compared with elastic stockings alone, venous stripping plus elastic stockings decreased the risk of ST extension and/or the recurrence rate, and seemed to be associated with a lower non-significant incidence of VTE.

Prevention of thromboembolic complications

As ST is associated with the risk of DVT and thromboembolic complications, prevention of progression of the thrombotic process is of utmost importance. For this purpose different antithrombotic therapeutic modalities are used.

It is not clear whether different locations of ST should influence the choice of treatment, Location of the thrombus in the trunk of either of the saphena magna or saphena parva may have the highest risk of extension into the deep vein system and thus could require an aggressive form of treatment, whereas other locations may be associated with a lower risk of extension and thus may warrant a less aggressive approach.

Low molecular weight heparin (LMWH)

Different studies included LMWH as a treatment option for patients with ST (21). Both prophylactic and therapeutic LMWH given for 8 to 12 days were associated with a significantly lower incidence of ST extension and/or recurrence, compared with placebo.

Combined therapy of LMWH plus elastic compression stockings seemed to reduce the incidence of VTE and ST extension and/or recurrence, compared with elastic stockings alone, although the difference was not statistically significant (20).

LMWH versus surgical treatment (saphenofemoral disconnection) was evaluated

in one study (19). A comparable reduction of VTE events and a similar safety profile were observed in the two study groups. Surgery seemed to be associated with a lower risk of ST extension and/or recurrence, although the differences were not statistically significant.

A therapeutic dose of LMWH was also evaluated in comparison to NSAIDs (22). Fixed-dose LMWH and dose-adjusted LMWH seemed to produce a similar reduction in VTE and ST recurrence relative to NSAIDs. However, this study was not properly sized for a direct comparison between LMWH and NSAIDs.

One study compared two regimens of LMWH (23). In a head-to-head comparison a one month therapeutic-dose, or a prophylactic-dose of LMWH, administered for the same period, lead to a similar reduction in ST extension and/or recurrence and VTE events over a three month follow-up. In the prophylactic LMWH group most of VTE events (77%) occurred while patients were still on treatment, whereas only 33% of patients on a therapeutic-dose LMWH developed VTE during LMWH treatment. Therefore the advantage of therapeutic LMWH was lost after drug discontinuation.

A prophylactic-dose of intravenous unfractionated heparin (UFH) was used as a comparative treatment in two studies (20, 21). Relative to elastic stockings alone, prophylactic i.v. UFH plus elastic stockings was associated with an 86% reduction in ST extension and/or recurrence, and with a non statistically significant lower VTE rate (24). One study compared a high-versus a low-dose of UFH. A non-significant reduction in VTE and a lower rate of ST extension was found in the high dose group of UFH (21).

The optimal duration of treatment for ST as well as the best LMWH remain unclear. In the only available head-to-head comparison of two LMWH doses, a one month prophylactic dose of LMWH seemed as effective and safe as higher doses over a three months follow-up period (23). Most of the events in the prophylactic LMWH group occurred while patients were receiving the drug, whereas almost two thirds of the events in the therapeutic LMWH arm occurred on drug discontinuation. These data would suggest that a longer therapeutic-dose of LMWH would give more effective protection against VTE and/or ST recurrence.

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Cas present and future

de Donato Gianmarco, Setacci Francesco, Chisci Emiliano, Setacci Carlo

Department of Surgery
Vascular and Endovascular Surgery Unit
University of Siena – Italy

Abstract

Carotid balloon angioplasty was first performed in 1980, and a stent was first used in 1989 to treat an intimal flap after angioplasty. Since then, there has been increasing interest in carotid artery stenting (CAS) and the industry contributed technical improvements with lower profile systems, better stents, and a variety of embolic protection devices.

However in the last decade some alarming data have come from randomized prospective trials comparing carotid endarterectomy with stenting. High adverse event rates for CAS performed in symptomatic patients were later reported, and in United states the Centers for Medicare & Medicaid Services has still determined not to expand coverage of CAS, which is now reimbursed only for selected patients.

In the light of these data, future for CAS seems to be questionable.

A positive answer comes from many individual experience of high-experienced operators from high volume centers, although we still need more data from well conducted RCTs, where both rigorous standard of practice and technical skills are required, to really comprehend the future for CAS.

Manuscript

Carotid balloon angioplasty was first performed in 1980, and a stent was first used in 1989 to treat an intimal flap after angioplasty. Since then, there has been increasing interest in carotid artery stenting (CAS), as interventional specialists who had little previous interest in treating carotid bifurcation arteriosclerosis rushed to apply their endovascular skills and tools in this new area of opportunity. Industry contributed technical improvements with lower profile systems, better stents, and a variety of embolic protection devices. Presentations, articles, registries, and courses proliferated dramatically.

It certainly appeared that CAS was an emerging technology that would replace the previous gold standard -- carotid endarterectomy (CEA). The emergence of this new

technology was potentiated by low adverse event rates that were observed when CAS was performed extensively in registries. All sorts of specialists rushed to get on the band wagon and learn how to perform the new disruptive technology before it was too late. These specialists included not only the colleagues of the many interventional cardiologists and the few interventional radiologists that had promoted CAS from the beginning, but also vascular surgeons and interventional neurologists. CAS appeared truly to be a better technology that would blow away an old inferior one.

At the same time the majority of the scientific community developed a general feeling of CAS being at least equivalent to CEA in daily practice.

However, around 2006 some disturbing cracks began to appear in the facade of the new technology. Unacceptably high adverse event rates were observed when CAS was performed in octogenarians, particularly those who were symptomatic[1,2]. High adverse event rates for CAS performed in symptomatic patients were later reported in several randomized prospective trials (RCTs).

Since the appearance of these data, many of the original CAS enthusiasts have expressed a note of caution and the need for those performing CAS to select patients more carefully, avoiding those with imperfect anatomy or ugly, very high-grade, or calcified lesions.

A Cochrane review, published in 2009, analyzed the outcomes of 3178 mainly patients – mainly symptomatic – undergoing carotid endarterectomy and CAS in 10 randomized trials.[3] For the primary outcome comparison of any stroke or death within 30 days of treatment, CAS was inferior to surgery (OR 1.35); however, the difference was not statistically significant. In addition, no significant differences between CAS and CEA were found for 30-day stroke, myocardial infarction, or death (OR 1.12); 30-day disabling stroke or death (OR 1.19); 30-day death (OR 0.99); and 24-month death or stroke (OR 1.26). Conversely, the endovascular treatment was statistically superior to surgery for cranial nerve palsy (OR 0.15) and myocardial infarction (OR 0.34). The authors of the meta-analysis concluded that the results did not support a change in clinical practice away from recommending CEA as the treatment of choice for carotid artery stenosis but acknowledged that the data were difficult to interpret because the trials were heterogeneous. In addition, they pointed out that an overestimation of the risks of endovascular treatment may have occurred because five of the trials were prematurely stopped.

However the results do not support a change in clinical practice away from recommending carotid endarterectomy as the treatment of choice for suitable carotid artery stenosis but support continued recruitment in the large ongoing trials.

A later meta-analysis, including the ICCS data recently presented[4], showed that indeed patients allocated to CAS had a significant increased risk of 30-day death or stroke compared to those undergoing CEA (OR 1.60, 95% CI 1.26 – 2.02). [5]Beyond 30 days, long-term follow-up of the trials previously reported suggest that both revascularization techniques are equivalent in terms of stroke prevention.

In the light of these data, it is questionable if there is a future for CAS.

A negative answer, at least for CAS in symptomatic lesions, seems to come from Peter Rothwell. The Author has recently published in *Lancet Neurology* a moratorium on carotid artery stenting because this therapy may jeopardize the outcomes of patients with carotid artery stenosis[6].

And more bad news come from the United States where the Centers for Medicare

& Medicaid Services (CMS) has recently determined not to expand coverage of CAS for high-risk asymptomatic patients[7]. CMS proposes to revise the national coverage determination (NCD) language regarding embolic protection devices (EPDs) as follows based on the Food and Drug Administration (FDA) clearance of new EPDs: *Coverage is limited to procedures performed using FDA-approved carotid artery stents and FDA-approved or cleared EPDs. The use of an FDA-approved or cleared EPD is required. If deployment of EPD is not technically possible, then the procedure should be aborted given the risks of CAS without embolic protection.*

CMS proposes to retain its existing coverage for the following patients with a slight revision to the language regarding EPDs:

- Patients who are at high risk for carotid endarterectomy (CEA) and who also have symptomatic carotid artery stenosis ≥ 70%. Coverage is limited to procedures performed using FDA-approved CAS systems and FDA-approved or cleared EPDs;
- Patients who are at high risk for CEA and have symptomatic carotid artery stenosis between 50% and 70%, in accordance with the Category B IDE clinical trials regulation, as a routine cost under the clinical trials, or in accordance with the NCD on CAS postapproval studies;
- Patients who are at high risk for CEA and have asymptomatic carotid artery stenosis ≥ 80%, in accordance with the Category B IDE clinical trials regulation as a routine cost under the clinical trials policy, or in accordance with the NCD on CAS postapproval studies

CMS considered that because there are no new completed, published randomized trials, and there are two nonsupportive registry studies, there is insufficient evidence to conclude that PTA of the carotid artery concurrent with stenting for asymptomatic patients with carotid artery stenosis ≥ 80% improves health outcomes compared to carotid endarterectomy or optimal medical therapy outside the clinical trial or postapproval study setting.

In summary, while available evidence suggests the potential for CAS for asymptomatic patients with anatomic high risk factors with carotid artery stenosis ≥ 80% and symptomatic patients with carotid artery stenosis of 50% to 70% to improve health outcomes, CMS believes that currently published data are not sufficient to expand coverage beyond the currently covered patient populations.

CMS stated that the current evidence, which has been collected under the authority of coverage for postapproval studies, is insufficient to conclude that PTA of the carotid artery concurrent with stenting for asymptomatic patients with anatomic high risk factors with carotid artery stenosis ≥ 80% and symptomatic patients with carotid artery stenosis of 50% to 70% can be performed with procedural complication rates to meet AHA/ASA guidelines. Due to the lower quality and limited quantity of published, peer-reviewed evidence available addressing the patient populations under consideration, CMS has determined that an expansion of coverage is not reasonable and necessary and has decided to make no changes to the NCD.

For carotid interventions in patients ≥ 80 years of age, CMS stressed that the key question is *should* it be done, and not whether it can be done. To answer this for patients ≥ 80 years of age, a consideration of long-term health outcomes and life expectancy is needed in addition to the periprocedural health outcomes reported in various case series and registry studies.

For asymptomatic patients, CMS stated that CAS enters the realm of primary

Table 1. Endovascular expertise in published RCTs

Trial (no. pts.)	Year	Requirements in terms of endovascular expertise
Leicester (n=17)	1998	8 CAS procedures
CAVATAS (n=504)	2001	Training in neuroradiology and angioplasty (but not necessarily in the carotid artery) required. Tutor-assisted procedures allowed.
SAPPHIRE (n=334)	2004	Procedures submitted to an executive review committee; CAS periprocedural death or stroke rate had to be <6%. No tutor-assisted procedures allowed.
SPACE (n=1200)	2006	At 25 successful CAS or assistance of a tutor for interventionalists having performed at least 10 CAS *(subsequently anamendment of the protocol allowed for tutoring of interventionalists who had a total experience of at least 10 CAS procedures)*
EVA-3S (n=527)	2006	≥ 12 CAS cases or ≥ 5 CAS and ≥ 30 cases of endovascular treatment of supra-aortic trunks. Tutor-assisted CAS allowed for centers not fulfilling minimal requirements.
ICSS (n=1710)	2009*	A minimum of 50 total stenting procedures, of which at least 10 should be in the carotid artery. Tutor-assisted procedures allowed for interventionalists with insufficient experience.

Legends: RCTs: randomized controlled trials; CAS = carotid artery stenting; BMT = best medical therapy.

prevention of stroke and a more rigorous evaluation of health risks and benefits with definite evidence is desperately needed.

CMS maintains that until long-term results from randomized controlled trials comparing CAS to optimal medical therapy are available for this important subgroup, CAS and possibly any carotid intervention should rarely, if at all, be performed in patients ≥ 80 years of age especially for asymptomatic individuals.

All these bad news for CAS future are the consequences of analysis of poor data from RCTs. Although RCTs are considered the gold standard of clinical investigation, and shouldn't be criticized, most of these comparison of CAS vs. CEA are to be considered not only scientifically but also ethically questionable because the endovascular experience required for operators to be eligible for the studies was minimal (Table 1).

SPACE randomized[8] 1,200 standard surgical-risk symptomatic patients (randomization CEA:CAS=1:1). No difference in the primary endpoint of 30-day death and stroke was noted, but the trial was originally projected to require 1,900 patients and was halted after sponsorship was withdrawn when slightly higher event rates than originally assumed in both arms increased to > 2,500 to prove noninferiority. The results in patients treated with CAS were reasonable (6.84%) but the difference of 0.51% (90% CI–1.89 to 2.91) between the two arms did not allow to confirm the non-inferiority hypothesis of CAS versus CEA.

EVA-3S[9] *enrolled* 572 standard surgical-risk symptomatic patients (randomization CEA:CAS=1:1). After the first patients, the audit mandated EPDs due to poor outcomes without them. The trial was stopped for safety and futility reasons, considering that the original statistical assumptions were probably overly optimistic and in error, leading to an underestimation of required subjects.

The results of this trial is discouraging especially for the CAS arm: although the patients were symptomatic, the 30-day stroke and death rates up to nearly 10% are not similar to those of contemporary CEA and CAS publications and registries.

As difficult as it is to say, we must admit that both EVA 3S and SPACE didn't match an acceptable level of physician training and credentialing. The consequences of this technical bias on the reported CAS results are left to the scientific community's evaluation.

The ICSS trial is a randomized double-blind study comparing stenting with endarterectomy in patients with symptomatic carotid stenosis of greater than 50% within 6 months prior to randomization. At total of 1710 patients were included in the intention-to-treat analysis, 853 randomized to stenting and 857 to surgery. At moment we have only preliminary data, that were presented at the XVIII European Stroke Conference in May 2009[10]. Patients allocated to carotid artery stenting had more events (Stroke, MI, or death rate = 8.5%) than those allocated to carotid endarterectomy (Stroke, MI, or death rate = 5.1%) with a difference of 3.4% in the risk of the 2 procedures that was highly statistically significant in favor of endarterectomy.

So similar alarms for CAS future seems to come from ICCS trial, but we are still waiting for the final report to be published to better understand these bad outcome after CAS and to better comprehend the level of expertise of physician involved in this Trial.

At this moment the real applicability of CEA and CAS is very different. CEA has been widely performed during the last thirty years by experienced and fully trained vascular surgeons, while CAS is a recently emerged treatment, that cannot yet be generalized.

A correct learning curve for this procedure is mandatory and cannot be reached with few cases or with generic PTA or stenting procedures of supraortic vessel as suggested by these RCTs.

To this regard, a published Consensus Document[11] among all the specialists involved in the CAS scenario, suggested that the minimum recommended training to achieve competence is at least 150 procedures of supra-aortic vessel engagement (during diagnostic as well as interventional procedures), 100 of which as primary operator, or at least 75 carotid stenting procedures, 50 of which as primary operator within two-years (table 2)

In the mean time the potential technical gap related to CAS has to be overcome by reliable programs for physician training and credentialing. CAS is a procedure that cannot be easily standardized: in clinical practice we have learned that a patient with a specific carotid plaque and supra-aortic anatomy needs a tailored procedure and additional expertise.

We are now waiting for the result from CREST trial to be published. A manuscript that will provide outcome results to medical community will be probably available in February 2010.

The CREST trial (Carotid Revascularization: Endarterectomy versus Stent Trial), which completed randomization on July 18, 2008, is the largest RCT comparing the efficacy of CAS to CEA, with 2522 patients including both symptomatic and asymptomatic carotid lesions.

Conventional-risk patients with symptomatic carotid stenosis (> or =50% by angiography, > or =70% by ultrasound) or asymptomatic carotid stenosis (> or =60% by

Table 2. Reccomended Training and Expertise for Carotid Stenting (from the Consensus Document of the ICCS-SPREAD Joint Committee)

Recommendation for basic skill

Once the basic skill for catheter-based intervention has been achieved by the already-active interventionist, the minimum reccomended training to achieve competence is as follows:

1. At least **150** procedures of supra-aortic vessel engagement (during diagnostic as well as interventional procedures) within 2 years, of which at least **100** as the primary operator.
2. At least **75** carotid stenting procedures, of which at least **50** as the primary operator , within a 2-year fellowship.

Recommendation to maintain technical skill

The minimum requirement to maintain technical skill (competence) is the number of **50** carotid stenting procedures performed and documented by each primary operator per year

angiography, > or =70% by ultrasound) were randomized to both treatment arms in a 1:1 ratio. The primary aim is to contrast the efficacy of CAS versus CEA in preventing stroke, myocardial infarction, and all-cause mortality during a 30-day peri-procedural period, and ipsilateral stroke over the follow-up period (extending up to four years).

Regarding qualifications to take part in the Trial, each surgeon and interventionalist underwent a rigorous credentialing process that included performance-assessment of prior CEA and CAS procedures. redentialing of interventionalists also included a review of additional CAS procedures enrolled into a CREST lead-in phase prior to entering patients into the randomized trial

We hope to received a positive answer to the question regarding CAS future from the publication of CREST results. In the meantime some considerations can be drawn regarding a number of limitations of such a Trial with long-period of patient recruitment. For examples indication and exclusions criteria for CAS were based on early nineties' experience and a single first generation stent and embolic protection device was used. With these restrictions stenting results may better represent 2000 to 2008 outcomes than outcomes we really expect in 2010 from CAS.

We are far away from the resolution of the dilemma and up to now, the analysis of more than 4000 patients treated within the published trials have not shown a clear evidence of CAS inferiority to CEA.

This number will increase in the future years with the ongoing trials ACST 2, TACIT,ACT 1 and SPACE2 and hopefully when the results of these trials will be diffused we will reach a better knowledge of the value and efficacy of CAS (table 3).

So we still need to wait for the results to be finalized, and we hope these trials are being conducted by experienced operators who can really offer a fair comparison between CAS and CEA in terms of procedural complications.

Conclusion

Many elements are necessary to safely perform CAS. Although many of these

Table 3. The ongoing trials comparing carotid endarterectomy with carotid artery stenting

Trials	Principal Investigator	Population	Estimated Enrollment	Arms	Study Start Date	Estimated Primary Completion Date
ACST-2 *Carotid Endarterectomy Versus Carotid Artery Stenting in Asymptomatic Patients*	Alison Halliday St George's, University of London	Asymptomatic	5000	1. CAS + BMT 2. CEA + BMT	January 2008	January 2018
ACT 1 *Carotid Stenting vs. Surgery of Severe Carotid Artery Disease and Stroke Prevention in Asymptomatic Patients*	Jon Matsumura, Northwestern Memorial Hospital, and Kenneth Rosenfield, Massachusetts General Hospital	Asymptomatic	1658	1. CAS + BMT 2. CEA + BMT	April 2005	May 2018
SPACE-2 Stent-protected angioplasty in asymptomatic carotid artery stenosis	W. Hacke, University of Heidelberg, Germany	Asymptomatic	3640	1. BMT alone 2. CAS + BMT 3. CEA + BMT	March 2008	July 2015
TACIT *Transatlantic Asymptomatic Carotid Intervention Trial*	Barry Katzen for United States, and Matthew Thompson for Europe	Asymptomatic	3700	1. BMT alone 2. CAS + BMT 3. CEA + BMT	2007	Not specified

Legends: CEA = carotid endarterectomy; CAS = carotid artery stenting; BMT = best medical therapy.

elements may seem obvious or intuitive, like the experience of physician who perform the procedure, their absence has not prevented flawed studies and conclusions from being published in high-impact journals and absorbed by a readership otherwise unfamiliar with these important factors' influence on the results. These studies and their noncritical consumption have had a major impact on the practice of CAS, and have ultimately led to limitation of access to this alternative therapy for patients.

In conclusion more data from well conducted randomized trial comparing CEA and CAS is needed, where both rigorous standard of practice and technical skills will be required and where the use of an embolic protection device will be mandatory.

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Evar in complex cases

Chisci Emiliano, Galzerano Giuseppe, Setacci Francesco, de Donato Gianmarco, Sirignano Pasqualino and Setacci Carlo

Vascular and Endovascular Surgery Unit, University of Siena, Italy,
Corresponding author:
Carlo Setacci
Department of Surgery
Unit of Vascular and Endovascular Surgery
University of Siena
Viale Bracci, 53100 Siena – Italy
Tel. +39 0577 585123
Fax +39 0577 233426
E-mail: setacci@unisi.it

Abstract

Nearly 40% of patients with an Abdominal aortic aneurysm (AAA) are denied endovascular AAA repair (EVAR) because of a complex anatomy (CA) due to a challenging access (calcified, narrowed, tortuous iliac arteries), or because of a short, angulated or otherwise challenging proximal neck. The aim of this study was to evaluate the outcome of EVAR in patients with CA (group A) versus patients with currently accepted morphological criteria (group B). Between September 2008 and December 2009, 103 consecutive patients (56 men; mean age 73 years, range 58-92) underwent EVAR for AAA. 41 out of 103 patients had at least one CA feature (group A). Clinical examination and CT scan were performed at 1 month and yearly thereafter. There was no statistically significant difference between groups A and B, regarding primary technical success rate, 30-day mortality, or late AAA-related mortality. Clinical success was 94.9% and 91.8%, for groups A and B respectively at 1 year follow-up. The early results of EVAR in CA with the use of a new designed endograft seem to be very encouraging in high-volume interventions centers. More patients and long-term data are needed to confirm these findings.

Introduction

Endovascular repair of abdominal aortic aneurysm (EVAR) has become a milestone in the treatment of patients with abdominal aortic aneurysm (AAA)since Parodi performed first endovascular repair of Abdominal Aortic [1]. The number of endovascular

procedures is constantly increasing both in the US and in Europe especially in patients deemed inoperable because of the presence of significant comorbidities. Randomized trials have shown better perioperative survival for endovascular repair over open repair, with fewer complications and a shorter recovery period[2,3,4]. In addition, endovascular techniques make it possible to treat patients whose comorbidities make conventional open repair difficult or hazardous[3]. Patient's selection is an important element of successful EVAR, requiring rigorous anatomical assessment. Stable proximal and distal fixations is a precondition to guarantee good long-term results after EVAR. Moreover, while long-term durability remains uncertain, patients and their physicians are willing to accept a degree of uncertainty in exchange for dramatic reduction in duration of hospital stay, need for blood transfusion and postoperative recovery time. In addition the incidence of secondary interventions after endovascular aneurysm repair had decreased significantly in recent years. Nearly 40% of patients with AAA are denied endovascular EVAR because of a complex anatomy due to challenging access (calcified, narrowed, tortuous iliac arteries), or because of a short, angulated or otherwise challenging proximal neck. Particularly severe infrarenal aortic neck angulation is strongly associated with subsequent proximal type I endoleak and represents a clear risk factor for endograft migration[5,6]. In complex cases, proximal and distal fixation still remains a challenge. New devices seem enlarging anatomical suitability for EVAR guarantying stable proximal and distal fixation in case of a complex anatomy, particularly in shorter and more angulated neck than older device. Aim of this study was to compare the outcome of EVAR with the use of a new stent graft device, in patients with complex anatomy (group A) versus patients with currently accepted morphological criteria (group B) considered unfit for open repair.

Methods

Between September 2008 and December 2009, 103 (56 men; mean age 73 years, range 58-92) consecutive patients operated for asymptomatic AAA were included in this study. All patients included had an AAA > 50 mm or an AAA of 40-50 mm with a growth rate > 5 mm within the last 6 months. Patients population was classified in two groups: group A (41 patients; 40%) in case of complex anatomy and group B in case currently accepted morphological criteria for EVAR was present (62 patients; 60%). Patients were indentified in the database, based on morphology of the proximal aortic neck (the portion between the most caudal renal artery and the beginning of the aneurysm; minor accessory renal arteries were disregarded in this context) and of the iliac axis. AAA morphology was assessed using preoperative contrast-enhanced computed tomography (CT). The AAA was classified as ''complex'' in the presence of one or more of the following criteria: (1) wide neck: widest diameter >28 mm, (2) angulated neck: >60 degree angle between the juxtarenal aorta and the long axis of the aneurysm sac, (3) short neck: neck length <10 mm, (4) significant thrombus: > 50% of the proximal neck circumference covered, (5) reverse tapered neck: neck dilated >2 mm within 10 mm of the most caudal renal artery, (6) neck bulge: focal neck enlargement >3 mm within 15 mm from the most caudal renal artery, (7) narrowed iliac vessels : diameter ≤7 mm, (9) angulated iliac vessels: >60 degree angle between the main iliac axis aorta and the long axis of the aneurysm sac or (10) circumferential calcification of the iliac axis. All data were analyzed retrospectively on an intention-to

treat basis. Technical success was defined as the successful passage of the delivery system to the landing zone, accurate placement of the prosthesis, and complete withdrawal of the delivery system after the deployment without significant limb stenosis and with freedom from conversion and absence of type I or III endoleak , as evidenced at angiography performed at the end of the procedure. Clinical success was defined as freedom from aneurysm rupture, expansion (>5 mm), conversion to open repair, type I or III endoleak, graft infection or thrombosis, and aneurysm-related death. All the perioperative, early (30 days), and midterm (6 months and 1 year) results were reported according to the standards published by the Ad Hoc Conjoint Committee of the Joint Council of the Society for Vascular Surgery and International Society for Cardiovascular Surgery and Society of Interventional Radiology[7]. All patients gave their written consent to the procedure. All interventions were performed in the operative room, equipped for conversion, with a mobile C-arm (OEC 9800GE Medical Systems, Waukesha, WI). Surgical cut down was made at the groin with exposure of common femoral artery bilaterally. The image intensifier was positioned on the basis of study of 3D reconstruction of preoperative CT scan to obtain the optimal degree to visualize the aortic neck and assess a correct deployment of the prosthesis. After the deployment of the stent graft, balloon dilatation of the neck, the gate and iliac legs was performed in all cases. The follow-up consisted of angio-CT and ultrasound examination at 30-day, then patients underwent ultrasound examination at 3, 6 months and 1 year while angio-CT was performed only in case of ultrasound evidence of endoleak/s or in case of enlargement of the aneurismal sac. Patient demographic data, risk factors, preoperative diagnostic assessment features, intraoperative details, and perioperative results were analyzed. Estimated 1-year results in terms of technical and clinical success were assessed with Kaplan-Meier curves. Statistical analysis was performed with software (SPSS 15.0 for Windows; SPSS, Chicago, Illinois).

Results

All stent grafts used were aorto-bi-iliac. 39 Endurant (Medtronic Cardiovascular, Santa Rosa, California) and 2 Anaconda stent grafts (Vascutek, Terumo, Inchinnan, Scotland) were delivered in group A. In group B the devices used were Endurant (n=12;Medtronic Cardiovascular, Santa Rosa, California), Talent Unidoc (n=43; Medtronic Cardiovascular, Santa Rosa, California) E-Vita (n=3; Jotec, Hechingen, Germany), Anaconda (n=3; Vascutek, Terumo, Inchinnan, Scotland) and Excluder (n=3; Gore, Flagstaff, AZ, USA). The group A had mean aneurysm diameter of 59.2mm (range 55-94mm), a mean proximal neck length of 6.9 mm (range 5-16mm), a mean neck diameter of 29.3 mm (range 27-32.5 mm), a mean neck angulation of 64 degree (45-90) and a mean iliac diameter of 6.3 mm (range 4.9-9mm). Severe tortuosity of iliac vessels was detected in 25% (n=24) patients and circumferential calcified iliac axis was present in 32% (n=31) patients. Technical success was achieved in all cases (103/103 cases). All procedures started with local anesthesia and only in 3 cases a conversion to general anesthesia was needed (2 (4.8%) in group A and 1 (1,6%) in group B) due the a prolonged procedure and patients' intolerance. A proximal extension was needed in 7 cases (all in case of short and angulated neck) while coverage of an internal iliac artery was necessary in two cases in group A (4,8%) and in five cases in group B (8.1%) (p=NS). At completion angiography neither renal artery occlusion,

ostial stenosis, or type I or III endoleaks were detected. A late type II endoleak was detected in five patients in group A (12.2%) and in nine patients in group B (14.5%) (p-NS). No intra and periprocedural deaths occurred in both groups. The differences between the two groups were not statistically significant in term of hospital stay, myocardial or renal complications (p=NS). No conversion was done in both groups at 30 days. During the follow-up, no new late type I or III endoleak was recorded, while type II endoleaks persisted in three cases in group A (7.3%) and in six cases in group B (9.6%) (p=NS). In these last 9 cases the lack of shrinkage of the sac with a continuous growth of it required a reintervention. In all cases the reintervention was performed endovascularly. The clinical success estimated by Kaplan Meier curves at one year follow-up was 94.9 % and 94.8% in group A and B respectively (p=NS).

Conclusion

In the second half of past century, surgical repair of AAA became the gold standard treatment providing good results in term of mortality and morbidity[2,8]. However, in the last years, despite improvement in surgical and anaesthesiological technique, we had not attended a concurrently improvement in survival and freedom from complications. Currently high volume centers with appropriate learning curve in endovascular procedures, consider the endovascular approach as first choice in elective treatment of AAA in patients with suitable anatomy, particularly in high risk patients for open repair. At the same time a high risk patient for open repair has often an not suitable anatomy for EVAR (complex anatomy). Only 60% of AAAs are suitable for standard EVAR according to a recent report [9]. The novel technology has increased the proportion of patients eligible for EVAR but the choice of open versus endovascular AAA repair in patients with a challenging neck remains controversial.

The present study suggests that the results of EVAR in patients with a complex anatomy are similar to those with a favorable anatomy. The presence of a complex anatomy is a negative predictor of periprocedural and late complications[5,6,10].Particularly an unsuitable proximal neck is one of the main factors limiting the wider applicability of EVAR[11]. For this reason, new grafts have been developed to treat patients with challenging and complex anatomy. In a multi centre series of the Aorfix device (Lombard Medical, Didcot, United Kingdom), including patients with severe neck angulation (>70°),the Authors demonstrated that EVAR is feasible and safe, but persistent type I endoleak rate still remained high (3.4%)[12]. Recently a preliminary single center study evidenced encouraging results with Anaconda stent graft (Vascutek, Terumo, Inchinnan, Scotland) in very angulated neck, unfortunately this prosthesis couldn't be used in neck shorter than 15 mm[13]. Ohrlander et al, the "Chimney technique" which allow preserving or rescuing aortic branch vessels in stent-graft sealing zones in very short neck[14]. In 2009 cheering data sprang off in vitro study about Endurant stent graft (Medtronic Cardiovascular, Santa Rosa, California) and Torsello et al. reported an estimated freedom from type I and type III endoleaks and secondary intervention of 97.8% (44/45 cases) and 93.3% (43/45 cases) respectively [15]. Recently, the introduction of fenestrated and branched graft seemed to change the management of short and angulated neck with interesting results in different series[16,17]. Despite these results use of fenestrated and branched graft did not became a treatment of choice in management of hostile neck, perhaps because of the long learning curve and long

time for customization. EVAR is a process of tailoring the endovascular procedure to a specific patient. We need to have in-depth knowledge of the patient's clinical status, vascular anatomy, the technical features of the materials and appropriate pre-operative planning. Only a correct learning curve can cover all these requirements. The EVAR of an AAA with a challenging and complex anatomy requires the institution to have an endovascular team with a fully completed learning curve (anaesthesiologists, vascular surgeons, nurses, interventionalists), appropriate patient's consent, knowledge of all available devices and of its own limits. Imaging is fundamental to the correct planning of the procedure. Improvements in stent graft technologies have contributed to enlarge EVAR indications to the treatment for AAA in our Department. EVAR outcome in challenge and complex anatomies seem to be encouraging but further follow-up and more data are warranted to confirm these findings.

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By pass surgery or transulminal angioplasty to treat critical lower limb ischemia

Speziale F., Ruggiero M., Marino M., Menna D., Kasemi H.

U.O.C. Chirurgia Vascolare B - "Sapienza" Università di Roma - Italy

Summary

Good technical and clinical results have been obtained with distal bypass technique in the treatment of critical limb ischemia (CLI). However, significant morbidity can be associated with distal bypass surgery. In these patients, percutaneous transluminal angioplasty (PTA) may represent a feasible revascularization technique rather than primary amputation. Recently, the Bypass Versus Angioplasty in Severe Ischemia of the Leg (BASIL) study suggested that if anatomy is conducive for angioplasty, primary PTA might be an appropriate first therapy, even if the patient is a good candidate for bypass. Ideal anatomy was not well defined in BASIL trial, however, and outcomes were not stratified by the distal extent of disease (superficial femoral/popliteal/tibial).

The TransAtlantic InterSociety Consensus (TASC) criteria represent a standardized definition for anatomic features. Stratifying patients by TASC classification, results from Literature seem to be encouraging with a technical success rate about 95%. The limb salvage rate was 84% at 1, 2 and 3 years.

Introduction

Good results have been obtained with distal bypass for the treatment of critical limb (CLI). However, significant morbidity can be associated with distal bypass surgery. Patients undergoing primary lower extremity arterial revascularization, for CLI represent a dynamic challenge for the surgeon and the anesthetist, that extends beyond the intricacies of the planned operation. These patients frequently have arterial disease affecting several vascular beds and suffer from other significant comorbidities such as diabetes, respiratory disease, and renal failure. Furthermore, CLI patients have an even greater risk of experiencing cardiovascular ischemic events[1-3]. Patients undergoing surgical revascularization are at increased risk of life-threatening peri- and postoperative cardiac adverse events, such as myocardial infarction[4,5]. Fifty percent of patients operated for CLI die within 5 years mainly due to cardiovascular

Type A lesions	■ Single stenosis ≤10 cm in length ■ Single occlusion ≤5 cm in length
Type B lesions	■ Multiple lesions (stenoses or occlusions), each ≤5 cm ■ Single stenosis or occlusion ≤15 cm not involving the infra geniculate popliteal artery ■ Single or multiple lesions in the absence of continuous tibial vessels to improve inflow for a distal bypass ■ Heavily calcified occlusion ≤5 cm in length ■ Single popliteal stenosis
Type C lesions	■ Multiple stenoses or occlusions totaling >15 cm with or without heavy calcification ■ Recurrent stenoses or occlusions that need treatment after two endovascular interventions
Type D lesions	■ Chronic total occlusions of CFA or SFA (>20 cm, involving the popliteal artery) ■ Chronic total occlusion of popliteal artery and proximal trifurcation vessels

CFA – common femoral artery; SFA – superficial femoral artery.

Fig. 1

events[6]. Moreover, not all patients are suitable for distal bypass surgery. Few years ago, the debate between surgery and endovascular treatment for CLI was still far from a clearly evident solution. In recent years, however, there have been notable continuing advances in imaging techniques, angioplasty equipment, and endovascular techniques, that allow an increasing use of angioplasty with or without stenting as a primary revascularization procedure for CLI[7]. Many reports have also supported the effectiveness of angioplasty, and the lower morbidity and cost. Angioplasty results are comparable to those of bypass surgery, supporting the increasingly significant role of angioplasty in the management of patients with CLI.

In the last ten years there was a changing pattern for treatment of this disease[7].

The Evidence

Bypass Versus Angioplasty in Severe Ischemia of the Leg (BASIL)

Recently, the Bypass Versus Angioplasty in Severe Ischemia of the Leg (BASIL) [8] study suggested that if the anatomy is conducive for angioplasty, primary PTA might be an appropriate therapy.

A multicentre randomized controlled trial, started in 1999 and finished in 2004, enrolling 452 patients, with primary endpoint amputation free survival. The aim was comparison between outcomes of surgery and angioplasty in patients with severe limb ischemia. The short term results showed higher morbidity for surgery (26% vs 9%) and higher reintervention rate for endovascular treatment (9% vs 0,5%), but most complication in surgical patients were correctable by percutaneous interventions. The long term analysis proved similar amputation rate between surgery and endovascular (10% vs 12%) and similar mortality (15% vs 14%). Still higher reintervention rate remained for endovascular treatment, but the message was clearly evident: surgery and angioplasty approaches are broadly similar, so endovascular therapy be performed as a first choice, before any surgical revascularization.

TransAtlantic InterSociety Consensus (TASC)

Nowadays, the debate between surgical and endovascular treatment for CLI is coming to a solution.

But we still need an anatomical classification with clear guidelines. Ideal anatomy was not well defined in BASIL, as well outcomes were not stratified by the distal extent of disease (superficial femoral/popliteal/tibial). Finally the TransAtlantic Inter-Society Consensus (TASC II) [9] criteria represents a standardized definition for lesion characteristics, according to number and extension of obstructive lesions, so that the type of treatment can now be chosen also on the basis of anatomical features (Fig 1). Stratifying patients by TASC, results from Literature seem to be encouraging with a technical success rate about 95%. The limb salvage rate was 84% at 1, 2 and 3 years. Postoperative complications occurred in 9% of cases. Overall survival was 81%, 65%, and 54% at 1, 2 and 3 years respectively[10].

TASC A and B femoro-popliteal lesions were fundamentally short-medium with sufficient patent distal runoff (Fig.2). These two classes of atherosclerotic lesions were assessed as relevance for endovascular technique. Literature's review showed that use of nitinol stents allowed satisfying results both for 1-year and 2-years patency rates (87-88%), which were significantly better than angioplasty and other metallic stents[11]. According to these results, we can assume that endovascular technique is the treatment of choice for TASC A and B lesions.

Concerning TASC C lesions (Fig. 3), the given recommendations indicate surgery as the treatment of choice. But in recent years, also for this kind of anatomical features, therapeutical approaches are changing. In facts, it has been observed that on TASC C lesions treated with endovascular approach, specifically with PTFE covered stents, primary and secondary patency rates were pretty good, just as an endoluminal bypass grafting[12]. Also long-term results showed PTFE covered stents to be an effective choice for this kind of lesions. According to these results, we can assume

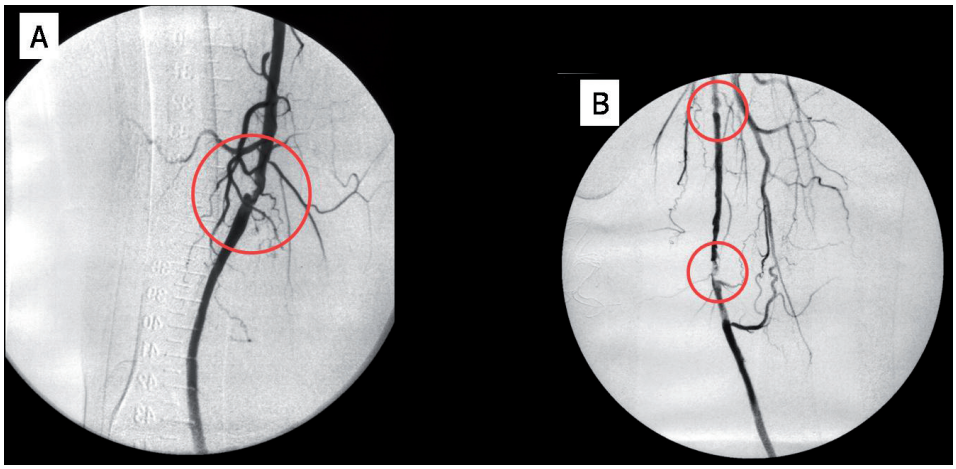

Fig. 2

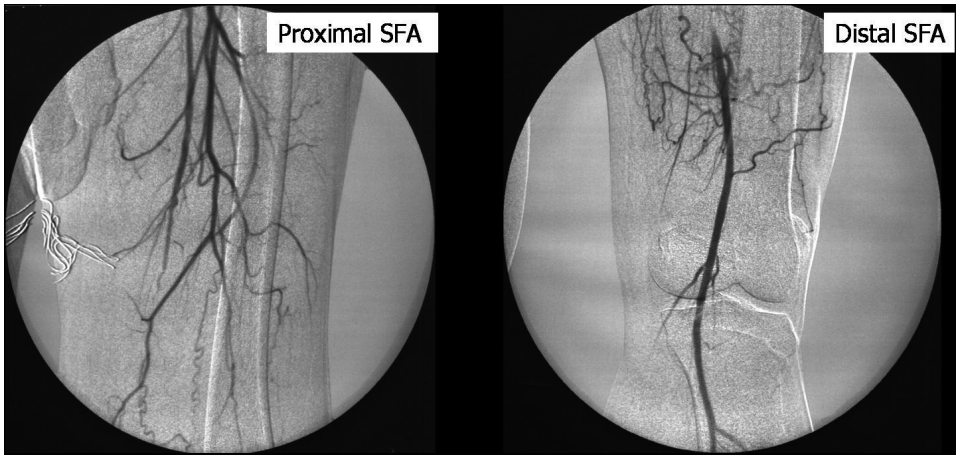

Fig. 3

that also in TASC C lesions, endovascular approach seems to be safe and effective as a first treatment[12].

So we have to use surgery only in extreme TASC D (Fig.4) revascularization? In literature, many Authors[13-15] report acceptable results in selected patients with complex lesions treated by endovascular approach[13-15].

Discussion

During the last decade a significant reduction has occurred in the number of infrainguinal bypass grafting. The reasons are unclear but may well relate to improvements

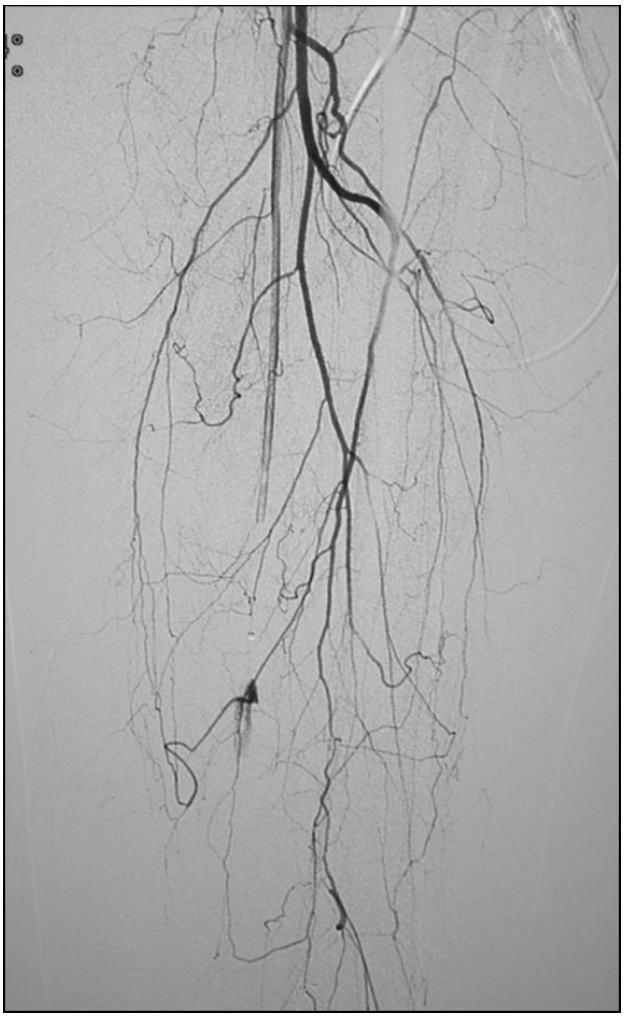

Fig. 4

in general medical care and risk factor modification, better access to interventional vascular therapy and improved endovascular techniques.

To improve outcomes and change trends of peripheral revascularization, many alternatives to angioplasty have been proposed, including stents, cutting balloons, cryo-balloon angioplasty, and drug-eluting stents[16-17]. Patency rates of nearly 90% at 1 year and 78% at 3 years have been reported on numerous observational studies[18-20].

PTFE-covered stents have better patency rates than dacron one, although they require long-term follow-up, a high rate of reintervention, and long-term use of aspirin and clopidogrel[21].

Sirolimus eluting stents have been tested on animal models, and results demonstrated

marked effects on smooth muscle proliferation and cell migration, with a reduction in intimal hyperplasia after stent placement. In the Sirolimus- Coated Cordis Self-Expanding Stent for the Treatment of Obstructing Superficial Femoral Artery Disease (SIROCCO) trial, the restenosis rates at 24 months for sirolimus eluting stents and bare SMART nitinol stents, were 22.9% and 21.1%, respectively[22-23].

In conclusion, BASIL trial and TASC document have offered sensible guidelines for the treatment of both infrainguinal and infrapopliteal disease.

Vein bypass surgery is in decline and endovascular treatment can be now employed also in complex femoro-distal steno-occlusive lesions.

For TASC C lesions, once treated preferrably with surgery, PTFE covered stents show good results.

In high-risk TASC D patients, endovascular approach can be the first therapeutical step for limb revascularization. We can assume that in few years, most CLI patients will be treated exclusively with endovascular technique.

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Clinical Outcomes in Women: Insights for Coronary Pathophysiology

Vaccarino V., MD, PhD

Emory University School of Medicine
Dept. of Medicine, Division of Cardiology
Atlanta, Georgia, USA

Despite women's inherent protection towards coronary heart disease (CHD), once women develop an acute myocardial infarction (AMI) they appear to lose much of their protection compared with men. In spite of smaller infarcts and less severe coronary narrowing, women hospitalized for AMI have more severe presentation, higher rates of complications and higher mortality compared with men. These gender-related outcome differences are much more marked for younger women, a group that one would expect would be even more protected. In part, these differences are attributable to the higher prevalence of pre-existing diseases and risk factors in women compared with men. However, in many studies the gender-related outcome differences remain unexplained. This presentation will review sex differences in coronary pathophysiology as possible explanation of outcome differences. One key aspect of CHD in women is that at least 20% of women presenting with chest pain have evidence of ischemia based on myocardial perfusion imaging or other tests, but no evidence of obstructive coronary disease. A leading hypothesis, therefore, is that many women with CHD have a different form of vascular disease that poses them at risk despite less severe coronary atherosclerosis. Differences in vascular structure, involving a more diffuse atherosclerotic process, smaller vessel sizes, and tendency towards plaque erosion versus rupture are some of the pathophysiological differences proposed. In addition, endothelial dysfunction, microvascular disease, and sex differences in vascular repair may be implicated. Although many possible mechanisms have been proposed, this area lacks adequately powered studies linking such mechanisms to hard cardiac endpoints in women. Studies providing meaningful comparisons between women and men are also needed to better define vascular processes that are unique to women.

Carotid Endoarterectomy with Remifentanyl conscious sedation: is the best option?

[1]Siani A., [1]Antonelli R., [2]Mounayergi F., [1]Accrocca F., [1]Giordano A. G., [2]Sbroscia A., [2]Pierettori G., [2]Casiraghi M., [2]Grandino A., [2]Grandino D., [1]Marcucci G.

[1]Department of Surgery, Vascular and Endovascular Surgery Unit
[2]Department of Emergency, Anaesthesia and ICU Unit
"San Paolo" Hospital, ASL RMF Civitavecchia – Rome (Italy)

Summary

This study shows the feasibility, the safety and the great advantages of general anaesthesia with Remifentanyl conserved consciousness in carotid endarterectomy (CEA) compared to the local (LA) and general anaesthesia (GA). From January 2005 to February 2009 we performed 447 CEA in 375 patients (M/F 256/119, age 75±24) using general anaesthesia with Remifentanyl conscious sedation. In all cases a superficial cervical plexus block with Naropine 0,5% 25 ± 5 ml was previously performed. We assessed mean arterial pressure, heart rate, clamping time, intra-operative complications, postoperative morbidity and mortality, shunt insertion, and patient compliance. 30-day mortality rate was 0.4% (2/447). TIA rate was 0.7% (3/447). Only 1 case of major stroke occurred, meanwhile 2 patients had a minor intra-operative stroke regressed in 3 months (0.4%). Haemodynamic parameters were essentially constant, with a slight increase in baseline blood pressure. We always had a highlight excellent assessment of neurological status, with selective use of the shunt and excellent acceptance of the procedure by both patient and surgeon.

Introduction

Despite the indications and surgical techniques in carotid endoarterectomy are well established, some issues still remain regarding the best anaesthesiological management. Indeed, general anaesthesia (GA) and loco-regional anaesthesia (LA) have advantages and disadvantages and no evidence from randomized trials seems to define the better anaesthetic technique(1). The introduction of new anaesthetic procedure that use Remifentanyl in patients intubated and ventilated but with conservation of the consciousness level that permits an awake monitoring shows to have the advantage of

TAB 1 Patients data

Age (years) mean +/- SD	75 ± 8
Male gender	256 (68.2%)
Coronary Artery Disease	180 (48%)
Diabetes	130 (34.6%)
Smoking	210 (56%)
Hypertension	244 (65%)
Symptomatic	206 (46.1%)
Asymptomatic	241 (53.9%)
Controlateral CEA	72 (16.1%)
Controlateral Carotid Occlusion	70 (15.6%)
ASA 2	166 (37.1%)
ASA 3	251 (56.1%)
ASA 4	30 (6.8%)

both GA and LA leading to safe neurological monitoring, airway control, hemodynamic stability, with good surgical early and long term results(1,2). Aim of the present study is to evaluate the effectiveness and the safety of CEA with conscious sedation under Remifentanyl with orotracheal intubation.

Matherial and Methods

From January 2005 to February 2009 447 consecutive CEA were performed in 375 patients (M/F 256/119, age 75±8) by means of Remifentanyl consciousness sedation (RCS). Demographic population profile has been reported in tab 1. All patients underwent non invasive preoperative assessment of carotid artery stenosis with Doppler ultrasounds. In 46 cases (12.2%) an angiographic study was performed. Angio CT-Scan and MRI angiography were performed in 142 (37.8%) and 130 (34.6%) patients. A cranial CT scan was performed in 300 patients (80%). Surgical data have been report in Tab 2. We assessed the postoperative morbidity and mortality, shunt insertion, mean arterial pressure, heart rate, intraoperative complications (Tab 3).

Our anaesthesiological protocol

A superficial plexus block with naropine 0.5% 25 ± 5 ml along the posterior border of sterno cleidomastoid muscle was performed. Anaesthetic management was carried out by means of induction with intravenous infusion of propofol 1% 1,5/2 mg/Kg with transmucosal topical application of lidocaine 2% 10 ml during tracheal intubation. After intubation, a continuous intravenous Remifentanyl infusion 0,12-0,25 µ./kg./min (Ultiva, GlaxoWellcome Inc., Research Triangle Park, NC, USA) was started. The patient was mechanically ventilated in IPPV modality

(TV 8-12 ml/kg, RR 11 ±2, O2/air 40/60%) . Before to clamp, the Remifentanyl was slowly reduced until the patient was awake and able to collaborate. The neuro-

TAB 2 Surgical Data

• Direct suture	1 (0.2%)
• Patch	367 (82.1%)
• Eversion	74 (16.5%)
• By-pass	5 (1.1%)
• Shunt	90 (20.1%)

TAB 3 Results

Minor Stroke	2 (0.4%)
Major Stroke	1 (0.2%)
Mortality	2 (0.4%)
Shunt	67 (14.9%)
TIA/RIND	3 (0.7%)
Haematomas	5 (1.1%)
Nausea/vomiting	20 (4.4%)
Clamping time	32 ± 17 min
Blood pressure	160/75 ± 30/25 mm Hg
Heart rate	75 ± 15

logical status was tested by means of foam-rubber toy squeeze and through the open and close eyes movement. The Remifentanyl was regulated to obtain a good motor evaluation avoiding pain and discomfort. After the clamping, the squeeze test was repeated every 15-30 second for two minutes. In case of patient intolerance to the carotid clamping showing no movements of the controlateral hand and no eyes opening to the request, immediately a F3 Pruitt-Inahara shunt (9 Fr LeMaitre Vascular) was inserted and the patient checked again to show recovery of the consciousness. At the end of the procedure, Remifentanyl was stopped and the endotracheal tube removed. In all cases a carotid bulb infiltration with 2-3 cc of 1% xilocaine through a short 25 gauge needle was given to avoid sinus reflex.

Our surgical protocol

The skin incision was carried out at the medial border of the sternomastoid muscle, with ligation of all crossing vein branches. A preventive clamping of the internal carotid artery after eparinization was carried out. A rapid and carefull dissection of the common and external carotid arteries were performed. The bulb was mobilized only in cases of eversion technique. An extensive endarterectomy of the plaque with Dacron patch closure were performed, limiting the eversion technique in cases of kinking or coiling. A selective Shunt policy was carried out.

Results

30 day mortality rate was 0.4% (2 cases, ASA 4) for MI at 6th and 27th postoperative days. . Three patients (0.7%) had transient ischemic attack (TIA). Only 1 case of major stroke (0.2%) occurred. Two patients (0.4%) showed a postoperative neurological accident. In the first, a transitory left side monoparesis with prompt regression after 2 hours occurred. In the second a minor stroke with monoplegia of the right arm was detected with partial improvement after 3 months. In all cases a prompt Duplex scan examination, Transcranial Doppler and CT scan were performed excluding ICA thrombosis, technical defect or hyperperfusion syndrome. The incidence of shunt deployment was 14.9% (67 cases). Five patients (1.1%) presented a postoperative haematoma. The clamping time was 32± 17 min. Haemodynamic parameters were constant, with a slight increase in baseline blood pressure. No significant intra procedural adverse cardiac events occurred. We always had an highlight excellent assessment of neurological status, with selective use of the shunt. In all cases the level of acceptance by the patient and the surgeon was excellent.

Discussion

Data recovered from randomized trials by the Cochrane reviews does not show a clear superiority of the LA vs. GA, but the non randomised studies seem to show a potential benefits by the use of LA(3). Currently the LA becomes the anaesthetic choice in many vascular centers either for better awake monitoring, either for the good cerebral auto regulation, cardiovascular stability and shorter postoperative recovery. Indeed, the discomfort for both patient and surgeon seems to be a major concern especially in cases of technically demanding intervention or intraoperative ischemia due to vessels clamping with problematic conversion to general anaesthesia due to dramatic difficult to achieve a quick and safe airway control by means of orotracheal intubation.(4,5)

The introduction of Remifentanyl conscious sedation in CEA by Muchada et coll. (2) leads to the possibility to combine the pro and cons of GA and LA. The advantage of this technique is that the duration of anaesthesia is not limited and an adequate ventilation and a maintenance of a safe monitoring of the neurological status are assured. Some authors, that compared the results of Remifentanyl conscious sedation CEA versus LA showed that the CEA performed in this way is safe, effective and satisfactory, but the complications due to intubation and side effects of the Remifentanyl need randomized control trials to prove the superiority of this method respect to the LA (6,7) .

We introduced these anaesthetic procedure in 447 consecutive CEA operations with a very safe neurological assessment during the arterial clamping without the necessity of instrumental neurological monitoring. A selective shunt policy was carried out in all cases with a deployment shunt incidence of 14.9% (67 patients). In our experience, we had a major number of shunt deployments in contrast with the other experiences reported in medical literature (8,9), especially in cases of very old or non compliant patients. These procedures can lead to a little overestimation of false positive cases but no false negative cases were reported, showing a neurological monitoring safe extendible in most of the cases. Indeed, we think that the shunt insertion in any way

is easy, safe and without particular contraindications. No alterations attributable to hemodynamic instability were observed regarding the blood pressure and cardiac frequency and the episodes of hypertension or hypotension. They were soon corrected without cardiac complications. The CEA with the Remifentanyl conscious sedation allowed to technically precise repair in a calm atmosphere also in cases of high bifurcation or very extensive lesion into the internal carotid artery, leading to precise vascular reconstruction and good haemostasis with very low incidence of postoperative haematoma. With a good level of analgesia the orotracheal tube and the operative position are well tolerated and the airways control is guarantee avoiding the patient anxiety and the stress due to long time fixed position. In all cases a prophylaxis of postoperative nausea and vomiting with 10 mg of metaclopramide was started as we reported an incidence of these complications at least in 20 patients (4.4%). Some series evidence important side effects due to hemodynamic instability during the induction with bradicardia, arterial hypotension or hypertension, especially in beta blocked patients or respiratory muscle contraction. (10,11,12,). In our experience all the occurred changes were prompt corrected on the basis of hemodynamic parameters and no higher cardiac complications in perioperative and immediate postoperative were detected. We never had serious major respiratory muscles contractions.

Conclusion

In our opinion, the general anaesthesia with the Remifentanyl conserved consciousness can be the new best option in anaesthetic management of the CEA, combining the advantage of the patient-awake neurological monitoring like LA and all the GA advantages as cerebral protection during clamping, better airway control and optimal haemodinamic stability. A selective shunt policy, good compliance for both patient and surgeon, calm environment during the endarterectomy, patching and haemostasis avoiding neck movements or patients discomfort can be achieved in all cases. The possibility of hemodynamic instability during the induction still remains a controversial topic and it seems to be the Achilles heel of the procedure. However, randomized studies that compare this procedure with LA or GA are necessary to validate this technique.

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Ten year experience of evaluation and treatment of abdominal aortic inflamatory aneurysms

Nuellari E., Caco G., Xhepa S., Gjergo P., Kuci S.*, Kapedani E.

Service of Angiology & Vascular Surgery
** Service of Anesthesiology & Intensive Care.*
University Hospital Centre "Mother Teresa", Tirana, Albania.

Summary

Aim: The aim of the study was to report a 10-year single institution experience, with the early and late outcomes of surgical treatment of inflammatory abdominal aortic aneurysms.

Method: In a 10-year period, 375 consecutive patients underwent elective surgical repair for non-rupture abdominal aortic aneurysm. 27 patients (7,2%) were classified as inflammatory abdominal aortic aneurysms. Early and late outcomes were analyzed.

Results: One patient died in the perioperative period, giving a mortality rate of 3.7%.

One patient died from a pseudoaneurysm rupture 8 months after operation.

Three patients developed an aortic pseudoaneurysm in the follow-up period (mean 6.1 years, range 1-10 years) and underwent a redo operation.

Conclusion: Overall surgical outcome of these patients, in terms of short-term and long-term is good. A high rate of pseudoaneurysm formation was observed.

Key Words: Infected aneurysm, Aorta, surgery – Aortic aneurysm, abdominal, surgery.

Introduction

Inflammatory abdominal aortic aneurysms (IAAA),non infectious, are characterized by marked thickness of the aortic wall, with dense perianeurysmal fibrosis involving adjacent organs[1,2] such as inferior vena cava, ureters, and the third poertion of the duodenum.

The prevalence of IAAA in autopsy material ranges between 2.5% and 10% of all aneurysms.[3,4] The first report of IAAA was by James in 1935, for a fatal case of uremia caused by inflammation and fibrosis.[5] The first morphological definition of IAAA was provided by Walker et al.[6] in 1972. The symptomatology and clinical findings of IAAA are not well established, and the epidemiological data are uncertain.

Table 1

Characteristics	Number	%
Male sex	20	74
Smokers (>10 cigarette/die)	11	41
History of aneurysm in family	1	3.8
Hypertension	12	44
Dyslipidemia	6	22
Diabetes mellitus	3	11
Peripheral arterial disease	5	18
Ischemic heart disease	13	48
Cerebro-vascular disease	2	7.4
Chronic obstructive pulmonary disease	3	11
Elevate erythrocyte sedimentation rate	17	63

The inflammatory process can be due to such conditions as syphilitic arterial disease, tuberculosis, giant cell arteritis and non specific infections, but the etiology of most IAAA cannot be estabilished.[4] Bacterial cultures from IAAA are usually negative.[7] Some authors suggest that autoimmune mechanisms are involved in the pathogenesis of IAAA. (However, Haug et al.)[8] in 150 consecutive patients undergoing surgery for IAAA revealed an IAAA in their first-degree relatives.

The aim of this study is to report a 10-year single institution experience with the early and late outcome of surgical treatment of IAAA.

Material and method

Between January 1997 and December 2007, 375 consecutive patients underwent elective surgical repair for non-rupture abdominal aortic aneurysm. 27 patients (7.2 %) were classified as IAAA. Aneurysms were classified as inflammatory when macroscopic or microscopic findings such as gross computed tomography or intraoperative appearance of marked thickening of the aneurysm wall were observed with encasement of surrounding retroperitoneal organs, infiltrates of lymphocytes and plasma cells, endoarteritis obliterans, and fibrosis around nerve as previously described in the literature.[6,9,10]

Demographic characteristics, clinical symptoms and co-morbidity factors, operative and follow-up data were collected retrospectively through the hospital records.

Patients underwent clinical examination by vascular surgeons and abdominal ultrasound examination at 6 months after the operation and annually thereafter. Every 3 years computed tomography was performed.

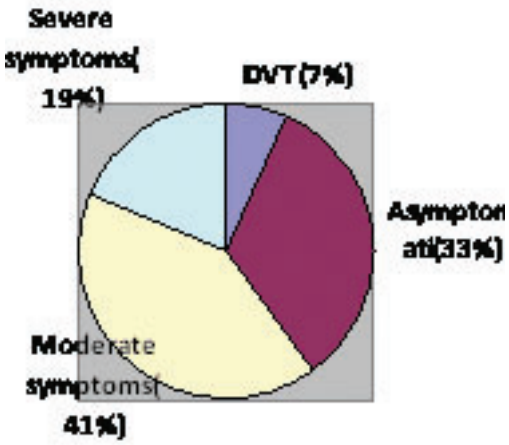

Figure 1

Results

The mean age of patients was 63 years (range 43-78 years). Preoperative demographics, co-morbidities and characteristics of the patients' are shown in Table 1.

17 patients (63%) had a high erythrocyte sedimentation rate. Nine patients were completely asymptomatic (Figure 1), while 11 patients reported moderate symptoms like abdominal pain lasting for weeks or pulsative abdominal pain. Five patients suffered severe symptoms such as severe abdominal pain, low back, and pelvic pain. One patient had clinical evidence confirmed by color duplex scanning of deep venous thrombosis, and case associated with hydronephrosis. In this last patient the intraoperative findings showed severe retroperitoneal fibrosis causing compression to the vena cava and ureters.

Preoperative ultrasound tomography was performed in 4 patients and in none of them was an inflammatory process detected. Computed tomography was performed in the 19 patients and detected inflammatory aortic or retroperitoneal fibrosis in 17 patients.

Four patients underwent angiography and the inflammation process was demonstrated in only 1 patient, where the aneurismal wall seemed very thin and multiple ureteral stenosis was present. The overall preoperative diagnosis was achieved in 18 patients, while in the remaining[9], the intraoperative findings confirmed the diagnosis.

The mean maximal aneurysm diameter was 68 mm (range 50-90mm).All patients underwent the routine operation technique for our department, with a midline xifo-pubic incision and a transperitoneal approach. In 8 patients (30%) tube graft interposition was performed, while in 14 patients (52%) bifurcated graft for aorto-iliac grafting was preferred; in the remaining[5] patients (18%) a bifurcated graft was used for aorto-femoral grafting. Mean operating blood loss was 1800ml (range 300-3200ml).

Intraoperative diagnosis was based on the characteristic appearance of an aorta encased in a thick white fibrotic tissue that appeared thick in all cases and especially

Table 2

Complications	Patients	%
Cardiac	*8*	*30*
Aritmia	6	22
Ischemia	2	7
Pulmonary	1	4
Pneumonia	0	0
Pulmonary embolus	1	4
Vascular	2	7
Acute limb ischemia	1	4
Deep vein thrombosis	1	4
Intestinal	*3*	*11*
Occlusion	0	0
Ischemia	0	0
Prolonged paralytic ileus	3	0
Renal	*8*	*30*
High creatinine	8	30
Infection	0	0
Wound	2	7
Abdominal	1	4
Inguinal	1	4
Mortality	*1*	*4*

in the anterior part of the aortic wall. In 7 patients the retroperitoneal fibrosis involved the ureters. In 19 patients specimens were obtained in the operating room and were sent to the laboratory to undergo histological examination. The main finding was fibrosis of the adventitia with lymphocyte and other plasma cell proliferation.

One patient died on the 4th postoperative day due to myocardial infarction giving a mortality rate of 3.7%. Other complications included deep venous thromboses and pulmonary embolism in 1 patient and creatinine arose in 8 patients. Table 2 shows the perioperative (30-days) complications. The extensive retroperitoneal fibrosis caused technical difficulties and increased bleeding in some cases; 8 patients were transfused in the postoperative period receiving 4 blood units (range 3-5).In one patient the inferior vena cava was damaged and reconstructed

with 6/0 Polypropilen sutures.

One patient underwent thromboembolectomy of the lower limb due to acute postoperative ischemia. Three patients were lost during follow-up. The mean follow-up length was 6.1 years

(1-10 years).One patient died from a pseudoaneurysm rupture 8 months after the

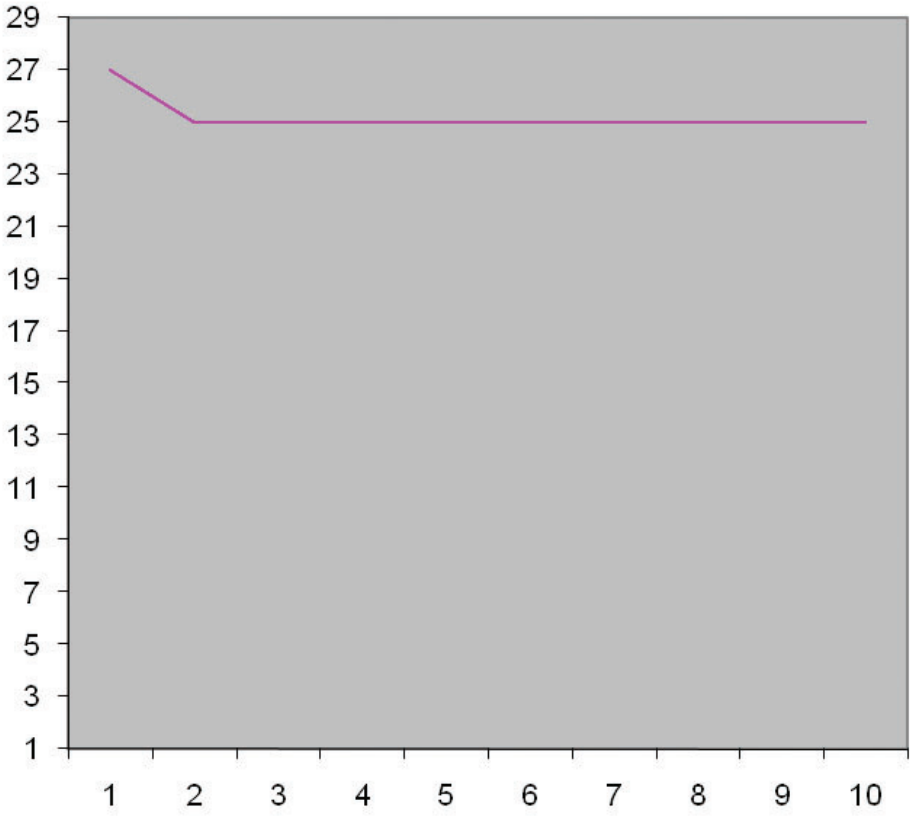

Figure 2

operation. Ten patients died from non-aortic correlated reasons, 5 myocardial infarctions, 1 stroke, 1 pneumonia, 2 neoplastic disease, 1 for other reasons. (Figure 2).

Three patients developed an aortic pseudoaneurysm and underwent a redo operation, one 2 years after operation,the second 3 years operation and the third 6 years after operation. One patient developed a femoral anastomotic pseudoaneurysm 7 years after operation and he was treated surgically. In two patients stenting of the ureters was performed by urologists for retroperitoneal fibrosis and compression.

Discussion

The pathophysiology of the IAAA remains unclear. Many investigators suggested various theories like infective causes (viral, bacterial), or non specific arterial infections), autoimmunity, giant cell arteritis, vasa vasorum deficiency.[4,11-13] Various theories have been suggested including infected causes .*Railo et al.*[3] found syphilitic arterial disease in 2 cases and tuberculosis in one case.

The sensitivity of computed tomography in our study was 85.5% and sensitivity of ultrasound examination 0%. These data confirm Railo et al's.[3] findings of high

sensitivity of computed tomography scaning and no sensitivity of the ultrasounds to the inflammatory nature of disease. L*inoet al.*[14] showed 90% sensitivity for computed tomography.

The fibrotic process complicated surgical dissection and exposure of the aorta, however it does not seem to influence the results of surgery in terms of survival. Surgical injury to the adherent organs has been reported in 4.5% to 15% of cases.[15] In one case the inferior vena cava was injured and re-construted with Polypropylen 6/0 sutures.

The transperitoneal approach was chosen for all patients.Because the anterior portion of the aorta is most affected by the inflammatory reaction, the retroperitoneal approach is thought to reduce risk for duodenal and left renal vein injury, as well as inferior vena cava injury and to gain proximal control more safely. In our series, the median laparotomy was demonstrated safe and effective.

Patients in this present series had acceptable short and long-term mortality rates which were quite comparable with those reported in the literature for non inflammatory AAA.[16,17] The only factor that seems to be different is the long term pseudoaneurysmal formation rate. In our series, one patient developed an aortic pseudoaneurysm 8 months after operation and three patients developed an aortic pseudoaneurysm from 2 to 6 years after the operation. Another developed a femoral pseudoaneurysm. The overall pseudoaneurysm formation rate was 13.7%.

In the Cleveland clinic experience of the surgical treatment of AAA,[16] a 0.4% rate of late graft complications was found, and included three graft infections and only one femoral pseudoaneurysm formation. A significant difference, regarding pseudoaneurysm formation was found by Bonati *et al.,*[1] in a case-matched study comparing patients with IAAA and non-inflammatory abdominal aortic aneurysms.

Conclusions

In conclusion, the presence of an abdominal aortic aneurysm in a patient with abdominal, back or pelvic pain, combined with elevated erythrocyte sedimentation levels, suggests an IAAA.

Computed tomography should be the examination of choice. Overall surgical outcome of these patients, in terms of short-term and long-term is good. A high rate of pseudoaneurysm formation was observed.

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