TREATMENT INDICATIONS IN MULTILEVEL ARTERIAL OCCLUSIVE DISEASE USING HYBRID REVASCULARIZATION TECHNIQUES

ABSTRACT

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KEY WORDS: multilevel peripheral arterial disease, hybrid revascularization, surgical revascularization, primary patency, limb salvage rate.

ABREVIATIONS:

ICA = internal carotid artery
CFA = common femoral artery
PFA = profound femoral artery (deep femoral artery)
SFA = superficial femoral artery
CIA = common iliac artery
EIA = external iliac artery
IOA = interosseous artery
CTA = computed tomography angiography
MRA = magnetic resonance angiography
PA = popliteal artery
ATA = anterior tibial artery
PstTA = posterior tibial artery
PAD = peripheral arterial disease
MAOD = multilevel arterial occlusive disease
CABG = coronary artery bypass grafting
O/E = open/endovascular
E/O = endovascular/open
I = inflow
ABI = ankle-brachial index
LL = lower limbs
O = outflow
PTA = percutaneous transluminal angioplasty
PTCA = percutaneous transluminal coronary angioplasty
S = simultaneous
TEA = thrombendarterectomy
PTT = posterior-tibial trunk

The thesis comprises of 160 pages, 98 images, 28 tables and 245 references.

Tables and images labeling is identical with the thesis labeling.
INTRODUCTION
Chronic lower limb ischemia, also known as peripheral arterial disease (PAD), is associated with a high morbidity and mortality. A well known clinical variation of PAD is multilevel arterial occlusive disease (MAOD), characterized by multiple occlusive lesions at different levels of the same vascular segment. Over the course of the last decade, the combined treatment (hybrid) which consists of simultaneous or successive endovascular and open surgical techniques on the same vascular segment appears to be the best treatment if an adequate inflow and outflow are to be obtained.

STUDY OBJECTIVE
The purpose of this paper is to compare the results obtained by open surgical treatment with those obtained by hybrid techniques, in patients with MAOD, depending on the localisation and the morphology of the lesions, the disease stage, comorbidities and risk factors. The study's main objective was evaluating the indication, feasibility and efficiency of the hybrid revascularization techniques used for patients with MAOD.

MATERIAL AND METHOD
This was an observational, non-randomized study, conducted on patients from two centers. It was done both retrospectively on a 20-month period (Jan, 2010 - Sept, 2011) and prospectively on a 24 month period (Oct, 2011 - Oct, 2013). The case-control subjects were treated in the Vascular Surgery Department of "St. Spiridon" Emergency University Hospital, Iasi, Romania. The patients in the study group had their hybrid techniques done in the Cardiovascular and Thoracic Department of the "Imelda" Hospital, Bonheiden, Belgium. The type of
The revascularization technique used was chosen according to the localization and morphology of the arterial lesions, disease stage, comorbidities, risk factors and necessary technical equipment.

Including criteria: age above 18 years old, patients with unilateral or bilateral MAOD, with recommended revascularization technique by sequential surgical treatment (aorto-femoral/bifemoral bypass, ilio-femoral bypass, femoro-femoral crossover, femuro-proximal/distal popliteal bypass, femoro-anterior/posterior tibial bypass, femoro-interoseos bypass or femoral artery endarterectomy +/- patch angioplasty - as the first open surgical technique used, followed by a more distal bypass) or by hybrid techniques consisting of endovascular therapy (baloon angioplasty, stenting or endoprosthesis) and open surgical techniques on the same arterial segment.

Exclusion criteria: patients who did not need a revascularization procedure, patients with a known allergy to contrast substance, pregnancy, patients who wouldn't consent for the procedure, patients with contraindications to anticoagulation, patients with considerable comorbidities which contraindicated the surgical procedure (NYHA III or IV chronic cardiac insufficiency, acute cerebral circulatory insufficiency, neoplasm) or the hybrid technique (acute renal insufficiency, diabetic nephropathy).

The study group was divided into: group 1 - for which the hybrid technique was done simultaneously and group 2 - for which the hybrid technique was done consecutively, as follows: open surgical revascularization as a first procedure, followed by the endovascular procedure (O/E).
or endovascular revascularization initially, followed by the open surgical procedure (E/O). The control group was divided as follows: group 1 - with open surgical procedures done simultaneously and group 2 - with revascularization procedures done consecutively. All patients had preop clinical and paraclinical evaluation, including their risk factors and comorbidities, followed by an imagistic diagnostic procedure: Doppler U/S, MRA and/or contrast enhanced CTA. Follow-up was on short, medium (6 months) and long term (3 years) and had the following endpoints: primary and secondary patency, initial technical success, complication rate, morbidity and mortality associated to each technical procedure, symptomatology improvement, and limb salvage rate.

Analysis of the operative indications as well as the risk factors with influence on the post-therapeutic outcome, was also done. All patients in the study and control groups gave written consent for their respective procedures. The study had full approval from the respective Hospital Ethic Committee.

**STASTISTICAL ANALYSIS** was done using version 13 of the SPSS statistical software (SPSS Inc., Chicago, IL, USA). A "p" value of less than 0.05 was considered as statistically significant. Primary and secondary patencies were estimated using Kaplan-Meier tables.

**RESULTS.** The study included a total of 152 patients with MAOD.

The study group included 94 patients with a mean age of 70.68 years old, 64.9% of which were males, with 42 of them having had bilateral revascularization procedures. The vast majority of the patients were in stage II and III
Leriche-Fontaine. Most of the lesions were located at the level of the femoral and iliac arteries. A number of 37 outflow procedures were done, 17 inflow procedures, 14 consecutive inflow and outflow procedures, 10 consecutive outflow followed by inflow procedures and 16 simultaneous inflow and outflow procedures.

A proportion of 13.8% of all patients were diabetics, most of them in the second and fourth disease stages; the presence of diabetes was correlated with the presenting clinical disease stage \((r=0.197, \ p=0.057)\). A percentage of 5.3% of all patients had chronic renal insufficiency stage III and IV, the presence of which had a significant statistical correlation with the clinical disease stage \((r=0.285, \ p=0.005)\). The patients also had previous revascularization procedures on a different vascular segment other than the lower limbs: internal carotid artery (TEA or stenting), coronary arteries (CABG or PTCA), renal artery (PTA/stenting), subclavian artery.

The patients benefited from 94 initial hybrid procedures: 33 simultaneous and 61 consecutive (fig. 30).

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**Fig. 28.** Types of hybrid techniques
The majority of the patients revascularized by simultaneous hybrid techniques were in Leriche-Fontaine IIInd disease stage. The 33 simultaneous hybrid procedures consisted of: 20 procedures of TEA +/- CFA angioplasty, associated with PTA/stenting of the CIA, EIA, SFA, PA and 13 bypass procedures at different levels associated with PTA proximally or distally to the surgical revascularization level.

The initial procedures included in our study period were done in 61.7% of all cases (58 patients) electively and in 38.3% of all cases (36 patients) as an emergency procedure. For our study period, secondary to the initial hybrid procedure, 251 assisted primary patency or secondary patency procedures were done: 139 of them electively and 112 as emergencies. The primary patency and the number of emergency procedures correlated negatively and with statistical significance (r=-0.499, p=0.000), which suggests a lower primary patency for emergency procedures secondary to an initial hybrid procedure.

The assisted primary patency and secondary patency procedures consisted of thrombolysis and thrombectomies using the Fogarty catheter on the bypass or the native artery; CFA TEA with or without angioplasty; endovascular angioplasties (PTA, PTA/stenting and recanalization) both on native arteries and on proximal and distal bypass anastomoses.

The initial technical success for all procedures was 100%. We recorded 19 immediate occlusions (under 30 days) and 78 late arterial occlusions (after 30 days). The mortality rate was 0%. The mean primary patency for our
consecutive endovascular/open procedures (E/O) was significantly higher than the one for consecutive open/endovascular procedures (O/E). The mean primary patency at 6 months and 1 year was 63% and 46% respectively. We recorded 19 amputations (20.21% of all cases), 11 of which were major (below or above knee - 11.7% of all cases). We had 10 cases of unilateral major amputations and one case of consecutive bilateral amputation.

**The control group** included 58 patients (with a mean age of 62.66 years old, 96.6% of which were males) with a total of 66 lower limb revascularization procedures: 50 patients with one lower limb revascularization procedure and 8 patients with both lower limbs revascularized. For 25 patients, the second procedure was done simultaneously and for the other 33 it was done consecutively. We recorded 54 distal revascularization procedures secondary to the initial one and four femoro-popliteal bypasses following an initial CFA endarterectomy. Seventeen synthetic grafts and 41 venous grafts were used. The majority of surgically treated patients in the control group (53.4%) were in Leriche IV disease stage. Most of the lesions were at the iliac and femoral levels. Initial inflow surgical revascularization was done for 51 patients, followed by an outflow procedure, one case of initial outflow revascularization followed by an inflow procedure and 6 cases with only outflow procedures. A number of 13 patients with acute or subacute onset of ischemia were operated as an emergency, requiring graft thrombectomy with or without a simultaneous distal revascularization procedure. In the control group, we had 25 patients with
a simultaneous surgical procedure and 33 patients with a consecutive surgical procedure. One patient died seven days postoperatively due to pulmonary embolism, 13 had a late graft thrombosis and two had a graft infection. During follow-up, we recorded 14 amputations (24.13% of all cases), of which 7 (12.06%) were major (above or below the knee). The mean primary patency of venous grafts was better than the mean primary patency of synthetic grafts, but the difference wasn't statistically significant. Weather the procedure was elective or done as an emergency didn't have a statistically significant influence on primary patency for the control group. The only risk factor which had a statistically significant influence on primary patency was hypertension. The mean primary patency at 6 months and 1 year was 93.2% and 82.5% respectively.

**Comparative analysis of the two study groups**
The primary patency was significantly higher in the control group, compared with the study group (p=0.003), for the patients in the Leriche III disease stage (p=0.014), but not for those in the IIInd disease stage (p=0.687) and IVth disease stage (p=0.085). The are no statistically significant differences between the major amputation rates of the two studied groups of patients. A clinical improvement was observed for 88.29% of the patients in the study group and for 87.93% of those in the control group. Limb salvage rate was 73.17% in the study group and 85.10% in the control group.

**DISCUSSIONS**
This was an observational, non-randomized study, conducted on patients from two centers. The 152 patients included in both study groups were consecutive series.
The patients were included in the study both retrospectively on a 20-month period and prospectively on a 24 month period. The patients in our study who benefited from treatment had symptomatic MAOD, with lesions at more than two different levels on the same vascular segment. Primary patency at 6 months for each studied group was comparable with the data from literature (1,2,3,4,5,6,7,8,9,10). Primary patency at 12 months had smaller values than up-to-date published data (2,4,5,6,7,8,9,10,11). The favorable short and medium term primary patency and limb salvage rates prove that hybrid techniques for patients with MAOD are both feasible and efficient, irrespective of the patient's clinical disease stage. The number of simultaneous hybrid techniques had risen in 2012 compared to previous years, which suggests an improved surgical experience for this type of surgical approach. The majority of patients revascularized by simultaneous hybrid procedures were in Leriche II disease stage and this observation further underlines that endovascular procedures are optimal for patients in the first disease stages. The mean number of late occlusions registered in 2010 is significantly higher than the mean number of late occlusions from 2012 and this occurrence can be explained by the modernization of endovascular procedures and the equipment used. For some patients who benefited from hybrid techniques, doctors in the "Imelda" Hospital used drug-eluting angioplasty balloons and stents, this hospital having been previously included in many european trials (12,13).
The feasibility and efficiency of the endoluminal procedures, as well as the possibility of repeating these procedures on the same arterial segment with multilevel occlusive disease is demonstrated by the large number of revascularizations prior to the study period and also by the large number of procedures secondary to the initial hybrid technique needed to achieve assisted primary patency or secondary patency. This is further proven by the fact that most patients who benefited from hybrid revascularization procedures were elderly. The simultaneous hybrid technique has some advantages, the first of which is that there is no delay in establishing the complete revascularization of the ischemic limb. The second advantage is the in-hospital stay. Last, but not the least, another advantage is minimizing the complication rate by utilizing the puncture site as a site for proximal anastomosis (14). By utilizing the hybrid revascularization technique, both the inflow and the outflow arteries can be revascularized simultaneously, which can have a positive influence on the patency rate (8). For the study group, the primary patency rate calculated for each studied year was inferior to the corresponding primary patency rate in the control group. This is explained by the difference in mean age between the two studied groups (older patients in the study group) and the associated comorbidities (more severe in the study group) and also by the previous procedures sustained by patients prior to the study period (more in the study group, compared with control). For the study group, primary patency was better for simultaneous revascularization, compared with the
hybrid techniques which consisted of an open surgical procedure followed by an endovascular procedure. A possible explanation for the increased primary patency rates in the control group could be the negative influence of the endovascular procedure in the hybrid technique, which can cause intimal hyperplasia, the main cause of stent restenosis or artery restenosis at the level of the previous balloon angioplasty. The intimal hyperplasia is less important when drug-eluting stents and angioplasty balloons are used, as demonstrated by the present literature (12,13).

Although endovascular techniques are continuously gaining ground, our study results allows us to recommend the classical open surgical techniques for patients with MAOD in those hospitals which don't have the necessary endovascular equipment used for the hybrid techniques studied in this paper.

A mortality of 5% in the control group versus a zero mortality in the study group demonstrates the minimally invasive character and superiority of the hybrid techniques for the elderly patients with high operative risk. It is our conclusion that for this category of patients the recommended surgical treatment is the hybrid approach, as long as the hospital benefits from the necessary equipment. Considering our results, we favour the hybrid surgical techniques in patients with MAOD, due to their less invasive character when compared with the classical open surgical procedures used to treat the same patients. Our study reveals some positive aspects of the simultaneous hybrid approach: the possibility of operating under local or epidural anaesthesia; the
reduction in the number of laparatomies necessary to treat aorto-iliac lesions by using limited surgical exposure of the inquinal area and endovascular approach of distant arteries; the endovascular techniques are easier to do if surgical exposure of the CFA is accomplished, which also yields a therapeutic value at times; simultaneous treatment of lesions with different localisations, and thus using less complex surgical interventions and bypass lengths, this having been proven also by other studies (4, 14).

Despite the benefits of the hybrid revascularization techniques, they haven't been validated up-to-date in comparative randomized studies, due to the fact that the clinical practice has been based on the experience of a single centre, and the medical literature doesn't have enough proof of the superiority of the hybrid techniques compared with endovascular or classical open surgical techniques.

The particularity of the study was that all hybrid procedures were done by a team composed only of vascular surgeons, specialized both in classical open surgery and endovascular surgery, as opposed to studies published in the international literature where the simultaneous hybrid techniques were accomplished by a team formed by both vascular surgeons and interventional radiologists (4).

STUDY LIMITATIONS
The non-randomisation of the study and usage of consecutive series of patients.
1. The retrospective nature of both study groups from year 2010, although the follow-up protocol was
identical to the one used for the prospective study groups.

2. The varied anterior procedures the patients had before the study period had a negative influence on the primary patency of the study group.

3. The heterogeneity of the study group: patients included had different types of MAOD, at different levels and had various revascularization procedures.

4. The absence of follow-up from a hemodynamic point of view (measuring ABIs) for all patients included in the study.

5. Because of having to finish the doctoral thesis before a certain date, long-term patient follow-up wasn't feasible.

POSSIBLE CONTRIBUTIONS OF THIS DOCTORAL THESIS

The Cardiovascular Institute from Iasi houses the only hybrid operating theatre in the country. The originality of the study is the modern surgical approach on patients with MAOD. The hybrid revascularization technique is in its early stages in our country, Romanian vascular surgeons having limited experience with this surgical approach for patients with PAD, due to the need to undergo specialized training in other countries. The method we proposed and studied during our research could be used routinely in future surgical practice in those hospitals that have the necessary equipment. We hope that our study will help implement the hybrid revascularization techniques into current surgical practice, so that the patient with MAOD will benefit as soon as possible from the best surgical approach which is
the least invasive, has minimal peri- and postoperative risks and the best long-term results.

CONCLUSIONS
1. Implementing the hybrid techniques into current vascular surgery practice and the possibility of doing them in hybrid operating theaters offers treatment options to the patients with high operating risk.
2. Endoluminal revascularization can be viewed as an useful adjunct to the classical surgical techniques.
3. Technical success and short and medium term results of primary patency and limb salvage rates for hybrid techniques are the same or better than conventional endovascular and open surgical procedures.
4. Hybrid techniques are a feasible and efficient treatment option for patients with MAOD, with favorable short and medium term patency and limb salvage rates, irrespective of the pre-procedural clinical disease stage.
5. Common femoral artery endarterectomy plays a vital role in accomplishing the hybrid procedures.
6. Classical vascular reconstructions will continue to play a significant role in the management of patients with PAD, despite the technical progress accomplished with endovascular procedures.
7. Endovascular techniques associated with classical open surgery make it possible to treat multilevel occlusive lesions simultaneously, thus avoiding more invasive surgical procedures and its inherent risks.
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