

Female gender may be a predictor of poor clinical outcome after infrainguinal bypass surgery in patients with foot gangrene

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Abstract:

Introduction: The effect of gender on the outcome of peripheral bypass surgery remains unclear. Aim of the study was to assess the impact of gender on clinical outcome of infrainguinal bypass procedures, in patients suffering by limb ischemia with foot gangrene.

Patients and methods: A retrospective study was designed. All consecutive patients who suffered by severe lower limb ischemia with foot necrosis (Rutherford 5 or 6), and had an infrainguinal bypass surgery with a venous or synthetic graft in a 3-year period were included in the study. We examined the effect of gender on early graft failure, 12-month graft overall (secondary) patency, and 36-month amputation-free survival and mortality. To reduce the effect of various factors that could potentially interfere with the results, propensity score matching was additionally applied.

Results: Sixty-seven patients were included (41 males, 26 females). Overall, females presented an increased risk of early graft failure (38.5% vs. 14.6%, $p=0.039$). Similarly, the 12-month patency appeared lower in females (35% vs. 66.3% in male group, $p=0.040$). Mortality and amputation-free survival at 36 months post the procedure were not statistically different between the two groups. In propensity score matched subsamples, the early graft failure was worse in the female group, 39% vs. 6% ($p=0.022$). Similarly, female patients presented inferior results regarding amputation-free survival (32.1% vs. 68.5%, $p=0.034$) at 36 months post the procedure.

Conclusion: Female patients seem to have an increased risk of early graft failure as compared to males, when they have an infrainguinal bypass graft for severe critical limb ischemia with foot tissue loss. Additionally they present worse patency, and potentially amputation free survival rates. Nevertheless, no difference exists with regard their long-term mortality.

Keywords

Peripheral arterial disease, arterial occlusive disease, blood vessel prosthesis, lower limb bypass, foot gangrene, gender

INTRODUCTION

Despite the advances of endovascular techniques, infrainguinal bypass procedures remain the cornerstone of lower limb revascularization. Although technical factors are known to be critical for the success of surgical revascularization, the effect of patient's gender has been controversial¹. Female gender has been proposed as a potential predictor of poor results especially in terms of postoperative mobility², and perioperative complications including mortality and amputations³. In the PREVENT III trial, female gender was found to be associated with an increased rate of bypass loss⁴. However, a nationwide study in Taiwan, considered males

to be at risk of future lower extremity amputation⁵. In contrast, from a study that analyzed the infrainguinal arterial revascularization over a 15 years period in more than 1450 procedures, Ballotta et al. concluded that gender did not seem to influence patency, limb salvage, and survival rate⁶. In the BASIL trial, the only one randomized controlled trial comparing open surgical bypass and angioplasty in patients suffering from critical limb ischemia, no effect of gender on outcome was reported⁷.

It is considered that patients with foot sepsis or gangrene, (Rutherford 5 or 6), have an increased need of foot arterial blood flow in order to heal tissue loss areas, as compared to patients with critical limb ischemia without tissue loss⁸. Nevertheless, scarce reports exist regarding the effect of various factors on the outcome of revascularization in this subgroup of critical ischemia patients. Aim of this study was to investigate the effect of gender on clinical outcomes of infrainguinal open revascularization procedures, in patients suffering from severe lower limb ischemia with foot tissue loss or gangrene.

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PATIENTS AND METHODS

A retrospective single-institutional clinical study was undertaken. The study was approved by Ethical Committee of the Attikon Teaching Hospital. All consecutive patients suffering by severe limb ischemia characterized by foot gangrene (Rutherford 5 or 6) and received an infrainguinal open arterial reconstruction within a 3-year period (2011 - 2013) were included. Patients who had a lower limb bypass for any other reason but foot gangrene were excluded from the study (i.e. patients suffering by intermittent claudication or critical limb ischemia without foot tissue loss, or patients with popliteal artery aneurysms that had a femoropopliteal bypass). Similarly, all the patients that were treated only with an angioplasty were excluded from the study. Data were retrieved from the electronic database of the hospital. Whenever data were missing, an additional research of the medical records was performed. Follow-up information were gathered either by patients' medical records of the outpatient clinics or by direct communication with the patients at the time of data collection.

Patients were divided in two groups based on their gender, the female and male groups. Various parameters were recorded as potential risk factors that could affect the outcome of revascularization (Table 1). These parameters included baseline characteristics (age, atherosclerosis predisposing factors), clinical characteristics (size of foot necrosis, urgency of the procedure, primary operation or operation after a failed bypass or a failed angioplasty), and various technical details (graft type, level of proximal and distal anastomosis). Males and females were compared across these potential covariates to assess whether the groups were similar enough and thus a univariate analysis on gender would be meaningful.

Surgical technique and patients' surveillance

All patients had a standard infrainguinal revascularization procedure. In case of existence of a concomitant aortoiliac component of ischemia, this had been dealt either before with an open or endovascular approach, or at the same time with a hybrid approach if this had been considered feasible. The proximal anastomosis was either at the femoral artery (including the superficial femoral artery or the profunda femoris artery) or at the popliteal artery (at a supra- or infra-genicular level). In case of severe stenosis of the inflow artery mostly the common femoral artery (CFA) and/or the profunda femoris artery (PFA), an endarterectomy was performed at the time of the procedure. The distal anastomosis was at a good quality vessel, which had an inline continuation to the plantar arteries (popliteal or any tibial or pedal artery). The graft was mainly a venous graft when a proper vein was available, as seen in the preoperative ultrasound vein-mapping scan. As proper vein was considered the vein with a diameter greater than 3 mm; whenever a single segment vein was not available, two or more pieces of proper veins of lower or upper limbs were sewn together to form a single vein graft. When a vein graft was unavailable a synthetic graft (PTFE), sized 6 to 8 mm on surgeon's preference, was used. Patients who had either a combined vein-PTFE graft or a venous collar at the distal anastomosis of a PTFE graft were considered to have a synthetic graft in the analysis. Debridement of the foot necrosis (including local amputation if necessary) was performed after revascularization, unless the lesion was considered grossly infected and the patient was septic. In the latter situation the de-

bridement was performed prior to the vascularization. After the procedure, all patients received long-term single standard antiplatelet therapy, as well as statin therapy targeting to a level of serum low-density lipoproteins less than 100 mg/dl. Patients who had an infrapopliteal synthetic graft received dual antiplatelet treatment for at least 12 months after the procedure. After bypass, patients entered a strict ultrasound and clinical surveillance program for 12 months.

Patients were advised to visit the outpatient clinic at 1, 6 and 12 months after the procedure, or when they developed a sudden significant deterioration of their condition indicating graft occlusion (acute onset of numbness, coldness or pain on their limb). In the latter situation, if patients had to be hospitalized in another hospital, they were advised to communicate with us and inform us about their situation the soonest possible. Subsequently, they were followed-up annually up to 36 months after the procedure.

Study endpoints

The study endpoints of the study were chosen based on those used in the BASIL trial⁷. The amputation-free-survival was the primary endpoint of the study. Amputation-free-survival was described the situation that the patient was alive with intact limb (without having undergone a major amputation). Early graft failure, graft patency, and patients' survival were the secondary endpoints of the study. As early graft failure was defined the situation where the graft was occluded within the first 30 days after implantation. If a patient with an early graft failure underwent immediately a graft repair and following this the graft remained patent after the 30-day post-operative period, the initial procedure was not considered a failure. Graft patency was considered the secondary patency. Amputation free survival and mortality were calculated at a 36-month interval after the index procedure, while the grafts patency at a 12-month interval, a period when the patients were under the ultrasound surveillance program.

Propensity Score Analysis

To minimize a possible effect of the various baseline characteristics to the outcomes, a further analysis using propensity score matching (PSM) was performed using the "one-to-one matching technique"⁹. PSM allows the analysis of observational non-randomized data, thus mimicking some of the characteristics of a randomized controlled trial⁹. Following PSM, two new female and male groups of equal size were created, both similar regarding the various baseline characteristics. Thus, any difference found regarding outcome could be attributed only on gender and not to any other factor. Then, the two new groups were compared towards the same endpoints as the original groups.

Statistical analysis

Non-parametric descriptive statistics were used for the description of the patients in the two groups (median, range). Life table analysis techniques (Kaplan-Meier and Peto's log-rank test) were used for the assessment of graft patency, limb salvage or amputation rate, patients' survival, and amputation-free-survival. The early graft failure between the two groups was assessed using the Fisher's Exact test. The comparison of the different baseline characteristics between the two groups was performed using parametric or non-parametric techniques (Unpaired t-test, Fisher's Exact test). Logistic

regression analysis, stepwise method, was used for the calculation of the propensity scores. The level of statistical significance of 0.05 (two-sided) was used throughout. The Stats-Direct software package was used for the statistical analysis.

RESULTS

During the 3-year study period, 209 patients were treated for various degrees of lower limb ischemia. One hundred eight patients had an endovascular treatment, while 101 had a surgical bypass procedure. Among the patients who underwent a surgical bypass, 67 suffered by severe ischemia with foot tissue loss (Rutherford 5 or 6), these being our study group. Forty-one patients were males (male group, 61%), and 26 females (female group, 39%).

Comparison of the two original groups

The two original groups were not similar regarding specific baseline characteristics (Table 1). The median age of the patients was 69 years (range 32 to 87), similar in both groups (69.5 in the female and 68.7 in the male group, $p=0.61$). However, the portion of patients aged above 75 years was lower in females (19% vs. 32%, $p=0.035$). The two groups did not appear to differ significantly in chronic renal failure needing dialysis (4% in female, 15% in male group, $p=0.159$), or diabe-

tes mellitus (58% in female and 66% in male group). However, men tended to be current smokers more often compared to women (88% vs. 65%, respectively, $p=0.028$). Regarding the various clinical details, female and male groups were not different in the extent of foot necrosis ($p=0.245$) or the urgency of the procedure ($p=0.431$). As it regards the technical details, female patients needed more often a PTFE graft due to unavailability of a vein (50% vs. 27%, $p=0.054$). Additionally, the two groups were similar regarding the locations of proximal and distal anastomoses. Finally, there was no difference between the number of forefoot amputations (digits or transmetatarsal) in the two groups (16/26, 61.5% in females vs. 28/41, 68.3% in males, $p=0.61$).

Primary and secondary endpoints

At 36-month post the procedure the amputation-free survival was 30.4% in female and 52.9% in male patients ($p=0.107$) (Figure 1). The early graft failure was superior in the female group (38.5% vs. 14.6% in male group, $p=0.039$) (Figure 2). The 12-month patency-rate was 35.0% in the female group, as compared to 66.3% in the male group ($p=0.040$) (Figure 3). Finally, no difference was found in overall survival at 36 months post the procedure (63.9% in females and 69.4% in males, $p=0.541$) (Figure 4).

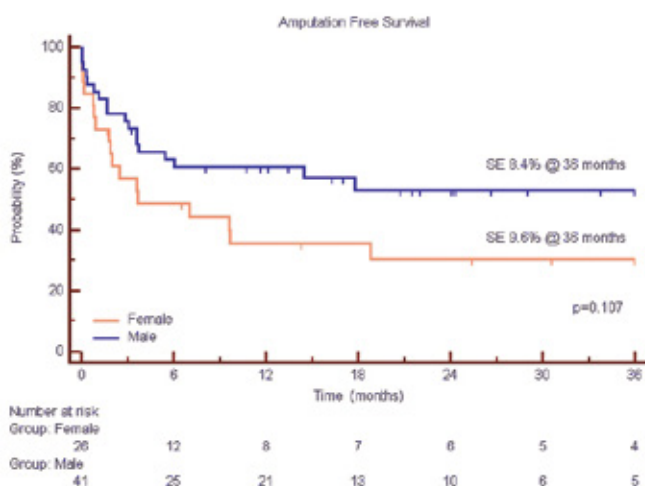


Figure 1. Amputation-free survival (@ 36 months) in the total cohort of patients.

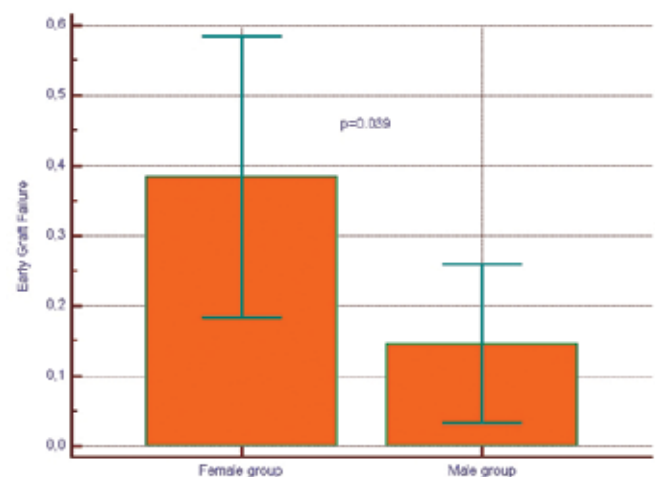


Figure 2. Early graft failure rates in the two groups

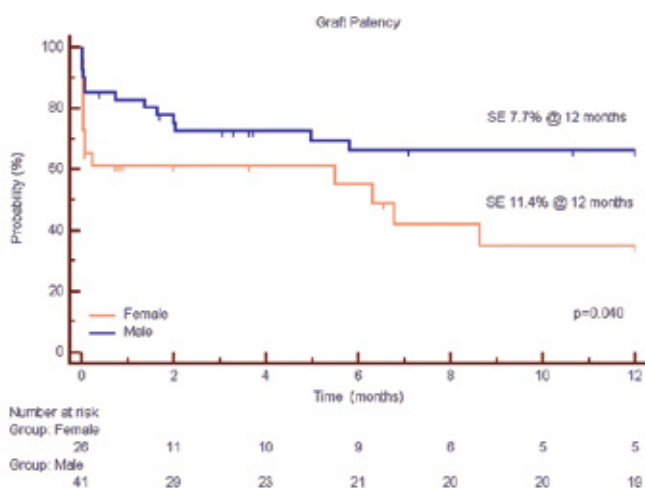


Figure 3. Graft patency (@ 12 months) in the total cohort of patients

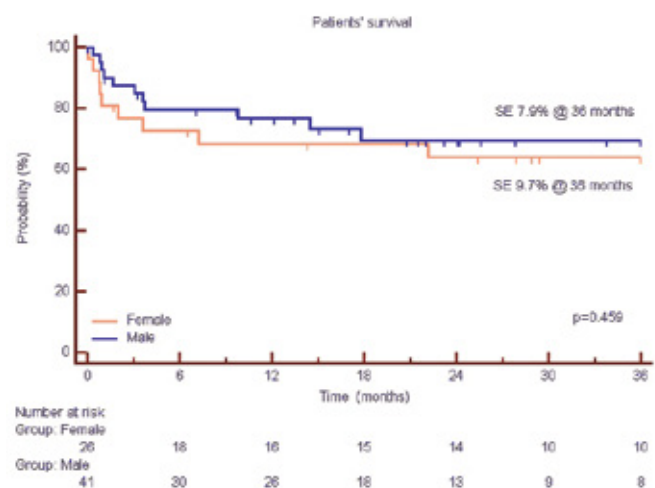


Figure 4. Patients' survival (@ 36 months) in the total cohort of patients

Propensity score analysis

Following propensity score matching, 36 patients were selected from the original group, 18 males and 18 females. These two new groups, similar regarding the various baseline characteristics (Table 1), were examined towards the originally predefined endpoints (Table 2). The 36-month amputa-

tion-free-survival was found worse in the female group (32.1% versus 68.5% in males, $p=0.034$). Early graft failure was worse in the female group, 38.9% vs. 5.6% ($p=0.022$). Similarly, the 12-month graft patency was 31.4% in females vs. 75.1% in males ($p=0.028$). No difference was found in the 36-month patients' survival (63.6% vs. 72.3%, $p=0.525$).

	Overall series			Propensity score-matched pairs		
	Female group 26 patients	Male group 41 patients	<i>p-value</i> (two-sided)	Female group 18 patients	Male group 18 patients	<i>p-value</i> (two-sided)
Age						
Median (range)	69.5 (48-87)	68.7 (32-87)	0.611	67.3 (48-87)	59.8 (32-75)	0.116
Age > 75 years	6 (19%)	20 (32%)	0.035	1 (6%)	0 (0%)	0.311
History of active smoking	17 (65%)	36 (88%)	0.028	14 (78%)	16 (89%)	0.371
Chronic Renal Failure (end-stage)	1 (4%)	6 (15%)	0.159	1 (6%)	0 (0%)	0.311
Diabetes Mellitus	15 (58%)	27 (66%)	0.501	11 (61%)	12 (67%)	0.729
Size of foot necrosis						
Digital	20 (77%)	26 (63%)	0.245	14 (78%)	14 (78%)	>0.999
Extensive	6 (23%)	15 (37%)		4 (22%)	4 (22%)	
Urgency of procedure						
Elective	21 (81%)	36 (88%)	0.431	16 (89%)	15 (83%)	0.630
Urgent	5 (19%)	5 (12%)		2 (11%)	3 (17%)	
Type of procedure						
Primary bypass	16 (61%)	23 (56%)	0.660	12 (67%)	13 (72%)	0.717
Bypass after previous angioplasty	10 (39%)	18 (44%)		6 (33%)	5 (28%)	
Type of graft						
Vein	13 (50%)	30 (73%)	0.054	13 (72%)	14 (78%)	0.700
PTFE	13 (50%)	11 (27%)		5 (28%)	4 (22%)	
Proximal anastomosis						
Femoral	22 (85%)	38 (93%)	0.293	14 (78%)	16 (89%)	0.371
Popliteal	4 (15%)	3 (7%)		4 (22%)	2 (11%)	
Distal anastomosis I						
Popliteal	12 (46%)	25 (61%)	0.234	6 (33%)	8 (44%)	0.494
Distal	14 (54%)	16 (39%)		12 (67%)	10 (56%)	
Distal anastomosis II						
Supragenicular	6 (23%)	6 (15%)	0.380	3 (17%)	2 (11%)	0.630
Infragenicular	20 (77%)	35 (85%)		15 (83%)	16 (89%)	
Minor amputations	16 (61%)	28 (68%)	0.606	11 (61%)	12 (67%)	>0.999
Propensity score (median)	0.322	0.691	<0.0001	0.691	0.691	0.676

Propensity Score Analysis			
	Female (N=18)	Male (N=18)	<i>p-value</i>
Amputation Free Survival @ 36 months	(%) 32.1	68.5	0.034
Early Graft Failure	(%) 38.9	5.6	0.022
Graft Patency @ 12 months	(%) 31.4	75.1	0.028
Patients Survival @ 36 months	(%) 63.6	72.3	0.525

DISCUSSION

In this retrospective analysis of consecutive lower limb infrainguinal bypasses performed in patients with severe limb ischemia with foot gangrene, females seemed to experience superior early graft failure as compared to male patients and similarly, short-term (12-month) graft patency. Additionally, the long-term (36-month) amputation-free survival although tends to be worse than in male patients although the difference is not significant. Similar results were found also in propensity score matched groups. On the contrary, long-term (36-month) mortality seemed to be similar in male and female patients.

The increased early graft failure among female patients after an infrainguinal bypass seems to be a consistent finding in the literature^{10 11}. On an analysis of the possible factors that might be related to an early graft failure after infrainguinal bypass, our group found that female gender is one of them, the rest factors being a previous ipsilateral angioplasty, a redo procedure and a distal bypass¹². All these factors were included as the components of FARP2 score used for the prediction of early graft failure of infrainguinal bypass surgery¹². Of interest is that Sahin and El¹³ validated externally this model, this indicating that in their group also female gender was an independent predictor of early graft failure. The smaller size of lower limb arteries in females has been proposed as a possible cause. Women with peripheral artery disease seem have smaller tibial arteries, which may be perceived as a factor that increases the technical difficulty associated with lower limb revascularization¹⁴.

Several studies have shown inferior patency of a surgical lower extremity revascularization procedure in women^{15 16}. Green et al¹⁷ found that the 5-year cumulative patency rates were 69.1% for men and 45% for women. Nguyen et al⁴ observed that black women have the greatest disadvantages in terms of a higher extremity saphenous vein bypass loss at 1 year. Although these reports suggest an inferior patency in the female population, some studies have not identified significant gender effects on patency among patients treated with endovascular procedures, surgical bypass, or hybrid techniques¹⁸. In our study, female patients present worse patency rates as compared to male patients at a statistically significant level. We attribute this result to the increased early graft failure in females rather than on a continuous effect later on.

The worse patency rates in female population with PAD, does not seem to translate always into differences in limb salvage¹⁹. This seemed to be the situation in our cohort where the amputation free survival, although lower in the female group, did not reach a statistical significance. If this is not real, then the small number of patients in our cohort may explain this finding. The overall amputation-free-survival (AFS) in the total group of our patients was 44.4%, which is lower than the results shown in the BASIL trial⁷ at the same interval (AFS about 50%). However, the BASIL trial cohort cannot be considered identical to our group. BASIL trial included patients with critical limb ischemia, while our study was limited in patients that had foot gangrene, excluding patients suffering by rest pain without tissue loss. Limb salvage has not been widely related to gender. Most authors agree that gender has no effect on limb salvage^{1 20}. Of note, Watson et al. reported a worse limb salvage rate in women (74% vs. 83%) at 12 months after

femorodistal bypass²¹. Similarly, Nguyen et al, after proper patients matching using propensity score analysis from the PREVENT III trial, found that black women had an increased amputation rate at one year compared with black men⁴. On the contrary, Malmstedt et al noted that male diabetic patients were at relatively higher risk of limb amputation than females²².

Various factors have been considered as potential predictors of the infrainguinal arterial revascularization outcome. The type of antithrombotic treatment is one of them. All our patients received single antiplatelet treatment (Clopidogrel 75 mg od or Aspirin 100 mg od), except patients with infrapopliteal synthetic grafts who received double antiplatelet treatment. A combination of antiplatelet and anticoagulant was not used. Data in the literature indicate a possible beneficial effect of vitamin K antagonists in the venous²³ or prosthetic²⁴ lower limbs bypass grafts. On the other hand, dual antiplatelet treatment is considered to improve the outcome of infragenicular synthetic bypass grafts²⁵. A potential positive effect of direct oral anticoagulant on this population has been documented²⁶, however randomized controlled studies are still ongoing²⁷. Furthermore, smoking has been considered to negatively affect the outcome of an infrainguinal bypass²⁸. In our group, smoking was not examined as a possible factor of graft occlusion. Although more active smokers were in the male group, they had a better outcome. This might be explained by the fact that males had more vein grafts than females. Finally, the type of graft (vein or synthetic) definitely has an impact in infrainguinal revascularization. Without doubt, vein graft and mainly a unique saphenous vein of good size and quality is the best graft that offers both instant effectiveness and longevity²⁹. Of note was the finding that our female group had more synthetic grafts as compared to males. This was also described recently by Arhuidese et al³⁰ in a population of hemodialysis patients suffering by peripheral artery disease who had a lower extremity bypass surgery.

The association between gender and patient' survival after lower extremity revascularization for peripheral artery disease is complex and appears to be influenced by differences in age, comorbidities, and procedural factors. Controversial evidence exists in the literature. Magnant et al reported similar perioperative mortality rates among men and women undergoing infrainguinal bypass for lower extremity ischemia, but an increased mortality in diabetic women³¹. Egorova et al.³² also noted an increased hospital mortality rate in women with peripheral artery disease. On the contrary, in their retrospective study of lower extremity saphenous vein bypasses, Belkin et al.³³ reported lower perioperative mortality in women. Hultgren et al.³⁴ identified an interaction between female gender and age as predictors of perioperative mortality among patients undergoing surgical or endovascular procedures for lower extremity ischemia. In their multivariate analysis, female gender was associated with improved long-term survival. Others have reported no gender effect on survival after treatment with endovascular³⁵ or open surgical techniques (4), as also seen in our study too.

The study suffers of various limitations. This is a single-institutional study with a small number of patients and therefore it is only powered to detect large differences between the two groups. In order to reduce the heterogeneity due to the diversity of the baseline characteristics (different levels of

distal anastomosis, different types of grafts, etc), propensity score matching was used so as to create comparable groups. Nevertheless hidden bias through unmeasured confounding may still remain. A subgroup analysis on specific sub-populations might be feasible only in large scale, possibly multicenter trials. Additionally, due to the small number of patients, the values of standard errors of the survival analysis exceeded the level of 10% in some instances. This confirms the necessity to assess the results of the study with caution. Another weakness of the study has to do with the results per se. All examined parameters, mainly the early graft failure and patency rates, are inferior to what is reported in the literature. There are two reasons for that. First, our cohort consisted only of Rutherford 5 and 6 patients where one can expect worse clinical outcome as opposed to those patients who do not suffer by that severe limb ischemia. This has been seen in our hands too. Within those of our patients who had a surgical bypass without a foot necrosis, the early graft failure was only 4.8% (unpublished data). As opposed to the current study, most results in the literature refer to mixed groups of peripheral vascular disease patients (including claudicants, and / or those suffering by critical limb ischemia but without foot necrosis). Secondly, today, as the majority of cases are treated endovascularly leaving only the most challenging cases to be treated with open procedures, surgical bypass could be expected to have worse results compared to the results of previous studies when the studied groups contained both “easy” and “difficult” cases together. Finally, no specific information regarding the quality of runoff is available. However, the two groups seem to have similar patterns of disease as this can be seen by the levels of proximal and distal anastomoses, which were similar in the two groups (Table 1).

CONCLUSIONS

Gender seems to may have a significant effect on early graft failure after open infainguinal revascularization procedures in patients with foot necrosis due to severe limb ischemia. Female patients present higher early graft failure and subsequently, they suffer a worse short-term overall patency as well as a potential worse long-term limb salvage and amputation-free survival as compared to males. This difference seems to be attributed to the fundamental difference of early graft failure between males and females, rather than on a continuous effect later on. The improvement of instant technical success and the decrease of early graft failure in female patients with peripheral vascular disease will possibly refine the long-term clinical results of lower limbs bypass surgery, offering comparable long-term clinical results as in male patients.

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