

Effect of drug-coated balloons versus bare-metal stents on endothelial function in patients with severe lower limb peripheral artery disease

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Abstract

Background: Research shows impaired endothelial function in patients with vascular diseases and improved endothelial function following revascularization and medical treatment. There is, however, a dearth of data on the effects of different endovascular therapeutic strategies on endothelial function. We sought to compare the effects of two endovascular strategies of drug-coated balloons versus stenting on endothelial function.

Methods: The reactive hyperemia index, the ankle-brachial index, and the toe-brachial index were measured in patients undergoing endovascular revascularization preprocedurally and on the 90th postprocedural day. After adjusting for baseline characteristics, reactive hyperemia index were compared between the two groups at baseline and at 90 days.

Results: Between January 2018 and March 2019, 86 patients were prospectively included in a non-randomized manner. Drug-coated ballooning alone was carried out on 46 patients, and bailout stenting after plain balloon angioplasty was performed on the remaining 40 patients. The post-revascularization reactive hyperemia index exhibited a significant rise in both groups (1.58 ± 0.21 vs. 1.43 ± 0.20 ; $P = 0.0001$). There was no difference in the postprocedural reactive hyperemia index between the two treatment groups. Additionally, the follow-up reactive hyperemia index showed no significant change compared with the postprocedural reactive hyperemia index (1.58 ± 0.23 vs. 1.57 ± 0.22). The results of subgroup analysis between a group of clinically high-risk patients and a group of patients with complex lesions were similar to the aforementioned results.

Conclusions: The reactive hyperemia index was significantly improved by endovascular therapy in our study population. However, no difference was observed between drug-coated ballooning and bare-metal stenting, which highlights the effects of vessel patency on endothelial function.

Keywords

Peripheral vascular disease, endovascular therapy, endothelial function, reactive hyperemia index

Introduction

Endothelial function is an indicator of the global health of the vascular system. It has been shown that patients with severe atherosclerosis, including those with coronary artery disease and those with peripheral artery disease, have endothelial dysfunction.^{1–3} Endothelial function in patients with severe atherosclerotic disease is amenable to medical treatment aimed at reducing the risk factors and revascularization.⁴ However, only a few studies have evaluated improvement in endothelial

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function after endovascular revascularization on lower limb arterial disease, and there are no studies on the assessment of the different effects of various endovascular approaches such as drug-coated ballooning (DCB) and stenting on endothelial function in patients with severe peripheral artery disease.^{5,6} Accordingly, in the present study, we aimed to compare DCB-only angioplasty and stenting in terms of their effects on endothelial function as assessed with the reactive hyperemia index (RHI) in patients with severe peripheral artery disease and claudication.

Methods

This is a prospective non-randomized study performed between January 2018 and March 2019 on patients referred for lower limb revascularization (Figure 1). All patients with symptomatic limb ischemia (Rutherford classification of 2–5) were included. PAD and CLI were confirmed using an ankle-brachial index (ABI) of less than 0.9 or a toe-brachial index (TBI) of below 0.7. Importantly, patients with Rutherford class 2 and 3 (i.e. without wound or rest pain) were only considered for endovascular revascularization if their symptoms persisted for at least three months with full medical therapy including cilostazol, antiplatelet therapy, and statins, along with cigarette smoking cessation and a structured exercise program according to our IRAN critical limb ischemia registry predefined protocol.⁷

Patients were excluded if they had thrombotic lesions or lesions confined only to below-the-knee (BTK) segments given the controversies regarding the use of DCB or stenting in BTK lesions. Also excluded were patients in whom the endothelial function of the brachial and radial arteries was affected access via the upper limb.

The patients' clinical and procedural characteristics, along with the results of their physiological assessment and the RHI (preprocedurally, postprocedurally, and during a 90-day follow-up period), were recorded.

Ultrasound evaluation of the treated vessel was performed to investigate vessel patency within follow-up period. Vessel patency was defined as peak systolic velocity ratio ≥ 2.5 cm/s without need for target lesion revascularization.⁸ The study protocol was approved by the Institutional Review Board, and written informed consent was obtained from all the participants before enrolment.

Endovascular approach

DCB was applied in the cases with femoropopliteal lesions if there was no flow-limiting dissection or more than 30% recoil. Bailout stenting was applied only if there was significant recoil or flow-limiting

dissection after plain balloon angioplasty. Stenting is the preferred strategy in our center for aortoiliac lesions. Complex lesions in the present study were defined as lesions with at least one of the following criteria: moderate-to-severe calcification, total occlusion, or length more than 150 mm. The Peripheral Arterial Calcium Scoring System was used to determine the severity of calcification and was determined by fluoroscopy,⁹ in which grades 0 and 1 were considered as minimal calcification, grade 2 was mild, grade 3 was moderate, and grade 4 was considered as severe calcification. Additionally, patients with diabetes mellitus and chronic kidney disease (CKD) were categorized as clinically high risk. CKD was defined as persistent estimated glomerular filtration rate (eGFR) less than 60 ml/min/1.73 m² for more than three months.

Definition and measurement of the RHI

Endothelial function tests are based on the ability of the endothelium-derived vasodilation response to ischemic tissue. Only a few tests are available to assess endothelial function quantitatively; they include the RHI or the Framingham RHI, peripheral artery tonometry (derived from the RHI), and flow-mediated dilation.¹⁰ Patients' diurnal changes, habits, diet, and background diseases can affect all of these tests. In the present study, the RHI was chosen for the assessment of endothelial function because not only it is simpler and cheaper but also it obviates the need for concomitant imaging. The operators who performed the test were trained physicians with at least two years of experience in vascular and arterial physiology tests.

The RHI was measured using PeriFlux 6000 Combined (Perimed-Instruments, Sweden). Before the test, blood pressure and heart rate were recorded three times while the patients were relaxed in the supine position, and the average of these recorded measurements was considered to be the baseline. The digital pulse amplitude of both upper arms was recorded continuously for 5 min before and after cuff inflation. Cuff inflation to induce hyperemia was performed using a standard-sized cuff. The exam was applied on one arm, and the control arm was not proceed the ischemia induction cuff inflation. The duration of cuff inflation was 5 min, and the inflation pressure was 60 mm Hg above the baseline systolic blood pressure. The RHI was calculated from the pulse wave amplitude (PWA) derived before and after the inflation of both arms through the following formula (Figure 2)

$$RHI = \frac{\frac{A}{B}}{\frac{C}{D}}$$

where A is the PWA post inflation in the arm with the inflated cuff, B is the PWA pre inflation in the arm with the inflated cuff, C is the PWA post inflation in the control arm, and D is the PWA pre inflation in the control arm.

All the measurements were performed at room temperature (21–24°C), and the patients were maintained in the supine position without any movement during the test.

Statistical analysis

The statistical analyses were conducted using IBM SPSS Statistics 22 for Windows (IBM Inc, Armonk, NY). The fitness of the interval data to a normal distribution was assessed using the one-sample Kolmogorov–Smirnov test. The data were described as the mean \pm standard deviation for the interval variables and the count (%) for the categorical variables. Repeated measure analysis of variance (ANOVA) models were applied to assess the over-time changes in the interval variables both within and between the study groups. Additionally, the groups were compared using the independent t -test and the Pearson χ^2 test. The correlations between the interval variables were assessed using the Pearson correlation coefficient (r). A P value of equal to or less than 0.05 was considered statistically significant.

Results

A total of 108 cases were included during the study enrollment period. Twenty-two patients were excluded from the study (Figure 1). The baseline demographic and clinical characteristic data of the remaining 86 patients are summarized in Table 1. Sixty-two (72.1%) patients were categorized as the clinically high-risk patients. Also, in 79 (91.2%) patients, the angiographic appearance of the obstruction in the culprit vessel was complex.

DCB-only angioplasty was performed on 46 and stenting on 40 patients. The baseline angiographic specifications of the study population are depicted in Table 2. Endovascular revascularization was successful in all included patients, and the postprocedural ABI and TBI increased significantly (preprocedural ABI vs. postprocedural ABI: 0.55 ± 0.16 vs. 0.94 ± 0.10 and preprocedural TBI vs. postprocedural TBI: 0.4 ± 0.16 vs. 0.67 ± 0.11 ; $P < 0.0001$). Accordingly, the RHI after endovascular revascularization was significantly improved in all the patients irrespective of the treatment modality (1.58 ± 0.21 vs. 1.43 ± 0.20 ; $P = 0.0001$) (Figure 3). This result persisted in each treatment group, and the RHI significantly rose after revascularization when it was analyzed in the two

divided treatment groups (1.53 ± 0.20 vs. 1.4 ± 0.19 ; $P < 0.001$ in the DCB group and 1.62 ± 0.25 vs. 1.53 ± 0.20 ; $P < 0.001$ in the stent group). Nonetheless, there was no statistical difference in the pre- and postprocedural RHI between the two treatment groups (Figure 4).

Sixty-five (75.5%) patients underwent follow-up RHI measurements within 90 days after endovascular revascularization. The follow-up RHI was not significantly different from the postprocedural RHI (1.58 ± 0.23 vs. 1.57 ± 0.22) (Figure 3). All these patients were free of ischemic symptoms, and noninvasive imaging showed the patency of the treated vessel. The measurement of the ABI and the TBI at follow-up showed no significant changes by comparison with the postprocedural measurements (mean follow-up ABI: 0.95 ± 0.11 and mean follow-up TBI: 0.67 ± 0.11 vs. mean postprocedural ABI: 0.94 ± 0.16 and mean postprocedural TBI: 0.67 ± 0.11).

In the subgroup analysis, the RHI increased significantly after revascularization among the clinically high-risk population (1.44 ± 0.21 – 1.61 ± 0.22 ; $P < 0.001$) and the patients with complex lesions (1.43 ± 0.20 – 1.58 ± 0.21 ; $P = 0.005$). Nevertheless, there were no differences in the postprocedural and follow-up RHI between the DCB and stent groups in our two subgroups. Further, the Rutherford class five patients (i.e. with wounds) had the same pattern of increment in the RHI after revascularization like other mentioned subgroups and also the total studied population. In the stent group, the RHI was 1.57 ± 0.26 before revascularization and 1.82 ± 0.24 after revascularization ($P = 0.02$); while in the DCB group, it was 1.40 ± 0.22 prior to revascularization and 1.57 ± 0.21 following revascularization ($P = 0.02$). Wound healing occurred in all the patients four months after revascularization.

In our analysis, the ABI and the RHI did not have any meaningful correlation. Of note, the comparison was still not significant even when cases with simultaneous BTK involvement were excluded from the analysis. In contrast, the preprocedural, postprocedural, and follow-up TBI had a significant correlation with the preprocedural, postprocedural, and follow-up RHI, respectively ($r = 0.20$, $P = 0.057$; $r = 0.37$, $P = 0.001$; and $r = 0.45$, $P = 0.001$, respectively). In addition, no meaningful correlation was observed between the RHI and the clinical characteristics (glucose and creatinine blood levels) or the procedural factors (lesion length, total stent length, and stent overlap).

Discussion

In the present study, we aimed to compare the effects of two different treatment modalities of DCB-only

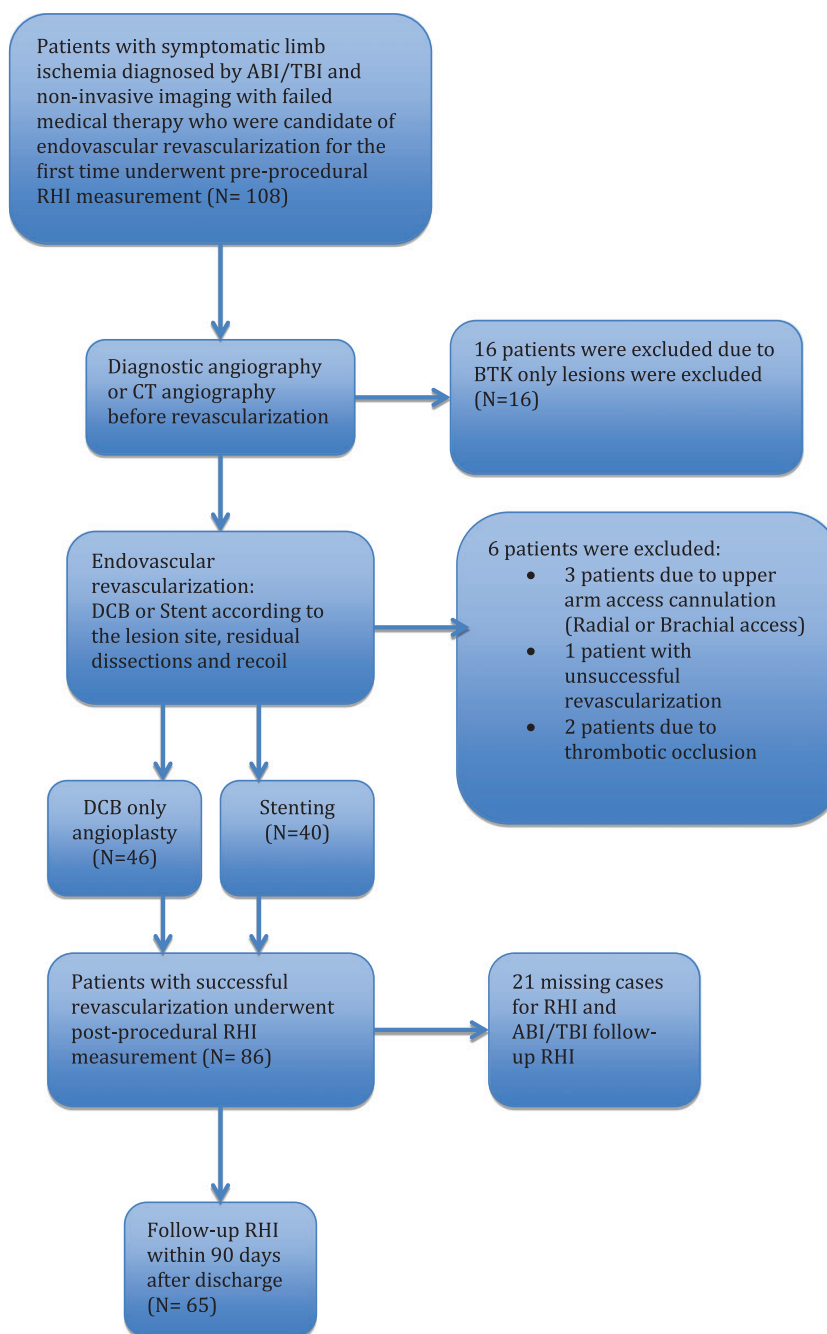


Figure 1. Flow diagram, illustrating the study design.

CT: computed tomography; ABI: ankle-brachial index; TBI: toe-brachial index; BTK: below the knee; DCB: drug-coated ballooning; RHI: reactive hyperemia index.

angioplasty and bare-metal stenting on endothelial function (measured with the RHI). We showed that the RHI rose significantly after endovascular revascularization by DCB and stenting equally. It is worthy to note that the RHI exhibited no change 90 days after revascularization in comparison with the postprocedural measurement. These results persisted in both groups of high-risk and complex lesions. We found no correlation between the ABI or

procedural characteristics and the RHI, whereas we observed a significant correlation between the TBI and the RHI.

The endothelial surface has multiple functions affected by many mediators that both secret and act on the endothelial surface. One of the most important contributors to the regulation of these mediators is the blood flow. It has been shown that low flow state and altered flow in the arterial system promote

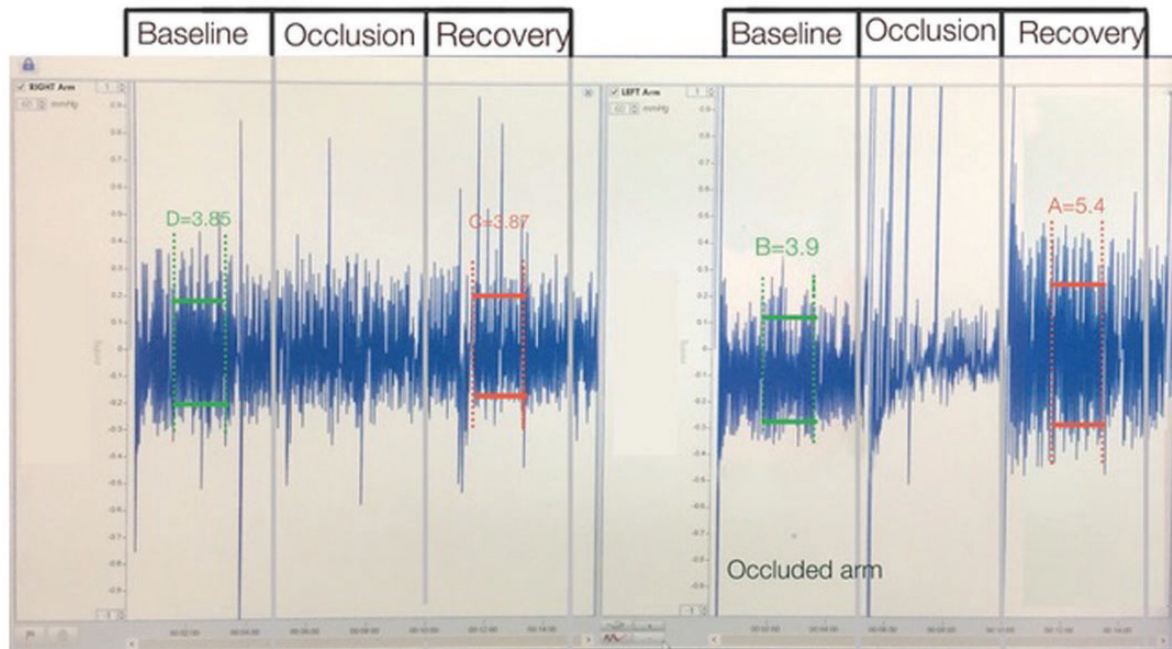


Figure 2. Example of the RHI calculation method. The left arm was occluded with an appropriately sized cuff. Before and 5 min after occlusion, the pulse amplitude was measured in both occluded and controlled arms: (a) PWA post inflation in the arm with the inflated cuff; (b) PWA pre inflation in the arm with the inflated cuff; (c) PWA post inflation in the control arm; (d) PWA pre inflation in the control arm. A, B, C, and D were used for the RHI calculation (see the text).
RHI: reactive hyperemia index; PWA: pulse wave amplitude.

Table 1. Demographic and clinical characteristics of the study population.

Variable/group	Stent group	Balloon group	P-value
Number of recruited patients	39	47	N/A
Age (mean)	63.5 ± 9.03	66 ± 7.75	0.29
Gender	34 (87%) male	42 (89.3%) male	
Diabetes mellitus	27 (69.2%)	31 (65.9%)	0.88
Hypertension	26 (66.6%)	29 (61.7%)	0.82
CAD	21 (53.8%)	22 (46.8%)	0.70
CKD	3 (7.7%)	12 (25.5%)	0.06
Clinically high risk patients	30 (77%)	43 (91%)	0.06
Cigarette smoking	23 (58.9%)	20 (42.5%)	0.38
Rutherford class			
2	1 (2.5%)	2 (4.2%)	0.85
3	23 (59%)	23 (48.9%)	0.35
4	6 (15.4%)	7 (14.9%)	0.94
5	9 (23.1%)	15 (31.9%)	0.82
Claudication	38 (97.4%)	43 (91.5%)	0.77
Wound	9 (23.1%)	15 (31.9%)	0.49
Creatinine level (mean)	1.07 ± 0.32	1.3 ± 0.74	0.06
LDL level (mean)	74.36 ± 25.25	86.36 ± 30.22	0.73
LDL level > 100	7 (17.9%)	9 (19.1%)	0.90

CAD: coronary artery disease; CKD: chronic kidney disease; LDL: low-density lipoprotein.

atherosclerosis.¹¹ The retrograde shear rate, which is increased with arterial occlusion, not only enhances the production and expression of endothelin 1, adhesion molecules, and reactive oxygen species

(ROS)-producing enzymes but also inhibits endothelial NO synthase expression.^{12,13}

Endothelial function is impaired in atherosclerotic arterial involvements, including peripheral artery

Table 2. Procedural characteristics of the study population.

Variable/group	Stent group	Balloon group
Access site		
Antegrade	20 (51.3%)	37 (78.7%)
Retrograde	26 (66.6%)	11 (23.4%)
Culprit lesion level		
Aortoiliac	3 (7.6%)	0
Isolated iliac	27 (69.2%)	4 (8.5%)
Femoropopliteal	9 (23%)	43 (91.5%)
Simultaneous BTK involvement	2 (5.1%)	10 (21.2%)
Lesion characteristics		
Calcification severity		
None and mild	22 (56.4%)	27 (57.5%)
Moderate to severe	17 (43.6%)	20 (42.5%)
Lesion severity		
Occlusive	32 (82%)	38 (80.9%)
Stenotic	7 (17.9%)	9 (19.1%)
Lesion length (mean)	140.48 ± 107.08	184.17 ± 148.42
Complex lesion	35 (89.7%)	43 (91.4%)
Length of coverage with each technique (median)	100 (IQR; 80)	150 (IQR; 180)

BTK: below the knee.

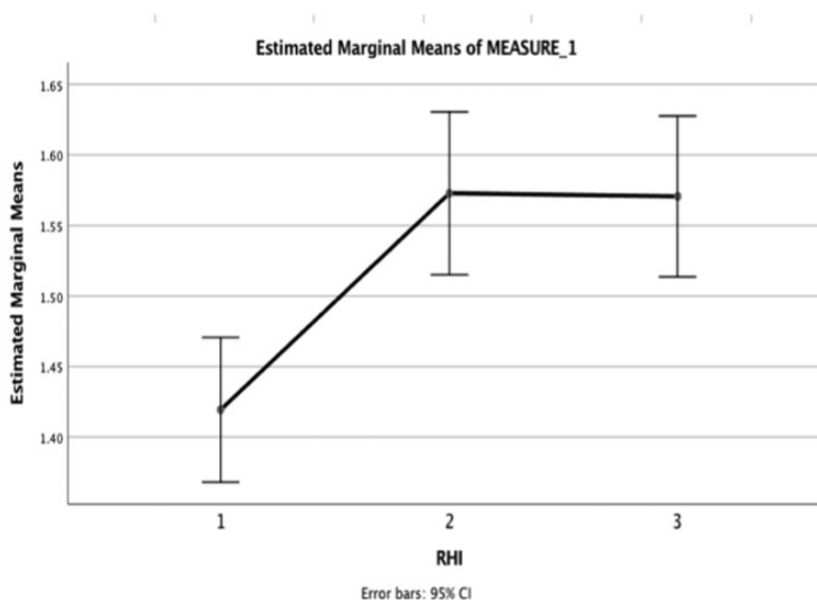


Figure 3. RHI of the patients before (1), after (2), and during the follow-up (3). The calculated RHI was 1.43 ± 0.20 (CI: 1.366–1.469) before revascularization, 1.58 ± 0.21 (CI: 1.514–1.631) after revascularization, and 1.57 ± 0.22 (CI: 1.513–1.627) during the follow-up. There was a significant increase in the RHI after revascularization compared with before revascularization, whereas the RHI did not change during the follow-up significantly.

RHI: reactive hyperemia index.

disease and coronary artery disease. Previous studies have shown that revascularization, either via open surgery or via endovascular intervention, improves endothelial function.^{5,6} Increased production of NO

synthase and decreased levels of ROS are the main contributors to this observation.^{5,6} In addition, claudication and physical activity are amenable to improvement by revascularization. Physical activity augments

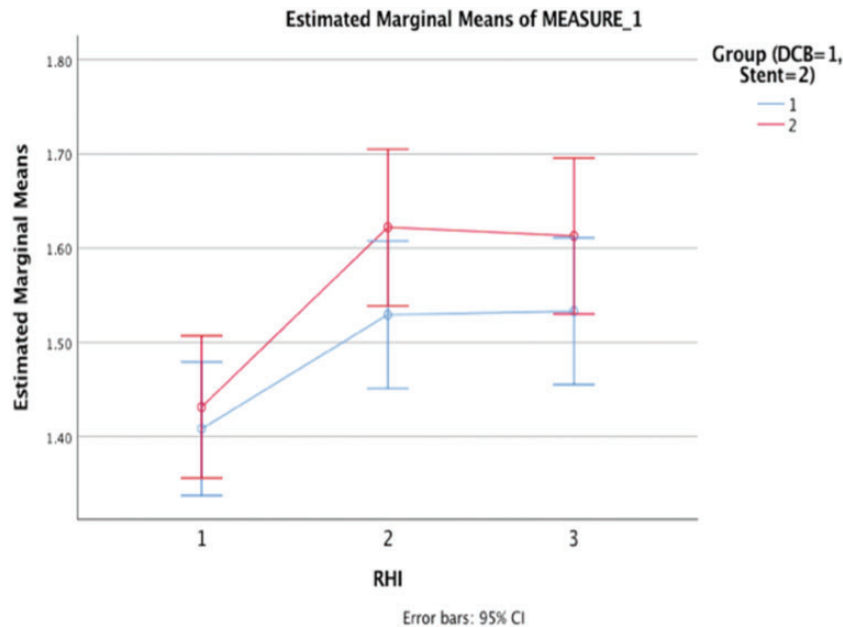


Figure 4. Comparison of the calculated reactive hyperemia index (RHI) before revascularization (1), after revascularization (2), and during the follow-up (3) between the 2 therapeutic groups (DCB-only angioplasty versus stenting). The RHI was lower in the DCB group, but the difference was not statistically significant. RHI: reactive hyperemia index; DCB: drug-coated ballooning.

shear stress, which in turn ameliorates the endothelial-dependent vasodilatation.¹⁴

Kandhai-Ragunath et al.¹⁵ assessed endothelial function using RH-PAT four to six weeks after primary percutaneous coronary intervention and demonstrated that a better endothelial function is anticipated in patients with acute myocardial infarction and patent culprit coronary arteries diagnosed during the intervention. Heinen et al.¹⁶ reported local changes in endothelial function within atherosclerotic occlusions that occurred after balloon angioplasty. They found that while the flow-mediated dilatation (FMD) of the superficial femoral artery decreased in pre and intra stenoses 6 h after balloon angioplasty, it had an increase after 24 h.¹⁶

Husmann et al.⁶ compared the effects of endovascular revascularization and medical therapy on endothelial function measured by FMD and reported that at four weeks, FMD and white blood cell counts exhibited significant improvements after revascularization. Of note, medical therapy failed to confer such improvements, and Husmann et al.⁶ observed no effect on high-sensitivity C-reactive protein (hs-CRP) or fibrinogen levels in both groups. In our study, revascularization successfully improved the RHI in our two treatment modalities.

Theoretically, bare-metal stenting in peripheral vascular lesions covers a large part of the endothelium, thereby aggravating endothelial dysfunction and hyperplasia.¹⁷ In contrast, we observed no difference

between the two modalities in our study; it should, therefore, be borne in mind that the effects of revascularization on the RHI may not have any dependency on the revascularization technique (endovascular or open surgical) and the endovascular approach (the use of DCB or stenting). Those observations may be interpreted as to suggest that distal tissue perfusion and vessel patency are key factors affecting endothelial function as assessed with the RHI. Previous studies on the retrograde shear rate have proven that the rate, which is created by transient arterial occlusion, can decrease endothelial function independently even after the elimination of confounding factors such as neuronal drive as seen in patients with spinal cord injury.¹⁸ Still, the impact of chronic flow disturbances, observed in chronic arterial occlusion, on endothelial function has yet to be investigated. Evidence shows that chronic flow disturbances seen in the reflux phenomenon in the venous system give rise to increased levels of inflammatory markers, which may lead to venous wall disease and insufficiency.¹⁹

Du et al.⁸ investigated the effects of endovascular therapy on endothelial dysfunction. They measured the level of von Willebrand factor (vWF) and hs-CRP as the surrogates of endothelial function and showed a rise in the levels of hs-CRP and vWF, and consequently, the exacerbation of endothelial function during the first two weeks of endovascular therapy. Apart from the early deterioration of endothelial function

proposed by Du et al.,⁸ these findings also underscore the fact that each of the studied modalities for the measurement of endothelial function can cover only a small portion of the pathophysiology of the phenomenon, and complementary tests may depict a better picture of the whole situation.

Finally, the recent systematic review by Katsanos et al.²⁰ showing the potential increase of mortality with the use of DCB has shocked the endovascular community. The main argument presented by Katsanos et al.²⁰ for the observed increased mortality was the late paclitaxel toxicity. Being one of the most exposed surfaces with circulating paclitaxel, endothelium might be endangered by this presumed toxicity. Although other confounding factors may play a role, our results showed no difference on the endothelial recovery between bare metal stent and DCB.

The limitations as regards the reproducibility of the RHI may have affected the results of our study. Diurnal variations, the use of specific medications such as nitrates, and the effects of smoking on the RHI should be taken into account. To reduce the effects of such factors on the RHI, we performed RHI measurements at specific times of the day (i.e. between 10 am and 12 pm) for the entire study population and asked all the patients to desist from smoking for at least 48 h before each measurement. Two other weaknesses of note in the present study are our lack of access to the laboratory markers of endothelial dysfunction such as hs-CRP and vWF and our failure to measure the improvement in physical activity and its possible correlation with the RHI.

Another salient issue is related to the total length of the stent and its effect on the RHI in comparison with the total length of the balloon in DCB in each case. Matching the length of stent coverage with balloon coverage in all patients is extremely hard; the difference in the length may exert some effects on endothelial function and the resultant RHI.

To conclude, the RHI exhibited a rise following revascularization with both DCB and stenting, and this improvement persisted in our patients who had patent vessels at mid-term follow-up. Our observation showed that vessel patency might have an important impact on endothelial function recovery, which has been highlighted as an important endpoint in the treatment of peripheral arterial disease.

Declaration of Conflicting Interests


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