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The effect of lower limb revascularization on the global endothelial function and cardiovascular risk.

Mini- review

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Abstract Endothelial dysfunction is an important pathomechanism of atherosclerosis. Among other things, it may be responsible both for a late outcome of lower extremity revascularization and occurrence of cardiovascular events in this high risk patient population. There are some papers available which show that improvement in leg perfusion, both after percutaneous or surgical intervention, may improve endothelial function, as well as decrease cardiovascular event risk and prolong overall and amputation-free patient survival. The potential mechanisms responsible for such a favorable effect of lower limb revascularization are as follows: recommendation of pharmacotherapy according to the recent guidelines, making possible the performance of percutaneous coronary interventions, an increase in nitric oxide release from the vascular wall, a decrease in vascular peripheral resistance, an increase in physical activity, improvement in glucose control, a decrease in inflammatory process activity, and oxidative stress reduction. In conclusion, there is an increased amount of data showing that lower extremity revascularization has a favorable pleiotropic effect, which should encourage the recommendation of a wider use of percutaneous and surgical intervention in the vascular bed, depending on individual indications.

Key words: peripheral artery disease, endothelial dysfunction, cardiovascular risk, atherosclerosis

Introduction

Atherosclerosis is the most common vascular disease. It is a systemic disorder and, therefore, may have multi-vessel clinical manifestations. One of these manifestations is peripheral artery disease (PAD), especially atherosclerosis of the lower limbs. PAD is often considered a marker of diffused, multi-level, multi-site or polyvascular disease [1-4]. It affects approximately 20-30% of the population over 60 years of age and 60% of patients with coronary artery disease (CAD) [1,2,5]. PAD is also considered as a risk factor of acute cardiovascular events. It doubles the risk of acute coronary syndrome and worsens the results of its treatment [1,2]. In this context, the determination of associations between PAD and CAD courses seems to be very important, especially due to aging populations and an increase in the percentage of persons with symptomatic and asymptomatic atherosclerosis of lower limb arteries (both types affect cardiovascular risk [4,5]). Many premises show global endothelial dysfunction as the pathomechanism explaining the coincidence of cardiovascular events in some vascular systems (peripheral, coronary, cerebral, and visceral) [6-30].

Endothelial dysfunction plays a crucial role in atherosclerosis pathogenesis. It is the effect endpoint for all known atherosclerosis risk factors. Endothelial dysfunction promotes atherogenesis through an influence on vasomotor reserve, the stimulation of arterial thrombosis, and the migration and proliferation of vascular wall cells [6]. It has a crucial role, not only in atherosclerotic process initiation, but also at the stage of advanced lesions [17-21]. Endothelial dysfunction is also recognized as a predictor of cardiovascular events [11-31].

The most prevalent cause of endothelial dysfunction is inadequate or delayed modification of atherosclerosis risk factors (e.g., smoking, hypertension, diabetes and hyperlipidemia). Their control and an increase in physical activity, pharmacotherapy (statins, angiotensin-converting-enzyme inhibitors, angiotensin receptor antagonists, renin inhibitors, the aldosterone receptor antagonist eplerenone, etc.), as well as the removal of endothelial toxins such as oxidative stress products, e.g., oxidized lipoprotein (ox-LDL), bacterial toxins, endotoxins and cytokines, can sometimes restore an endothelial function, including its vasomotor and antithrombotic properties [18-22,32]. In patients with PAD, a potential source of oxidative stress, besides NADPH oxidase stimulation and free radical scavenger deficiency, may be recurrent ischemia-reperfusion episodes and inadequate physical activity limited by intermittent claudication [33]. Therefore, it seems very probable that lower limb revascularization, the known effects of which are prolongation of walking distance, an increase in general physical activity and capacity [34], and, probably, a decrease in the frequency of ischemia-reperfusion processes in the legs, may lead to global endothelial function improvement and via this way to a decrease in cardiovascular risk [35]. The last assumption resulted from the fact that endothelial dysfunction is a systemic (global) disorder [6-31]. This means that endothelial function in peripheral arteries shows a strong correlation with the endothelial function of coronary, cerebral, and renal arteries [6-31,36,37]. Therefore, both acute and chronic disturbances in blood circulation in peripheral arteries, especially in the lower extremities, may affect endothelial function of the other circulatory systems, and may lead to an increase in cardiovascular event occurrence [1-4, 6-31]. The last hypothesis is supported by the known data showing that the value of the ankle brachial index (ABI; the ratio of systolic arterial pressure on ankle and arm) is not only the best predictor of deterioration of PAD (e.g., the need for arterial surgery or major amputation), especially when it falls below 0.5, but is also recognized as a prognostic factor for all-cause mortality and cardiovascular event occurrence [2]. In this context, the hypothesis seems to be very logical that the amelioration of blood circulation in lower limb arteries and an increase in ABI value after revascularization should lead to improvement in global endothelial function, and, in this way, to decreased cardiovascular event occurrence. It would be of great significance to find that revascularization of the legs together with lifestyle modification, risk factor control, appropriate pharmacotherapy and supervised walking training could not only improve patients' health-related quality of life [38], but also decrease the risk of coronary and cerebral events [39] and prolong patient life [40] via improvement in endothelial dysfunction. However, until now, only some observational studies with a small number of participants, designed only to measure single endothelial dysfunction parameters before and after lower extremity revascularization, without evaluation of clinical endpoint prevalence, have been performed [39-43].

This paper addresses a review of the data concerning the role of lower limb revascularization in endothelial function improvement and clinical benefits resulting from such action.

The effect of peripheral artery revascularization on endothelial dysfunction

Until now, there are only some studies available concerning the associations between lower limb revascularization and endothelial function [41-43]. One of these studies investigated the effect of vascular surgery, and two studied the effect of percutaneous interventions on brachial artery flow-mediated dilatation (FMD) in response to five minutes of arm ischemia. FMD expresses the percentage of brachial artery diameter change after five minutes of arm ischemia [41-43]. In a study by Unal et al. [41] in 54 patients with lower limb ischemia four weeks after femoropopliteal bypass grafting, a significant increase in ABI and FMD values was observed. Moreover, the nitric oxide, interleukin-6, high-sensitivity C-reactive protein, and tumor necrosis factor-alpha levels decreased significantly after four weeks postoperatively as compared with the preoperative levels. The authors concluded that their study demonstrated that successful lower extremity revascularization improves endothelial function, expressed as FMD, through reduction of muscle ischemia and systematic inflammatory response to recurrent ischemia-reperfusion processes and oxidative stress. Whereas, in a prospective, open, randomized, controlled, single-center study by Husmann et al. [42] of 17 patients with chronic and stable claudication (Rutherford 2 to 3) due to femoropopliteal obstruction, the endovascular leg revascularization increased average ABI value, ameliorated FMD and decreased blood leucocyte count by the fourth week of follow-up. The best medical treatment recommended for the remaining 16 individuals did not affect these parameters' values. Budzyński et al. [43] studied some endothelial function parameter values in 17 patients with life-limiting claudication and occlusion of the superficial femoral artery treated percutaneously with stenting during a one-year follow-up. The parameter values were as follows: (a) ABI and walking distance on the running track, as hemodynamic parameters of leg perfusion; (b) FMD and brachial artery dilatation after sublingual 0.4 mg nitroglycerin application (nitroglycerin-mediated vasodilatation, NMD); artery dilatation independent of endothelial function (endothelial-independent vasomotion) with proximal brachial artery occlusion; the premise of NMD investigation was to estimate the vasodilatation function of vessels' smooth muscles which may theoretically accompany endothelial dysfunction and vessel wall injury [31]; (c) measurement of temporal blood flow velocities using Doppler ultrasonography and the calculation of pulsation index (PI) as a ratio of peak-systolic (PSV) and end-diastolic (EDV) blood velocities, both for brachial and common carotid arteries; (d) common carotid artery intima-media complex thickness (IMT) as a marker of morphological vascular injury; (e) measurement of intervals between peaks of an R wave in ECG and the beginning of the blood flow ultrasound wave in the carotid and brachial arteries; (f) calculation of the arterial distensibility coefficient (DC) for brachial and common carotid arteries; DC expressed as the difference between systolic and diastolic diameters of the common carotid artery divided by the values of the diastolic artery diameter; and (g) pulse pressure. The last three parameters - pulse wave velocity, DC and pulse pressure - may be recognized as simple and cheap parameters of arterial stiffness. During the one-year follow-up period, the authors showed only a significant increase in ABI value, just one day after the endovascular procedure. The value of ABI greater than before intervention maintained till sixth month of observation. Although the authors failed to show significant changes in the values of the remaining parameters in the whole subject group, interesting observations were made in the subgroup analysis. Patients with some atherosclerosis risk factors, such as diabetes, elevated LDL cholesterol level or smoking, achieved greater improvement after superficial femoral artery stenting in the respective vascular function parameters (FMD, PSV, EDV, PSV/EDV, IMT). The values of these respective vascular function markers, significantly different before the procedure, became similar to those found in subjects without these clinical conditions [43].

The favorable effect of peripheral artery revascularization on endothelial dysfunction also concerns endovascular interventions in renal arteries. Koivuviita et al. [36] in 19 patients with unilateral (n = 9) or bilateral (n = 10) renal artery stenosis (RAS) found that FMD, systolic blood pressure and left ventricular mass were improved after bilateral renal artery stenting. However, myocardial perfusion and coronary flow reserve (CFR), measured using quantitative positron emission tomography (PET) perfusion imaging at the baseline and during dipyridamole-induced hyperemia, did not change after the renal artery dilatation in these subjects. Whereas, Jacomella et al. [37] in 24 hypertensive patients with RAS prior to and one day after this artery unilateral revascularization showed significant improvement in FMD, an increase in hyperemic blood flow in the brachial artery, a reduction in rest and hyperemic shear stress, and a decrease in systolic and diastolic blood pressure and pulse pressure. In this study, NMD and hyperemic brachial blood flow after nitroglycerin sublingual application did not change after renal artery stenting.

To summarize, the above-mentioned, low-number studies showed that peripheral artery revascularization, including lower limb and renal vessels, improved global endothelial function and decreased arterial stiffness. These effects might potentially result from: (a) a greater release of nitric oxide from the endothelium; (b) an amelioration of blood run-on and run-off; (c) an increase in walking distance enabling training and collateral development (angiogenesis stimulation); as well as (d) a reduction in the activity of inflammatory processes (leucocyte count, hsCRP, TNF-alpha) and oxidative stress. As any of the aforementioned pathomechanisms leading to global endothelial function improvement also plays an important role in the course of atherosclerosis in extra-leg vascular beds, it seems possible that lower extremity revascularization might affect both its own late outcome and patient life expectancy.

The role of endothelial dysfunction in the early and late outcomes of lower limb revascularization

The technical efficacy of endovascular and surgical vascular procedures (correct blood flow restoration) depends on the treated place (artery localization) and the presence of artery narrowing or occlusion, but is generally greater than 90% [2]. Unfortunately, the immediately favorable outcomes of vascular procedures do not corroborate significantly worse percentages of late vessel patency [1,2,29]. The most frequent causes of this condition are: (a) thrombosis, in-stent or in-bypass (acute: up to 24 hr; subacute: between 1-30 days after procedure; late: between one and 12 months; and very late: over one year after intervention), and (b) in-stent restenosis (narrowing recurrence in a previously dilated place due to neointima proliferation), which may concern 3-50% of subjects within three years. The potential causes of target vessel thrombosis are similar to those during venous thrombosis, i.e., enumerated in the modified Virchow's triad as follows: (a) advantage in pro-coagulative blood components and platelet hyperreactivity, (b) defect in blood flow through the stent (insufficient blood inflow and outflow, e.g., due to endothelial dysfunction), and (c) vessel wall injury, e.g., secondary to neointima proliferation, stent fracture, endothelial damage or local activation of the inflammatory process in vessel walls [44]. The mentioned pathomechanisms show various potential roles in endothelial function (e.g., vasodilatatory, anti-thrombotic, anti-proliferative) in the maintenance of stent patency [45]. Endothelial function also plays an important role in in-stent restenosis pathogenesis. Mizia-Stec et al. [29] have shown that the occurrence of early in-stent restenosis after elective percutaneous coronary intervention of the left anterior descending coronary artery was associated with impaired FMD at the time of the one-year follow-up. Whereas the type of stent, especially the use of a drug-eluting stent (DES), introduced into clinical practice as a medium for reducing the assumption of the risk of restenosis, did not affect the prevalence of this complication. Whereas, in a study by Hafner et al. [46] the IMT, but not the FMD, value was associated with restenosis after angioplasty of leg arteries due to claudication in a 12-month long duplex-ultrasound follow-up. In other studies, in which endothelial function was not investigated, restenosis prevalence after lower limb artery revascularization was related to the kind of endovascular treatment (e.g., balloon angioplasty vs. stent, atherectomy, rotablation), the type of stent (BMS, DES, covered) [47], and comorbidities (diabetes, kidney insufficiency) [39,40,48].

The effect of lower limb revascularization on main cardiovascular endpoints

Chronic lower limb ischemia is defined as a clinical condition with an ABI value below 0.9 or a prior history of lower extremity revascularization [2]. Patients with a chronic type of PAD are qualified for revascularization due to work- and lifestyle-limiting claudication or critical limb ischemia [2,3]. One proposed criterion for endovascular revascularization effectiveness is an increase in ABI value of 0.15 [34,49-52]. On the other hand, an almost linear relationship was proven between ABI and fatal and non-fatal cardiovascular events, and every decrease in ABI value by 0.10 was associated with an approximately 10% increase in relative risk of a major vascular event [1,2,4]. This might suggest that successful leg revascularization, both percutaneous (balloon angioplasty, stenting, atherectomy) and surgical (endarterectomy, bypass), should decrease the cardiovascular endpoint hazard by at least 15%. In this way, efficient lower limb revascularization could be linked, not only to a reduction in amputation rate and an improvement in patients' health-related quality of life, but also a decrease in cardiovascular and general mortality [34]. However, it should be underlined that the prognosis in patients with PAD also depends on atherosclerosis severity in the other vascular beds [2, 53-54], lesion localization in the vessels of the lower extremities [55], and classification according to TASC II A-D [56]; baseline and post-interventional ABI and the nature of leg symptoms [34,57]; gender [58], initial patient functional status [59,60], and recommendation and effect of supervised treadmill training and resistance training [61]; pharmacotherapy (antiplatelets, anticoagulants, ramipril, statins, cilostazol, prostanoids) [62-67] and comorbidities [68], such as chronic kidney disease [48], diabetes [8], depression [69], and inflammatory processes (e.g., expressed by leucocyte blood count) [42,69].

In a study by Giugliano et al. [40] during a median follow-up of 21 months, the incidence of cardiovascular events was markedly lower in patients with intermittent claudication (n = 264) treated with leg artery angioplasty (PTA) in comparison to 215 subjects on only the best medical treatment (6.4% vs. 16.3%; p = 0.003). Patients in the medical treatment group showed a fourfold increased cardiovascular risk compared to patients in the PTA group, even after adjustment for potential confounders. In an earlier investigation of the same group [39], the researchers showed that successful revascularization of lower extremities due to intermittent claudication in 236 diabetic patients was related to a significant reduction in major cardiovascular events in comparison to 137 diabetic patients in whom intervention was not undergone. The mentioned association remains significant after adjustment of survival analysis for classic cardiovascular risk factors, previous myocardial infarction or stroke, maximum walking distance, leukocyte count and ABI [39]. Faglia et al. [71] followed-up 564 consecutive diabetic patients with critical limb ischemia (CLI) for approximately 5.93 ± 1.28 years. Four hundred and thirteen subjects were treated with PTA, 114 with bypass graft (the revascularization group amounted to 527 pts), and revascularization was not undergone in 27 patients. They found that lower limb revascularization, both percutaneous (angioplasty, stenting) and surgical (bypass graft), not only improved patients' functioning and decreased risk of minor and major amputations, but also prolonged patient life. In this study, the Cox model showed significant hazard ratios (HRs) for mortality with age (1.05 for 1 year [95% CI 1.03-1.07]), unfeasible revascularization (3.06 [1.40-6.70]), dialysis (3.00 [1.63-5.53]), cardiac disease history (1.37 [1.05-1.79]), and impaired ejection fraction (1.08 for 1% point [1.05-1.09]) [71]. In this study, similar data were obtained for risk of major amputation, although in such an aspect the risk related to the absence of efficient limb revascularization was much more greater and amounted to OR 35.9 [CI 12.9-99.7] [71]. Similar observations were made by other authors [72-74]. In a cohort study by Ortmann et al. [75] conducted in 356 consecutive patients (394 limbs) with CLI, immediate revascularization, both surgical (81 limbs) and endovascular (211 limbs), was associated with a significantly better, but only for women (41%), overall survival (HR 2.37; 95% CI 1.29-4.34) and amputation-free survival (HR 2.11; 95% CI 1.30-3.43) in comparison to only medical treatment (112 limbs), irrespective of whether surgery or percutaneous intervention was performed. The clinical importance of these favorable effects of immediate lower extremity revascularization is the greater because the women were significantly older than the men, had higher systolic blood pressure and cholesterol level, although they more seldom presented with renal failure, and fewer of them were smokers. Kalbaugh et al. [38] showed that endovascular intervention in arteries of the lower extremities in comparison to historical results of open bypass, both in patients with intermittent claudication (n = 54) and CLI (n = 30), leads to a statistical improvement in health-related quality of life, including physical functioning, as well as better survival, which, in the authors' opinion, should link to a more liberal use of percutaneous intervention for patients with vasculogenic claudication. In a retrospective study by Malgor et al. [76] in patients with CLI, overall mortality at one year and five years after leg revascularization was better than reported in other works [2]. Moreover, subjects with the 6th grade in the Rutherford chronic limb ischemia classification achieved better limb salvage, reintervention, and survival rates when distal revascularization (n = 93) added to endarterectomy (CFE) of the common femoral artery was undergone in comparison to CFE alone (n = 169).

The mentioned favorable outcomes of such extended lower extremity revascularization for main cardiac outcome in patients with PAD may be explained by a number of suggested pathomechanisms, which are as follows: (a) diagnosis of atherosclerotic vascular disease and recommendation of therapy in accordance with the recent guidelines on cardiovascular disease prevention [77]; (b) global endothelial dysfunction amelioration [41-43]; (c) the outcomes of coronary interventions are worse in patients with PAD [1], i.e., due to lack of required vascular access, and, therefore, lower extremity revascularization makes possible the performance of percutaneous coronary interventions which may strongly affect PAD patients' prognosis because they mainly die due to cardiovascular events [1,2]; (d) an increase in shear stress in the leg arteries resulting from increased walking distance and blood flow, leading to greater release of nitric oxide by the endothelium [42]; (e) a decrease in vascular peripheral resistance (blood outflow facilitation); (f) an increase in physical activity (walking distance), which per se may decrease cardiovascular risk [35,60,78] and an increase in peripheral circulation reserve due to endothelial function improvement [42]; (g) improvement in glucose control in diabetic patients [79]; (h) a decrease in inflammatory process activity related to oxidative stress, cytokines, and adhesive molecules released from ischemic muscles [18-22,32,33,41-43,46]; as well as (i) oxidative stress reduction due to diminishing recurrent leg muscle ischemia-reperfusion episodes [18,32,33,39,42]. It should be added that oxidative stress in treated subjects with PAD may also be diminished by the pleiotropic effect of lifestyle modification and drugs recommended for atherosclerosis therapy. They show additional properties for regulating NADPH oxidase activity (statins, angiotensin-converting-enzyme inhibitors [ACEI], angiotensin II receptor antagonists [ARBS]; and, probably, renin inhibitors -

aliskiren; mineralocorticoid receptor blockers - spironolactone, eplerenone, calcium channel blockers, hydralazine) or acting as antioxidants (e.g., polyphenols from red wine) [32,33,67].

Conclusions

There are few but significant data showing that lower limb revascularization in patients with PAD improves general endothelial function and reduces the level of inflammatory biomarkers and patient mortality. There are conflicting data concerning the effect of leg perfusion amelioration on stent and bypass patency. The mentioned data showed a pleiotropic effect of lower extremity revascularization and encourage the recommendation of a wider use of percutaneous and surgical intervention in the vascular bed, depending on individual indications.

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