

FEATURES IN ANGIOGRAPHIC EVALUATION OF THE DIABETIC PATIENT

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Abstract

Currently it is estimated that there are over 382 million patients with diabetes worldwide and their number is increasing, which makes this metabolic disorder the most common non-contagious disease, particularly related to obesity and physical inactivity. There is a close relationship between diabetes and cardiovascular disease, statistics showing that over 50% of deaths in patients with diabetes are produced by cardiovascular complications. This requires a close collaboration between diabetologists and cardiologists. The mortality caused by atherosclerotic complications is 65-80% for diabetic patients compared to 33% in non-diabetic patients. Moreover, 20% of the patients requiring coronary revascularization procedures are diabetics and over 30% of patients with angiographic exploration have diabetes. Among the patients with diabetes the coronary lesions are present in 50% of cases and the peripheral arteries lesions in 30% of cases.

key words: *diabetes mellitus, cardiovascular revascularisation, angiography.*

Preparing the angiographic procedure

The patient with type 2 diabetes, often obese, has a status of hyperinsulinemia caused by insulin resistance. Insulin resistance alters myocardial contractility by reducing calcium influx through L-type channels, resulting in dilated cardiomyopathy in diabetic patient without coronary disease. Endothelial dysfunction and vascular inflammation leads to the formation of atherosclerotic plaques, rich in lipids. Insulin resistance and hyperglycemia induce cardiac changes by accumulation of reactive oxygen species, damaging the coronary circulation, and producing fibrosis and

ventricular hypertrophy. Systemic inflammation, oxidative stress, endothelial dysfunction combined with coagulation disorders and fibrinolysis lead to accelerated atherosclerosis and thrombosis [1,2].

The patient with diabetes has an increased risk of complications during diagnostic angiographic procedures or percutaneous myocardial or peripheral revascularization, which requires some precautions. There was a higher incidence of contrast nephropathy, especially in patients with severe renal disease [3]. This can be prevented by: a good hydration of the patient with 1-1.5 ml/kg/min for 3-12 hours before and 6-12 hours after the procedure,

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the use of contrast agents with low osmolality, avoiding excessive use of the contrast agent and recording as few images as necessary in order to establish a correct diagnosis so that the volume contrast/creatinine clearance ratio does not exceed 3.7. If the patient requires a revascularization procedure, it is preferred that this is performed in the same session with the diagnosis rather than in successive sessions shortly one after the other.

When using a high amount of contrast, monitoring of the renal function should not be done before 48-72 hours after the procedure. From the oral antidiabetic drugs, classically it was recommended to stop metformin before the procedure and restarting it 48 hours after the procedure in order to avoid lactic acidosis. Hypoglycemia or hyperglycemia should be avoided by adjusting the medication, in particular insulin doses. The evening insulin dose in the day before the procedure should be halved and the morning dose should not be administered. Diabetics should be scheduled for angiographic imaging in the morning in order to avoid hypoglycaemia. Note that in patients treated with insulin NPH (containing protamine) it has been described the existence of anaphylactic reactions at the administration of protamine for reversal of the heparine effect [4].

Diabetes mellitus is an important predictor for complications at puncture site, especially because of arterial calcifications. During the last years, the trend for angiographic procedures approach is using the radial artery, which means a lower incidence of complications at the puncture site and allows early ambulation of the patient. However, diabetic patients have an increased risk of radial artery spasm [3]. Femoral approach is not without complications such as hematoma, arterio-venous fistula, rarely infection at puncture site, common femoral artery thrombosis due to vessel dissection and

low caliper. Advanced and early atherosclerosis in diabetics involving the aorta and its large branches leads to the additional risk of accidents no matter of the approach, such as transitory ischemic attack or ischemic stroke.

Angiography for coronary artery disease

Mortality due to coronary heart disease is two to four times higher in patients with diabetes. It has been proven that diabetic patients have a decrease in coronary flow reserve in the absence of epicardial coronary damage, which proves the existence of microvascular dysfunction. The presence of diabetic retinopathy is associated with increased basal coronary flow, decreased coronary flow reserve and default coronary microvascular dysfunction [5]. Coronary impairment is severe, extensive, involving multiple vessels with significant calcification of the arterial media, and the predominance of the left main coronary artery involvement and weak collateral circulation [6].

Revascularization procedures such as Percutaneous Transluminal Coronary Angioplasty (PTCA) and Coronary Artery Bypass Grafting (CABG) are difficult due to diffuse atherosclerotic damage, small vessels, long-term mortality because of the increased risk of occlusion of the grafts, increased stent restenosis and thrombosis rates.

The absence of pain or the presence of atypical forms of angina in diabetics explains why revascularization procedures are not necessarily followed by symptomatic relief to the extent that this takes place in non-diabetics. Coexistence of diabetic cardiomyopathy may prevent improvement of ventricular function after revascularization, observed in a part of the non-diabetics. Tracking clinical outcome of percutaneous coronary interventions (PCI) is also more difficult in the absence of recurrence of angina in some patients with diabetes. This is

why the methods of revealing silent ischaemia become more important and the angiographic control indication can be made easier.

There is controversy regarding the appropriate procedure for revascularization of diabetic patients with multivessel disease, with three large studies of different structure that provide data regarding the best technique of revascularization: percutaneous or surgical. The BARI (Bypass Angioplasty Revascularization Investigation) trial compared the balloon angioplasty with the aorto-coronary artery bypass, excluding patients with left main lesions, and assessed mortality at five years (34.5% for PTCA and 19.4% for CABG) and the need for revascularization (69.9% to 11.1% for PTCA and CABG). The conclusion of BARI trial was that the best way to manage the diabetic patient with multivessel coronary disease is the CABG [7].

Later, the SYNTAX (Synergy Between PCI With Taxus and Cardiac Surgery) trial (with a more complex structure) compared angioplasty with a drug eluting stent (Taxus –Paclitaxel eluted stent) with the surgical revascularization and was not able to prove the superiority of CABG over the drug eluting stent (DES) [8]. Over 3 years follow-up of the diabetic group in the SYNTAX trial, the rates of death, stroke, myocardial infarction and cardiac death were not significantly different between the treatment groups, but the presence of diabetes increased the need to repeat revascularisation (28% for PCI vs. 12.9% for CABG) and also of major adverse cardiac and cerebrovascular events (MACCE): 37% for PCI vs. 22.9% for CABG. A higher incidence of stroke was noted in the CABG group (3.5% for CABG vs. 2.4% for PCI). Using the anatomical SYNTAX score to evaluate the complexity of the lesions, the patients were divided in three categories. Those with intermediate (23-32) or high (>33)

SYNTAX score had an increase rate of MACCE at 3 years. This is why the standard of care for complex coronary artery lesions remains the CABG [8].

Given these data, what should a doctor do in front of a diabetic patient with multivessel coronary disease? This was the question when the BARI 2D trial appeared [9]. It compared maximal medical therapy with myocardial revascularization and showed that the 5-year mortality and the risk of heart attack or stroke were similar in the 2 groups, but 42% of patients treated with medication are requiring revascularization by any of the two methods (surgical or percutaneous). Overall, in the BARI 2D trial there were no significant differences in the incidence of death and major cardiovascular events between the patients treated with optimal medical therapy and the revascularisation group, but in the group treated by CABG the rate of major cardiovascular events was lower [9].

Finally, the FREEDOM (Future Revascularization Evaluation in Patients with Diabetes Mellitus) trial, compared the revascularisation of the diabetic patients with multiple coronary vessel disease (excluding the left main) using DES (sirolimus or paclitaxel eluted stents) or CABG. The study results support the superiority of CABG over first generation DES in reducing the rate of cardiac death, myocardial infarction, with a higher rate of stroke [10].

Diabetes is an important risk factor for in-stent restenosis given the reduced vessel caliper and lesions length. Restenosis inside DES, although far less frequently than in bare metal stents (BMS), occurs more frequently in diabetic patients. Restenosis occurs most frequently in the first year [11] and is associated with increased risk of 5-year mortality (25.4% for diabetics vs. 17.9% for non-diabetics) [3]. Restenosis has a higher incidence in diabetics

after coronary balloon angioplasty or BMS due to the negative remodeling and accelerated neointimal hyperplasia. Vascular inflammation, endothelial dysfunction and insulin resistance promote stent restenosis because insulin has a growth factor-like effect on neointimal cells and vascular smooth muscle cells. DES should be used for coronary revascularisation of diabetic patients because of the low rate of in-stent restenosis and better outcome on long lesions (>20 mm of length) and small vessels (<3 mm of diameter), although diabetes is a risk factor for in-stent thrombosis for DES [12].

The SCAAR registry showed that diabetic patients treated with sirolimus eluting stents (SES) and zotarolimus eluting stents (ZES) have an increased risk of restenosis compared to those treated with paclitaxel eluting stent (PES). In patients treated with PES, the rate of restenosis was not influenced by the glycemic status [13]. The TAXUS II, IV and VI trials showed how effective the drug eluting (paclitaxel) stent is, with a 12 months restenosis rate for BMS of 14.2% in patients without diabetes, 21.4% in diabetics treated with oral antidiabetic drugs and 19.3% in diabetics treated with insulin. The restenosis rate for PES (TAXUS) was 4.6% in patients without diabetes, 6.2% in diabetics treated with oral agents and 5.6% for insulin-treated diabetics [14].

The studies comparing the treatment of diabetic patients using revascularization with SES vs. BMS showed similar rates of mortality and incidence of postprocedural myocardial infarction. The differences in the rate of death, myocardial infarction were not significant in the use of SES vs. PES, but the restenosis rate was lower for SES (ISAR-DIABETES, DES-DIABETES, DiabeDES) [15]. With the advent of second generation polymers, it was observed in the SPIRIT V study that treatment with everolimus eluting stents (EES) significantly

decreased at 1 year the risk of cardiac death (by 1.1%), the risk of myocardial infarction (by 3.5%) and the need for target lesion revascularization (by 1.8%), with the lowest rate of stent thrombosis of 0.66% in one year [16]. Studies comparing the biodegradable polymer (Biolimus A9), and slow release polymer (everolimus) found no significant differences in one year mortality, cerebrovascular events, myocardial infarction, and need for revascularization [17].

Considering all the available data, the diabetic patient with STEMI is a good candidate for implantation of DES in the acute phase after using thromb aspiration and removing thrombotic material [1].

Diabetic patients with a high risk of stent thrombosis and acute coronary syndromes are a group of patients who can benefit the most of the long term dual antiplatelet therapy for over 12 months [18]. Diabetic patients have a high variability in clopidogrel response. Mechanisms are still unclear, possibly due to changes occurring in platelet aggregability and increased platelet activation, increasing P2Y₁₂ receptors and GP Ib, GP IIb / IIIa proteins. Moreover, clopidogrel is a prodrug, unlike newer P2Y₁₂ inhibitors (prasugrel and ticagrelor) that do not require activation, the effectiveness of which is superior, without higher risk of bleeding [19].

Peripheral artery disease

Diabetes mellitus is an important risk factor for atherosclerosis, affecting both the coronary arteries and the peripheral arteries. Peripheral artery disease (PAD) itself is a risk factor for coronary and cerebrovascular events [20]. The prevalence of PAD is 1.5 to 6 times higher in diabetic patients than in those without diabetes. It should be noted that diabetes also increases the incidence of severe atherosclerotic carotid lesions by three times, with an increase in stroke

mortality in patients with diabetes. Intermittent claudication in diabetics occurs 3 times more frequently in men and 8 times more frequently in women, with an incidence of amputation increased 10 times and even 20 times in patients aged between 65 and 74 years. There is a more severe injury with important vascular calcification of the media, with a predilection for infrapopliteal vessels but with relative preservation of the leg vessels. Duration and type of diabetes does not play a major role in the incidence or severity of PAD. Independent predictors of progression of PAD are the decreased ankle-brachial index (<0.9) after exercise, smoking and high systolic blood pressure. Because of the vascular calcification, the ankle-brachial index (ABI) can be falsely increased (>1.2), which has a prognostic as bad as a low ABI and requires evaluation by measuring the pressure in the hallux or the transcutaneous partial pressure of oxygen in the fingers. Neuropathic symptoms and lack of patient education are risk factors for amputation, the patient being frequently asymptomatic. Often the first symptom is ulceration. Diabetic foot ulcers have three etiologies: ischemic, neuro-ischemic and neuropathic [21].

Gracile and calcified vessels are difficult to treat by peripheral balloon revascularization, best results being obtained using drug eluted balloons, stents and newer DES dedicated for peripheral vessels. Dual antiplatelet therapy after

percutaneous balloon or stent angioplasty is given for a month, continuing thereafter only with long-term aspirin therapy.

Conclusions

The best method for revascularisation of complex coronary lesions in the diabetic patient is the CABG. Even if the trials indicate CABG as standard of care for complex and multiple coronary lesions, the accessibility, the lower costs, the longer experience with PCI, better materials and stents, made the use of DES to be more frequent in clinical practice. For patients with lesions with a low SYNTAX score or with contraindications for the surgical procedure, the PCI using a drug eluting stent added to the optimal medical therapy is the procedure of choice. EES is the DES with the safest profile regarding the myocardial infarction and stent thrombosis in diabetic patients. The revascularisation of the iliac, femoral and popliteal arteries with stents (BMS or DES) has a better long-term outcome than the balloon angioplasty. The leg arteries, due to the small caliber, they have a very high rate of restenosis with balloon angioplasty. Dedicated peripheral drug eluted stents are the indicated treatment for the distal arteries of the leg.

Conflict of interests: none.

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