

R E V I E W

Use of perfusional CBCT imaging for intraprocedural evaluation of endovascular treatment in patients with diabetic foot: a concept paper

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Summary. Diabetes mellitus (DM) is one of the most common metabolic diseases worldwide; its global burden has increased rapidly over the past decade, enough to be considered a public health emergency in many countries. Diabetic foot disease and, particularly diabetic foot ulceration, is the major complication of DM: through a skin damage of the foot, with a loss of epithelial tissue, it can deepen to muscles and bones and lead to the amputation of the lower limbs. Peripheral arterial disease (PAD) in patients with diabetes, manifests like a diffuse macroangiopathic multi-segmental involvement of the lower limb vessels, also connected to a damage of collateral circulation; it may also display characteristic microaneurysms and tortuosity in distal arteries. As validation method, Bold-MRI is used. The diabetic foot should be handled with a multidisciplinary team approach, as its management requires systemic and localized treatments, pain control, monitoring of cardiovascular risk factors and other comorbidities. CBCT is an emerging medical imaging technique with the original feature of divergent radiation, forming a cone, in contrast with the spiral slicing of conventional CT, and has become increasingly important in treatment planning and diagnosis: from small anatomical areas, such as implantology, to the world of interventional radiology, with a wide range of applications: as guidance for biopsies or ablation treatments. The aim of this project is to evaluate the usefulness of perfusion CBCT imaging, obtained during endovascular revascularization, for intraprocedural evaluation of endovascular treatment in patients with diabetic foot. (www.actabiomedica.it).

Keywords: MRI bold, CBCT, radiology, interventional radiology, diabetic foot, perfusion imaging, cone beam

Introduction

Diabetes mellitus (DM) is one of the most common metabolic diseases worldwide; its global burden has increased rapidly over the past decade (1), enough to be considered a public health emergency in many

countries. Diabetic foot disease (DFD) and, particularly diabetic foot ulceration (DFU), is the major complication of DM: through a skin damage of the foot, with a loss of epithelial tissue, it can deepen to muscles and bones and lead to the amputation of the lower limbs.

Generally, DFD is characterized by a classical triad of neuropathy, ischemia, and infection (2). Neuropathy is manifested in the motor, autonomic, and sensory components of the nervous system (3). The most common type of diabetic peripheral neuropathy is distal symmetric polyneuropathy which accounts for approximately 75% of all diabetic neuropathies (4,5); atypical forms include mononeuropathies, (poly)radiculopathies, and treatment-induced neuropathies (6).

Changes in nerve sensitivity can lead to both increased and decreased foot sensation: the feet can become super sensitive with even light touch, creating significant pain, or, on the contrary, completely numb. This can be dangerous as a simple cut or ingrown nail can go unnoticed; even more, the foot muscles can weaken and alter the ability to walk, negatively affecting the maintenance of balance.

From the circulatory point of view, although atherosclerosis of diabetics is pathologically like that of non-diabetics, in the case of patients with DM it is more generalized, occurs prematurely and progresses at an accelerated rate. It carries macrovascular obstructions (macroangiopathic changes) especially in the coronary, cerebrovascular and peripheral arterial districts.

In particular, peripheral arterial disease (PAD) in patients with diabetes, manifests like a diffuse macroangiopathic multi-segmental involvement of the lower limb vessels, also connected to a damage of collateral circulation; it may also display characteristic microaneurysms and tortuosity in distal arteries (7).

More specifically, DM lower limb atherosclerosis tend to occur more distally (7-9); it is found at all levels of the arterial limb tree, but atheroma seems to have an apparent predilection for arteries below the knee, distally to the tibial-peroneal trunk, particularly the peroneal and posterior tibial arteries, whereas arteries proximal to the knee joint are often spared or moderately diseased and aortoiliac disease is usually less severe.

The role of PAD in the pathogenesis of DFU is to aggravate the foot infection, delay the healing of the ulcer and thus prepare for the onset of gangrene, since the reduced arterial contribution is not able to cope with the increased metabolic demand of the infected foot (10,11).

Moreover, critical limb threatening ischemia (CLTI) due to PAD, can lead to microcirculatory deficiencies with altered capillary flow and tissue oxygenation. Microcirculation, in fact, includes the terminal arterioles and capillaries beyond the arteries, which are involved in transporting oxygen and blood nutrients to the tissues. Microangiopathy, inducing thickening of capillary basal membrane, alters nutrient exchange and causes tissue hypoxia and microcirculatory ischemia; the latter represents an important point of contact between vascular and neuropathic problems related to diabetes, because among the affected micro-vessels we find vasa nervorum.

However, PAD may remain undiagnosed until the patient presents severe tissue loss, since many diabetic patients lack the classic initial symptoms of PAD such as claudication or pain at rest (12,13).

Despite DFUs result from the simultaneous actions of multiple contributing causes such as vasculopathy, neuropathy, structural deformity, and decreased immunity, the leading underlying causes are noted to be peripheral neuropathy and ischemia from PAD.

Thus, considering that about 35% of all patients with DFU have a concomitant PAD (14), early diagnosis and treatment are mandatory.

Diagnosis

The location and morphology of the PAD must be characterized prior to carrying out any revascularization to determine adequate inflow and appropriate outflow, required to keep the revascularized segment functioning and thus, the most appropriate intervention planning.

A variety of methods yielding both anatomic and physiologic information are available to assess the arterial circulation. The evaluation of a precise localization of the disease, of its extension and of its grading allow a correct therapeutic approach.

The most appropriate diagnostic approaches for the detection of macrovessels disease are represented by three techniques: duplex ultrasound (DUS), computed tomography angiography (CTA), and magnetic resonance angiography (MRA).

The location and morphology of the PAD must be characterized before any revascularization procedure is performed; the evaluation of the precise location of the disease, its extent and classification, the proper identification of adequate inflow and outflow, necessary to maintain the functioning of the revascularization segment allow the most appropriate planning of the intervention

Several methods are available to assess arterial circulation, providing both anatomical and physiological information; among them, the most commonly used diagnostic techniques for the detection of macrovascular alterations are duplex ultrasound (DUS), computed tomographic angiography (CTA) and magnetic resonance angiography (MRA).

DUS is a non-invasive, repeatable, and radiation and contrast media-free technique; it lets see vessel course and size, the wall plaques characterization, and the patency/occlusion of blood vessels.

On the other hand, DUS is operator-dependent; it has a time-costing for the sub-knee district since the average time for the study of the lower limbs is 40–60 min; it has a difficult assessment of the aorto-iliac arteries in some cases due to patient habitus (obese patients) or bowel gas; the evaluation of the leg arteries can be limited due to vessel position or extensive calcification; and its images are not useful for therapeutic planning (no panoramic images).

Multi-slice CTA is having a fast scan of wide volume, a high spatial resolution, a high quality reconstructions and it has different post-processing techniques, such as MPR, MIP, CPR, VR (15). All this, however, in the face of radiation and injection of contrast media.

MRA is a radiation-free technique and it doesn't need contrast media injection. On the other hand, MRA has a long acquisition time, a directional dependence, a predetermined sensitivity, it is dependent on flow speed and it requires to be perfected for evaluation of patients with arrhythmias (in case of Fresh Blood Imaging of the peripheral vasculature).

Treatments: Endovascular Revascularization

The diabetic foot should be handled with a multidisciplinary team approach, as its management requires

systemic and localized treatments, pain control, monitoring of cardiovascular risk factors and other comorbidities (16).

Offloading and debridement are certainly fundamental in the healing process of DFU (17); the former is useful to redistribute force from the ulcers sites or pressure points at risk, to a wider area, through the use of methods of pressure relief, such as half shoes, wheelchairs and so on (18).

DFU could require debridement if necrotic or unhealthy tissue is present in order to eliminate the surrounding callus or the unhealthy tissue helping to reducing colonizing bacteria in the wound. In particular, in presence of infection, this must be treated aggressively. Depending on the depth of the infection, the DFU is treated with debridement, oral antibiotics, and regular dressings or it may also need hospitalization and broad-spectrum antibiotics (19).

Certainly, metabolic control, through multiple injections or continuous infusion of insulin, plays a fundamental role both in the treatment and in the prevention of diabetes complications, but considering that PAD remains the most important cause of compromised foot perfusion in diabetics (20), revascularization remains the treatment of choice for patients with DFU, and even more for patients with CTLL: a timely restoration of adequate arterial blood supply facilitates resolution of the underlying infection and therefore wound healing.

It should be pointed out that endovascular approach in infra-popliteal vascular territory is challenging, because its vessels have a small caliber, there is a slow flow of the distal bed and there is a need to preserve a run-off capacity. However, CLTI patients with severe comorbidities or with a very limited chance of successful revascularization (overwhelming infection that threatens the patient's life; rest pain that cannot be controlled; extensive necrosis that has destroyed the foot), are not candidates for revascularization: in the latter cases a primary amputation may be the most appropriate treatment.

Generally, macro-vessel endovascular revascularization is always recommended in all patients with DFU and PAD, regardless of bedside test results, when the ulcer does not heal within 4–6 weeks despite good treatment (21). More specifically, revascularization

aims at restoring arterial flow in at least one of the arteries of the foot, preferably the one afferent to the anatomical region of the ulcer (21): direct revascularization allows to restore the pulsatile blood flow through the feeding artery to the area where the ulcer is located, while indirect revascularization is given by the opening of collateral vessels from nearby “angiosomes”.

About twenty years ago, in fact, Taylor and Paller introduced the count of “angiosome”, as an anatomical unit (skin, subcutaneous tissue, fascia, muscle and bone) fed by a specific artery and drained by specific veins. In the ankle and foot region, six angiosomes are identified, fed respectively by the anterior tibial artery (one angiosome), the peroneal artery (two angiosomes) and the posterior tibial artery (three angiosomes) (22). Adjacent angiosomes are bounded by anastomoses of small or artery-like size, which connect them together; these vessels are important safety conduits that allow a given angiosome to indirectly provide blood flow to an adjacent one, if the artery of origin of the latter is damaged.

The endovascular revascularization based on the perfusion model of the angiosome, should be a more effective method than simply finding the best vessel, as the latter is not said to supply the area where the ulcer is located. In addition, it has recently been shown that indirect revascularization is associated with poorer results than direct one (23), because diabetics are poor in collateral circles.

Therefore, restoring flow to an artery directly supplying the affected area seems the best approach during an endovascular procedure (24).

Technical success is proven with an objective measurement of restored perfusion (21): any increase in volume flow to the foot has proven clinically beneficial when it also results in sufficient capillary perfusion with adequate oxygenation of foot tissue.

In patients with PAD and especially in diabetic macroangiopathy, pressure measurement is often unreliable due to the severity of calcified arteries (25, 26). Furthermore, perfusion of the foot does not only depend on the state of the artery inflow, but also on the state of the microcirculation.

There are currently no validated tests to predict the outcome of the treatment; functional methods such

as transcutaneous partial pressure oxygen monitoring (TcPO₂) (27, 28), individual tissue oxygen saturation (Sto₂) (29) and so on are currently under development. However, these techniques are not so easily accessible at the time of surgery and allow to evaluate the functional level of perfusion instead of macro-circulation.

Actually, the most widely used method of validating the technical success of revascularization is digital subtraction angiography (DSA) at the time of endovascular procedure in Angio-suite. However, a technically successful revascularization on DSA is not necessarily predictive of good clinical success, and vice versa.

Other emerging techniques, especially those based on magnetic resonance imaging, make it possible to map areas of poor tissue oxygenation and perfusion throughout the foot, beyond the skin, even if not immediately available during a revascularization procedure for decision making.

Among the imaging techniques based on the use of simple old DSA data for the evaluation of foot perfusion during interventional procedures, there are two types: two-dimensional (2D) and three-dimensional (3D) techniques.

Two-dimensional CT perfusion (also known as perfusion angiography), as a representation of the time density curve of the contrast volumetric flow in the foot, has been most widely used (30, 31), but as a 2D technique, it cannot calculate the 3D volume of foot perfusion. For this reason, the emerging 3D perfusion angiography technique (called Cone-Beam CT - CBCT) has started to take hold.

CBCT is an emerging medical imaging technique with the original feature of divergent radiation, forming a cone, in contrast with the spiral slicing of conventional CT (32, 33); it performs a complete rotation around the patient and the collimated axis projected on the patient generates a complete set of 3D volumetric data; moreover it includes C-arm rotation, flat panel detector acquisition and CT reconstruction technologies.

The technique involves the use of DSA for image acquisition, followed by the transfer of image data to a workstation for volumetric reconstruction, multiple planar reconstruction and maximum intensity projection reconstruction, resulting in 3D layered images

similar to CT. It can also provide projection radiography, fluoroscopy, DSA but also volumetric CT capabilities directly in the operating room before and after procedures, without the need for patient transport, resulting in effective assessments and potentially decreasing time to retreatment (Fig. 1).

This is why, over the years, CBCT has become increasingly important in treatment planning and diagnosis: from small anatomical areas, such as implantology, to the world of interventional radiology (34, 35, 36,37, 38), with a wide range of applications: as guidance for biopsies (39) or ablation treatments (40); for perfusion evaluation of brain (41-44) and liver, such as for assessing the technical success after transarterial chemoembolization of HCC or identifying the changes in blood volume in the tumor tissue and in the adjacent liver tissue with melanoma liver metastases (45, 46). But not only, in fact it has also been used in musculoskeletal surgery, such as in total ankle replacement or for evaluation of the patello-femoral alignment after medial ligament reconstruction (47), and finally in pediatric patients for common periprocedural complications after neuro-interventions (48), for the detection of ventricular size/subarachnoid spaces changes and large volume hemorrhage.

Although for the diabetic foot CBCT has only been applied for diagnostic evaluation (49), nowadays thanks to post-processing software based on the principle of subtraction between the mask image and the contrast fill image on dual-phase CBCT with the provider-specific vascular flow detection algorithm and automatic scaling, it is possible to have CBCT-based, color-coded perfusion images (50) and to measure the skin blood volume evaluated by CBCT data, which allows further evaluation of the blood volume increase during the procedure.

In this perspective, the purpose of our project is to evaluate the usefulness of CBCT-based foot perfusion imaging, obtained during endovascular revascularization in patients with diabetic foot, for assessing foot vascularity, technical success of the procedure, and treatment response, as an alternative to perfusion angiography.

To prove its effectiveness, we'd like to propose MRI of dependent blood oxygenation (BOLD) as a validation method, to investigate foot microcirculation in patients with DFD using skeletal muscle BOLD MR, immediately after revascularization, comparing with CBCT, and during its follow-up, also preventing continued radiation exposure and, using deoxygenated

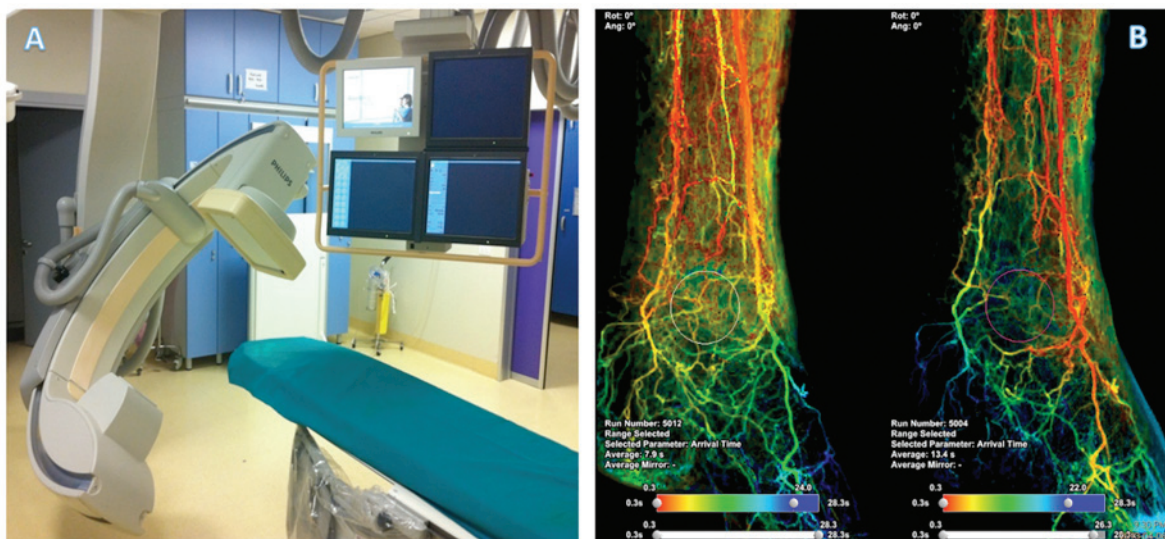


Fig. 1 - “3D Cone Beam CT perfusion angiography technique” – A. CBCT included in C-arm in angiography room; B. CBCT color-coded perfusion images.

hemoglobin as an endogenous contrast agent to perform non-invasive assessment of tissue oxygenation levels, avoiding contrast media-related reactions.

From a technical point of view, in the microvasculature, as in the large veins, hemoglobin iron changes its spin state from diamagnetic low-spin in the oxygenated state to paramagnetic high-spin in the deoxygenated state (51). This causes local magnetic field distortions in the surrounding tissue, which results in dephasing of the proton signal, consecutively leading to a signal decay with increasing intravascular deoxyhemoglobin content (52). These local field disturbances cause nearby stationary and slowly moving spins to have different resonance frequencies and phase shifts. The resultant “intravoxel dephasing” is a classic T2*-shortening effect accentuated by use of Gradient Echo (GRE) sequences with echo times close to T2*. Thus, changes in T2* in response to an ischemia-reperfusion paradigm can serve as a relative marker of tissue oxygenation (53).

It is also important to keep in mind that the oxygenation level of intravascular hemoglobin is not only dependent from oxyhemoglobin supply and deoxygenation rate of the respective tissue, but it is also sensitive to changes in perfusion, cellular pH, vessel diameter, and vessel orientation (54–59), considering the origin of BOLD-MRI signal as multifactorial. However, it has been postulated that the BOLD signal changes primarily result from changes in the concentration of deoxyhemoglobin in muscle microcirculation (60).

As already pointed out above, DM is associated with impairment of macro and microcirculation (61–63); while macroangiopathic alterations can be studied with Doppler ultrasound, MRI angiography or plethysmography (64, 65), the diagnostic evaluation of microangiopathic alterations still remains a challenge. In this scenario, since BOLD-MRI predominantly reflects oxygenation changes in peripheral microvasculature, it could be the best diagnostic tool to be used in patients with DM (66, 67) to correlate with microvascular oxygenation state (53, 68, 69).

In the past, BOLD-MRI was used to assess brain activation (52), but now it can also provide information regarding activation and oxygenation of many other tissues including the kidneys (70) and skeletal

muscles (54, 60, 68), as already done by Ledermann et al. and Potthast et al. that demonstrated the value of BOLD-MRI of skeletal muscle in assessment of microvascular function in patient with PAD (71, 72). Moreover, BOLD-MRI has also been used to evaluate the efficacy of PTA of superficial femoral artery in patients with symptomatic stenosis (73), underlying its potential usefulness in evaluation of treatment approaches, as endovascular revascularization.

Conclusion

The aim of this project is to evaluate the usefulness of perfusion CBCT imaging, obtained during endovascular revascularization, for intraprocedural evaluation of endovascular treatment in patients with diabetic foot. Furthermore, we'd like to propose BOLD-MRI to validate this method, as a diagnostic tool for a non-invasive, radiation and contrast media-free follow-up helpful in evaluation of microvessels in patients with DFD undergone to endovascular revascularization.

Consent for Publication: Consent for publication was obtained for every individual person's data included in the study.

Human and Animal Rights and Informed: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Informed Consent: Informed consent was obtained from all individual participants included in the study.

Authors Contributions: Each author has contributed to conception and design, analysis and interpretation of the data, drafting of the article, critical revision and final approval.

Conflict of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

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