Original Article

Quantitative assessment of tissue perfusion before and after peripheral angioplasty guided by perfusion angiogram, early and mid-term outcomes: A multicenter trial

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ABSTRACT

Aim: To evaluate the hemodynamics of contrast arrival and its tissue distribution. Also, provide objective assessment of different time-patterns both before and after endovascular intervention in patients with critical limb threatening ischemia. Moreover, to assess the technical feasibility and reproducibility of quantitative tissue perfusion in patients with peripheral artery disease through detecting changes in special tissue perfusion parameters after endovascular intervention.

Patients and Methods: This is a multicentric prospective study conducted over a period of 2 years from 2020 to 2022, the study enrolled 16 patients presented with critical limb ischemia and/or nonhealed ulcer in which a special predetermined protocol was applied in all patients aiming to perform endovascular procedures and perform objective assessment of tissue perfusion after the procedure guided by perfusion angiogram.

Results: Using the tissue perfusion parameters before and after endovascular interventions. A significant reduction was noted for arrival time (mean 6.12 pre vs. 2.29 post, $P<0.001$) and time to peak (mean 6.95 pre vs. 3.46 post, $P<0.001$). Also, a significant increase was found in wash in rate (mean 10.73 pre vs. 18.81 post, $P<0.001$) and area under the curve (mean 8.90 pre vs. 15.02 post, $P<0.001$).

Conclusion: Tissue perfusion parameters measurement is feasible and helpful to provide an endpoint for endovascular revascularization. Also, allow functional imaging that may help objectively select patients who will get benefit from additional revascularization. Moreover, applying tissue perfusion parameters is of great benefits in terms of reducing the length of the procedure, radiation exposure, and the volume of contrast.

Key Words: Critical limb ischemia, diagnostic accuracy, tissue perfusion.

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INTRODUCTION

Unfortunately, despite the advancement in revascularization techniques, some of the wounds in patients who underwent revascularization fail to heal and may progress to limb amputation, likely due to diabetic-related alterations to microcirculatory perfusion[1,2].

The endovascular interventionalist should keep in consideration some crucial points when planning an intervention for patients with critical limb ischemia (CLI). First is the revascularization of large vessels will eventually improve chance for wound healing or not. If yes, should the treating physician stick to the angiosomal revascularization concept and target the wound-related artery of concern or not? To get an answer to these questions precisely, it could be more reliable to measure tissue perfusion at the location of the wound preintervention and postintervention[2,3].

Noninvasive methods for objective measurement of tissue perfusion include transcutaneous O2 tension and skin perfusion pressure measurement, but this could be quite difficult to get these measurements during the angioplasty for CLI[3,4]. For this situation, tissue perfusion has become an evolving reliable technique for obtaining both qualitative and quantitative evaluation of tissue perfusion by creating virtual maps of blood flow and volume also can estimate mean transit time (MTT) for blood flow[2,5]. Application of tissue perfusion to the foot before and after revascularization can be used as an objective method for assessment of adequacy of wound perfusion[6,7].

PATIENTS AND METHODS:

This is a multicentric prospective study conducted for 2 years between 2020 and 2022 including 16 patients with CLI and/or nonhealed ulcers in which a special predetermined protocol was applied in all patients aiming to perform endovascular procedures and perform an objective assessment of tissue perfusion after the procedure guided by two-dimensional (2D) computed tomography (CT) perfusion angiogram. All interventions were done at Kasr Alainy Hospital and Al-Shiekh Zayed Specialized Hospital.

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Patients with a history of congestive heart failure, impaired kidney function, and patients with medical conditions that significantly reduce the chances of obtaining reliable data like dementia or psychiatric disorders were excluded from intervention.

All patients were loaded with clopidogrel (300 mg), and transferred to (Philips Allura Xper FD20 and Interventional Workspot; Philips Medical Systems, Conglomerate, Amsterdam, Netherlands) machines catheter laboratories.

After local anesthesia, we used ultrasound (US)-guided (9-MHz linear probe, GE Logic E9; General Electric Medical Systems, Milwaukee, Wisconsin, USA) to obtain the arterial access. An antegrade femoral access was used in most cases. However, brachial and/or cross-over femoral accesses were used in certain cases. a 6-F end-hole introducer sheath or a 7-F end-hole long sheath (Radifocus; Terumo, Tokyo, Japan) was used.

Administration of fentanyl (50–200 μg) and/or midazolam (dose up to 5 mg) was done to obtain conscious sedation in patients who experienced pain during the intervention.

Patients were anticoagulated with i.v. administration of 5000 IU unfractionated heparin.

Ultravist (Bayer Healthcare, Leverkusen, Germany) was used as a contrast medium for image acquisition during the endovascular intervention, this is preferred over other contrasts because it is associated with minimal burning sensation and subsequently, less likely to provoke motion of the patient.

The technique requires special software that does not add extra radiation exposure or require additional contrast to obtain a special image acquisition. This software analyzes tissue perfusion based on a calculation of the change in density per pixel over time for images that were obtained before the intervention in comparison to images obtained after the intervention.

For better assessment using this software, the foot should be kept immobilized during the evaluation. The reconstructed images can be evaluated for several items like contrast arrival time (AT), time to reach peak, contrast washout rate, and area under the curve (AUC).

The treating physician chooses the area of wound/ulcer (termed region of interest) (ROI) to determine a contrast time plotted to the density curve. A comparison of the image density before and after the intervention is then performed. Usually, the change in perfusion images is best illustrated by the changes in the AUC and the time to peak (TTP).

The software depends on the condensation of a sequential series of digital subtraction images into a single 2D color-coded map. At the area of the wound, ROI were manually selected at the area of the wound or nonhealed ulcer before starting the intervention, and then automatically the software started to create an identical ROI in the postangioplasty images.

Image density values were analyzed for each pixel of the DSA-images acquisition preangioplasty and postangioplasty. Recording of data for the obtained image was automatically done regarding special parameters like AT, TTP, WI, and AUC. AT reflects the inflow time for contrast to reach the target area. It is measured by calculating the time between the first frame and from of contrast appearance (measuring time of contrast appearance) and it indicates the flow changes proximal to area of interest (AOI). TTP reflects the time needed for contrast to travel into the tissues. It measures time laps between contrast arrival to the area of interest and achievement of maximum image density. WI represents the rate of blood flow through the ROI. It depends on both arterial flow and tissue resistance. Finally, AUC points to the total amount of volume that traverses through tissue. The AUC is standardized by calculating the AUC from the AT to the end time of the shortest acquisition for a given patient and this was applied to make sure the AUC is calculated over the same period and independent from acquisition time (Fig. 1).

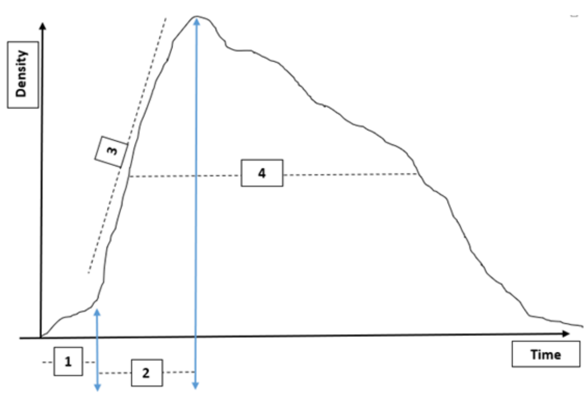

Fig. 1: Illustrative diagram for measured parameters. 1: arrival time (AT), 2: time to peak (TTP), 3: wash in rate (WI), and 4: area under the curve (AUC).

DSA of the foot usually has a special pre-requisite for imaging and should be done in two views with a relatively prolonged time to provide adequate filling time of the foot collateral circulation. The contralateral oblique view was usually first obtained to allow optimum visualization of the foot plantar artery and its two terminal branches (medial and lateral plantar arteries), as well as the dorsalis pedis and its continuation to the pedal arch. Then ipsilateral cranial view should be obtained to provide better visualization of the course of the planter arch and dorsalis pedis artery within the foot. It is to be mentioned that a high frame rate of 4 fps is recommended to get the best view images and to easily discriminate between overlapped vessels through their differential filling time.

Nitroglycerin 100–300 μg intra-arterially was administrated when arterial spasm was encountered (it is used when arterial spasm was found in the completion angiogram and affecting the parameters of tissue perfusion especially AT and TTP. Administration of nitroglycerine can positively improve these parameters after correction of the arterial spasm).

Evaluating the results of the intervention is better provided by measuring the relative increase of AUC and the maximum peak density.

Data were coded and entered using the Statistical Package for the Social Sciences (SPSS), version 28 (IBM Corp., Armonk, New York, USA). Data was summarized using mean and SD for quantitative variables and frequencies (number of cases) and relative frequencies (percentages) for categorical variables. Comparisons between pretest and posttests were done using paired t tests. *P values* less than 0.05 were considered statistically significant.

Study approval was obtained from the medical ethical committee review board and was performed in agreement with the 1990 Declaration of Helsinki and subsequent amendments. Written informed consent was obtained from all patients for the acquisition protocol.

RESULTS:

The baseline demographics of this study are summarized in (Table 1). The baseline demographics of this study were age 61±55, 28 (57.1%) male patients and 21 (42.9%) female. Thirty-three (67.3%) were diabetic, 31 (63.3%) were hypertensive, smoking was found in 30 (61.2%) patients, dyslipidemia was observed in 22 (44.9%) patients and ischemic heart disease was recorded in 14 (28.8%) patients.

Patients' presentations were variable. Claudication was the main presentation in two (12.5%) patients, rest pain in four (25%) patients, cyanosis in the toes in three (18.8%) patients, foot infection in two (12.5%) patients, foot gangrene in five (31.3%) patients, and fixed color over the foot in one (6.25%) patient.

All patients were treated by successful restoration of blood flow with underlying or offending lesions located in superficial femoral artery (SFA) in seven (43.8%) patients, tibials in two (12.5%) patients, combined SFA and tibials in two (12.5%) patients, popliteal and tibials in one (6.25%) patient, combined SFA, popliteal, and tibials lesion in one (6.25%) patient, bilateral iliac in one (6.25%) patient, combined iliac and SFA in two (12.5%) patients. The anatomical distribution of the lesions is summarized in (Table 2).

Common femoral artery access (ipsilateral antegrade, ipsilateral retrograde, and contralateral cross-over) was used during the endovascular intervention in 14 (87.5%) patients, brachial access in one (6.25%) patient and combined femoral and brachial access in one (6.25%) patient.

A preplanned AOI was applied for all the treated patients to assess their perfusion after the intervention. Foot was the main domain as AOI in 12 (75%) patients, knee in three (18.8%) patients, and groin in one (6.25%) patient.

Using the tissue perfusion parameters before and after endovascular interventions was routinely applied for all treated patients. It is used to identify several patterns of arrival and contrast diffusion patterns (Fig. 2). A significant reduction was noted for AT (mean 6.12 pre vs. 2.29 post, $P<0.001$) and TTP (mean 6.95 pre vs. 3.46 post, $P<0.001$). Also, a significant increase was found in WI (mean 10.73 pre vs. 18.81 post, $P<0.001$) and AUC (mean 8.90 pre vs. 15.02 post, $P<0.001$). All detailed data about perfusion parameters are described in (Table 3).

To be mentioned, in patient number 14, the pedal-planter arch was identified as AOI before the start of endovascular intervention, and at the end of the intervention, all angiographic images were satisfactory apart from a small nonflow limiting dissection flap in the mid-popliteal artery. However, AUC did not increase in the postinterventional tissue perfusion parameter, for which a "supera" stent was applied for the popliteal artery dissection flap with subsequent increase in the AUC parameter. This denote that despite the adequate angiographic images for the foot but the tissue perfusion parameters could be helpful to unmask the missed or hidden lesions that may hinder better clinical outcome for the patients (Fig. 3).

Successful revascularization and technical success were achieved in all patients with few procedures-related complications, two (12.5%) patients with minor groin hematomas, and one patient with CIN which were managed conservatively and regained normal serum creatinine levels within 10 days.

After 1 month, follow-up showed patent previously treated arteries in 15 (93.75%) patients and unfortunately, the remaining patient died after 10 days from septicemia and multiple organ system failure.

After 3 months, follow-up showed patent previously treated arterial segments in 14 (87.5%) patients and one patient developed in-stent restenosis (ISR) within the deployed stent which was treated by paclitaxel drug-coated balloon (DCB) with satisfactory angiographic imaging results.

After 6 months, follow-up showed patent previously treated arterial tree in 12 (75%) patients. And three patients developed ISR and these patients were re-treated by Paclitaxil DCB (one of them has already been treated by Paclitaxil DCB in the previous follow-up visit, and unfortunately, this patient ended up with above knee amputation after 8 months from spreading foot infection).

Accordingly, clinically driven target lesion revascularization was needed in three (18.75%) patients in the form of re-do angioplasty for ISR using Paclitaxil DCB.

Major limb adverse event (MALE) unfortunately happened in one patient who ended up with knee amputation due to a spreading foot infection. However, minor amputations were done in four (25%) patients. All data for MALE and minor amputations was described in (Table 4). Only one (6.25%) case died 10 days postoperatively from septicemia and multiple organ system failure.

Table 1: Patient characteristics and demographics

	Count	%
Sex		
Male	11	68.8
Female	5	31.3
DM		
Yes	11	68.8
No	5	31.3
HTN		
Yes	11	68.8
No	5	31.3
Smoking		
Yes	13	81.3
No	3	18.8%
Dyslipidemia		
Yes	10	62.5
No	6	37.5
IHD		
Yes	4	25.0
No	12	75.0

Table 2: Anatomical distribution of the lesions

	Count	%
Anatomical location of the lesion		
SFA	7	43.8
Tibials	2	12.5
SFA+Tibials	2	12.5
SFA+popliteal+Tibials	1	6.3
Popliteal+Tibials	1	6.3
Iliac+SFA	2	12.5
Bilateral iliac	1	6.3

Table 3: Comparison between perfusion parameters preintervention and postintervention

	Mean	SD	Minimum	Maximum	*P* value
AT (pre), s	6.12	1.79	2.99	9.44	<0.001
AT (post), s	2.29	0.70	0.91	3.11	
TTP (pre), s	6.95	2.02	3.25	10.50	<0.001
TTP (post), s	3.46	0.64	2.10	4.25	
WI (pre)	10.73	2.11	7.20	15.25	<0.001
WI (post)	18.81	1.98	15.15	23.10	
AUC (pre)	8.90	1.65	6.25	11.67	<0.001
AUC (post)	15.02	3.45	10.50	20.21	

Table 4: MALE and minor foot amputations

	Count	%
MALE		
TMA	1	6.3
Lateral 4 toes amputation	1	6.3
Big toe amputation	2	12.5
AKA (8 months)	1	6.3
No	10	62.5
N/A (died 10 days postoperative)	1	6.3

MALE, major adverse limb event; (TMA, transmetatarsal amputation.

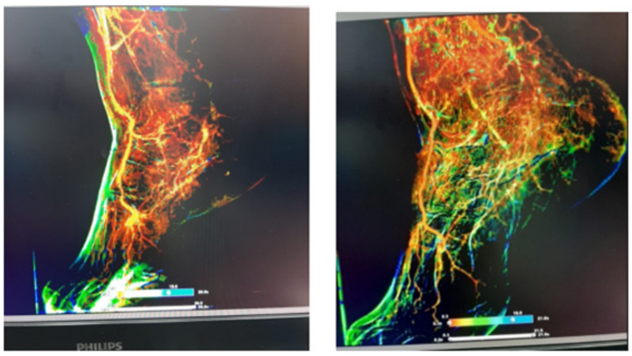

Fig. 2: Case underwent successful peripheral angioplasty with ROI was manually chosen at the medial malleolus (area of ischemic saphenous harvesting wound for CABG) which showed improvement of perfusion parameters after angioplasty. ROI, region of interest.

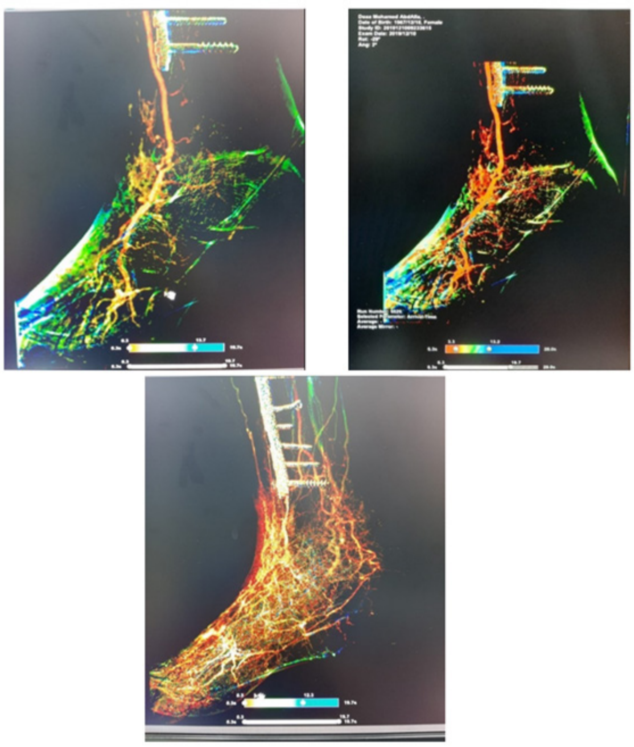

Fig. 3: Before and after peripheral angioplasty with ROI was manually drwan at the mid and forefoot (gangrenous big and second toes). Angiographic images were satisfactory apart from a small nonflow limiting dissection flap in the mid-popliteal artery. However, AUC did not increase in the postinterventional tissue perfusion parameter, for which a "supera" stent was applied for the popliteal artery dissection flap with subsequent increase in AUC parameter. ROI, region of interest.

DISCUSSION

Based on physics and hemodynamics, "perfusion" is defined as flow per unit of tissue (ml/min/g) and this should be differentiated from "flow" which is defined as volume over time (l/min)[8].

Using the traditional angiographic images of macrovessels for evaluation of clinical success may be in adequate in certain situations, as these methods only show blood flow through the main vessels, but do not evaluate tissue perfusion which reflects the liability of wound healing[8].

Other authors have observed that macrovascular disease is not the only incriminated part in poor foot perfusion, but also problems with local tissue microcirculation can play a significant role, especially in diabetic and renal impairment patients[9].

From both practical and theoretical perspectives points of view, usually, it is not always possible to technically provide a direct angiosomal revascularization. Also being rational that the more vessels to be reopened and treated the better the clinical outcome; however, these extended endovascular procedures could be time-consuming and expensive[9].

Many literatures suggest that tissue perfusion angiogram can be used to test how adequate the tissue microcirculation is, subsequently, it could help us to select the patient who may benefit from angioplasty, also tissue perfusion could judge and evaluate the adequacy of tissue revascularization[10].

Previously, many treating physicians used to rely on angiographic "wound blush" which may indicate a higher possibility of wound healing and limb salvage for patients with CLI. And this angiographic wound blush is not related to the angiosomal concept because it relies on the qualitative assessment of tissue perfusion, moreover, there is no solid method to quantify the wound blush as it relies on the visual assessment of the treating physician. Some authors suggest using indocyanine green and tissue O2 saturation. However, these methods are quite difficult to implement in the angio-suite[10–13].

In contrast to nitrates, which mainly act on the macro-circulation, tolazoline is a nonselective α-adrenergic receptor blocker that causes an increase in capillary bed arteriovenous shunting. In patients with diabetic microangiopathy, arteriovenous shunting is usually diminished. For the above-mentioned reason, tolazoline is used to test the functionality of the tissue capillary bed and subsequently tissue perfusion[9]. Reekers and colleagues have introduced the term capillary resistance index which is obtained by dividing the maximal peak density after tolazoline stimulation by baseline maximal peak density. Provisional results showed that patients with a capillary resistance index of less than 0.9 may have a better outcome and less MALE[9,10].

DSA is considered as an indirect diagnostic evaluation of perfusion at the level of the capillary bed. However, with the addition of perfusion parameters, a much more detailed picture is obtained. This is done by measuring the AT in addition to the flow volume traversed through the previously selected ROI thus describing the distribution within the microcirculation[14,15].

To properly assess foot perfusion, the ROI was chosen manually on the foot perfusion image panel, as calculated from the DSA. Then obtained a time-to-density curve from these DSA images for the previously chosen ROI, in which time was plotted on (x-axis) and contrast density was plotted on (y-axis). The procedural functional parameters were then automatically calculated from this curve before and at the end of the intervention. Parameters include: AT indicated the initial time of contrast detection at the previously chosen ROI. Time to peak indicates the interval of time from the AT to the maximum density of contrast. WI was the contrast flow velocity. The AUC was the estimated total tissue perfusion within the previously determined ROI. These values for functional parameters were expressed as means±SEM. The functional parameters of 2D perfusion angiogram allow for intraoperative assessment of quantitative peripheral perfusion data[16,17].

Initially, a 2D perfusion angiogram was used to perform quantitative intracranial perfusion[18,19]. Then 2D perfusion angiogram was applied in other clinical fields like assessment of reduction of tumor perfusion after chemoembolization of hepatocellular carcinoma[20].

in a review of cases published by Jens *et al*.[15], the authors documented that increased AUC post successful below-the-knee angioplasty and AUC left unchanged after failed angioplasty which could highlight the feasibility of tissue perfusion for postangioplasty assessment.

Also, Murray *et al*.[14], have published a retrospective single-center study and compared tissue perfusion parameters before and after peripheral angioplasty with ROI at the mid and hind foot. The authors documented changes in tissue perfusion parameters after successful endovascular revascularization especially changes in AUC.

In another retrospective single-center study published by Hinrichs and colleagues, the tissue perfusion parameters were correlated to ankle brachial pressure index (ABI) before and after peripheral endovascular interventions for 24 patients with above and below-the-knee lesions. The authors demonstrated a strong correlation between tissue perfusion parameters and ABI before and after interventions especially TTP which showed a significant correlation[17].

In a cohort study published by Kim and colleagues, foot tissue perfusion parameters (AT, TTP, WI, AUC, and MTT) were measured and correlated to ABI for 31 patients with peripheral arterial disease. The ROI was manually selected at the level of the medial malleolus. The authors have proven that tissue travel time decreased while blood flow volume (AUC) increased after successful angioplasty revascularization. In addition, a significant correlation was found between perfusion parameters and ABI[21].

Reekers and colleagues, have published a prospective observational study in 89 patients with CLI who underwent angioplasty for below-the-knee arterial disease. The preinterventional and postinterventional perfusion parameters were observed and recorded. They found volume flow increased (increased AUC and TTP) after successful angioplasty. Moreover, the authors have tested the perfusion functionality by parenteral administration of tolazoline and repeated the acquisition of parameters before and immediately after administration of tolazoline. They suggested that perfusion angiogram in combination with pharmacological stimulation of microcirculation can highlight more functional information about the foot microcirculation[9].

Kagadis and colleagues, have published a prospective single-center study including five patients who were scheduled for infrapopliteal angioplasty. Perfusion parameters especially perfusion blood volume, MTT, and perfusion blood flow maps were acquired and analyzed on time-intensity curves. The results were recorded from the previously user-determined (ROIs). They have found that MTT decrease after successful angioplasty was observed in four out of five cases, and these findings proved an increase in tissue perfusion. These parameters have reflected on the clinical outcomes regarding wound healing at 6-month follow-up[22].

Other tissue perfusion parameters were used by Parsson and colleagues, in a prospective cohort study for 37 patients with CLI who were underwent infrainguinal angioplasty, 33 patients of them were enrolled in the study and the remaining patients were excluded due to motion artifact. They demonstrated a significant reduction in AT between preangioplasty and postangioplasty (2.5–4.2 vs. 1.6–3.4) and TTP (3.6–5.0 vs. 2.3–3.9) with significant ($P=0.009$). Moreover, an increased WI rate was also observed (12.6–21 vs. 22–30.5, $P = 0.001$) between preangioplasty and postangioplasty acquisition images[8].

Recently, 3D perfusion angiogram was invented and started to be applied for tissue perfusion assessment on a small scale. This technique is quite more challenging from the technical point of view, it provides a direct method for volume measurement for tissue preprocedural and postprocedural. This technique was acquired through rotational angiography with a 6-s acquisition within a 28-cm field of view. The acquired images were plotted and analyzed for the intensity of the perfusion signal. To date, only 35 patients with CLI have been reported to be evaluated with 3D perfusion angiography preprocedural and postperipheral endovascular revascularization. In 25 patients, tissue perfusion illustrated an improved tissue perfusion after revascularization[2].

CONCLUSION

Two-dimensional perfusion angiography is a clinically helpful assessment tool that can aid in determining an endpoint for endovascular intervention. It provides a real-time functional assessment that could facilitate selection of patients who may benefit from extra-revascularization options. Being available during the endovascular treatment, the decision to open more outflow arteries or not before finishing the procedure to achieve optimal inflow is clearly defined. This advantage give potential benefits in terms of reducing the operative time, radiation exposure contrast volume, and total cost.

Study limitations

The most important one is that the number of patients investigated was small. Therefore, regardless of the aforementioned promising results, the small number of patients included in the analysis deteriorates the generalization properties of the proposed approach.

CONFLICT OF INTEREST

There are no conflicts of interest.

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