EJVES Short Reports (2019) 45, 1–6

ORIGINAL RESEARCH

Assessment of Flow after Lower Extremity Endovascular Revascularisation: A Feasibility Study Using Time Attenuation Curve Analysis of Digital Subtraction Angiography

Jun J. Ng *, **Evangelos Papadimas, Rajesh B. Dharmaraj**

Department of Cardiac, Thoracic and Vascular Surgery, National University Heart Centre (NUHCS), Singapore, National University Health System (NUHS), Singapore

Objectives: Endovascular revascularisation is the mainstay of the treatment of lower extremity peripheral arterial disease. Improvement in perfusion after treatment is often quantified by a corresponding increment in ankle or toe brachial indices. These measurements are difficult to obtain in patients with foot wounds, and have to be performed at a separate time and setting after revascularisation. This preliminary study aimed to evaluate the use of parametric colour coding and analysis of time attenuation curves as a real time quantitative measure of perfusion after endovascular revascularisation.

Methods: Forty-seven consecutive patients with critical limb ischaemia were retrospectively enrolled and analysed. Parametric colour coding and generation of time attenuation curves in the main pedal vessel was performed for pre- and post-intervention digital subtraction angiograms of each patient. The change in time attenuation curve parameters was compared with the change in ankle or toe brachial indices before and after intervention.

Results: Comparing before and after lower extremity endovascular intervention, there were significant changes in the washout parameters derived from the time attenuation curve. The percentage of contrast decay 4 seconds after peak (I_{4s}) demonstrated the strongest correlation ($R = .482$) with the change in ankle or toe brachial indices.

Conclusions: Parametric colour coding and time attenuation curve analysis might be a helpful tool that can provide real time intra-procedural quantitative data on pedal perfusion which can improve clinical outcomes.

Article history: Received 23 April 2019, Revised 25 July 2019, Accepted 28 July 2019,

Keywords: Endovascular, Perfusion, Revascularisation

INTRODUCTION

Lower extremity peripheral arterial disease (PAD) is responsible for more than 400 000 inpatient admissions annually in Europe and North America, and is estimated to affect up to 12% of the global population. In the more affluent and developed countries, risk factors for atherosclerosis such as diabetes mellitus, hyperlipidaemia, hypertension, and metabolic syndrome are rising, leading to a corresponding increase in the incidence of PAD.[1] Percutaneous endovascular intervention by angioplasty, or stenting, or a combination of both, is one of the main modalities of treatment to improve foot perfusion in patients with PAD. In current practice, measurements such as the ankle brachial index (ABI), absolute toe systolic pressure, toe brachial index (TBI), or transcutaneous oxygen pressure are used, which are recorded before and after surgery, to assess the severity of PAD, and to quantify the improvement in foot perfusion after lower extremity endovascular intervention.[2–4] Unfortunately, these measurements are often hampered by issues such as prior transmetatarsal or toe amputations, open wounds, or falsely elevated values secondary to medial calcific sclerosis.[5] In addition, these measurements have to be performed at a discrete separate setting after revascularisation, and, hence, cannot be used to provide a real time assessment of perfusion in the lower extremity. Often, the effectiveness of endovascular intervention and improvement in foot perfusion is assessed by interpreting the two dimensional image of contrast flow through a three dimensional vessel, which can be subjective. Parametric colour coding of digital subtraction angiography (DSA) acquisitions is a post-processing technique that has been used in the treatment and evaluation of cerebrovascular diseases and patients after liver transplant.[6–12] The aim was to evaluate the feasibility of using parametric colour coding in DSA and numerical analysis of time

* Corresponding author. Department of Cardiac, Thoracic and Vascular Surgery, Level 9, NUHS Tower Block, 1E Kent Ridge Road. 119228, Singapore.
E-mail address: .jun_jie_ng@nuhs.edu.sg (Jun J. Ng).

https://doi.org/10.1016/j.ejvssr.2019.07.005

attenuation curves (TACs) to objectively quantify and assess in real time the haemodynamic changes and improvements in foot perfusion after lower extremity endovascular intervention.

METHODS

Patient selection

Following approval by the local institutional review board, 47 consecutive patients with 47 lower extremity endovascular interventions from the period of January 2015 to August 2015 were retrospectively enrolled in the study from the angiographic database. All lower extremity endovascular interventions were performed for patients with PAD and chronic lower extremity critical limb ischaemia, as defined by the presence of rest pain, or with tissue loss. None of the patients were on intravenous vasodilators before or during the procedure.

Ankle brachial or toe brachial index measurement

All enrolled patients were investigated with a pre-intervention lower extremity arterial duplex scan and underwent pre- and post-intervention ABI or TBI measurements in the affected lower extremity using an automated device (Multilab Series II LHS, Unetixs Vascular, North Kingstown, RI, USA). ABI values were obtained first, and if determined to be falsely elevated secondary to medial calcific sclerosis, TBI values were recorded. The differences in pre- and post-endovascular intervention ABI or TBI values were then used for comparative analysis.

Digital subtraction angiography

DSAs were performed using a robotic flat panel, multi-axis, interventional angiographic system (Artis zeego, Siemens Healthcare, Forchheim, Germany) in a hybrid operating theatre. A 10 mL bolus of 50% diluted iohexol contrast medium (Omnipaque, GE Healthcare, Amersham, UK) was hand injected via an antegrade transfemoral 10 cm 5 F sheath for the DSA sequence. In all patients, access was obtained via the common femoral artery. No saline flushes were used during the DSA acquisition phase. Pre- and post-endovascular intervention DSA images of the foot were acquired at four frames per second until all foot pedal vessels were fully opacified and subsequently washed out.

Parametric colour coding and time attenuation curve analysis

Parametric colour coding of pre- and post-intervention DSA acquisitions were performed using commercially available post-processing software (syngo iFlow, Siemens Healthcare) installed on the standard angiography workstation (Fig. 1). Parametric colour coding assigns a particular colour to each pixel within the two dimensional DSA image, ranging from red to blue based on the time delay between contrast injection and maximum opacification, demonstrating the temporal evolution of contrast flow. Besides colour coding the DSA sequences, the post-processing software also allowed generation of a TAC for a specific region of interest (ROI) on the main run off pedal vessel to the foot, which is a graph comparing contrast intensification against time. The resulting TACs were then exported from the post-processing software for further numerical analysis in a research

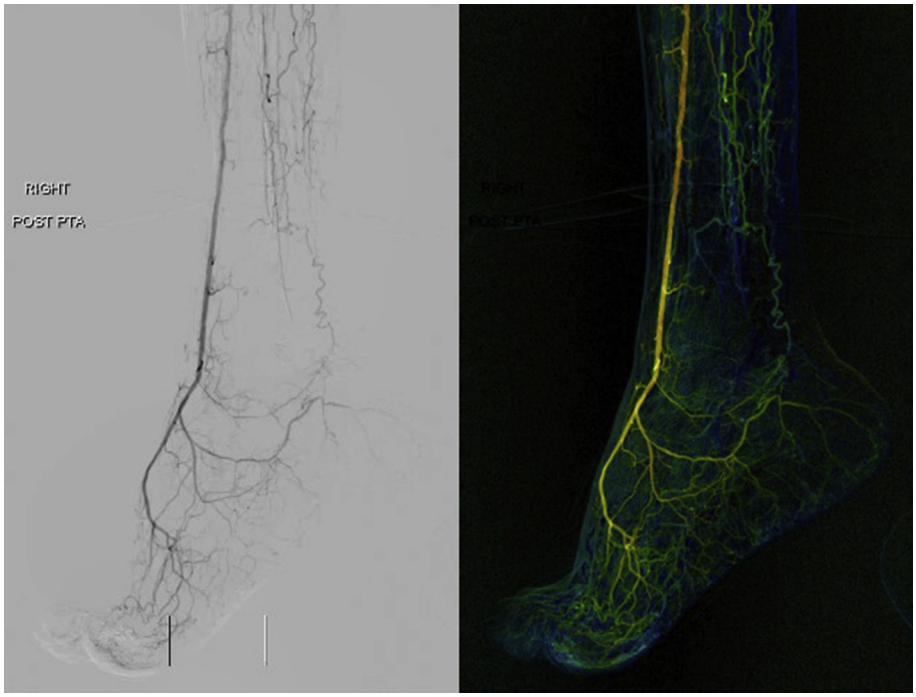

Figure 1. (A) Standard digital subtraction angiographic sequence of the foot. (B) Parametric colour coding of same standard digital subtraction angiographic sequence using post-processing software. PTA = posterior tibial artery.

software prototype developed and provided by Siemens Healthcare. From numerical analysis of each TAC, parameters such as the time to peak (T_{max}), maximum contrast intensity (I_{max}), washin and washout gradients could be derived (Fig. 2). The T_{max} of a ROI is defined as the time needed to reach maximum contrast intensification. The washin gradient represents the average contrast flow velocity before reaching maximum contrast intensity and is a function of maximum contrast intensity over the time to peak. In contrast, the washout gradient represents the average flow velocity from maximum contrast intensification to complete contrast washout and is a function of maximum contrast intensity over washout timing after the time to peak. The washout phase of the TAC was further quantified by deriving additional variables (Fig. 3), such as the percentage of contrast decay at various time intervals (i.e. 1, 2, and 3 sec) after peak (I_{1s}, I_{2s}, and I_{3s}), or the time required for contrast intensity to decay to a certain percentage (i.e. 90%, 80%, and 70%) after peak intensity ($T_{90\%}$, $T_{80\%}$, $T_{70\%}$). The differences in the parameters derived from the washout phase before and after endovascular intervention were quantified and correlated with the change in ABI or TBI values.

Statistical analysis

Statistical analysis was performed using SPSS version 22.0 (IBM Corporation, New York, USA). The Wilcoxon signed rank test was used to compare washout phase parameters before and after endovascular intervention whereas the Pearson's correlation coefficient was used to quantify the linear correlation between changes in washout curve parameters against changes ABI or TBI. A confidence level of 95% was used and $p < .05$ was considered to be statistically significant. A Pearson's correlation coefficient of between 0 and 1 was considered a positive correlation.

RESULTS

The baseline demographics and characteristics of the patient population are shown in Table 1. Most patients were of Chinese ethnicity with an average age of 66.2 years, and an equal gender distribution. A significant majority of the patients had pre-existing diabetes mellitus (89.4%) and chronic renal impairment (46.8%). More than half of the patients with chronic renal impairment had end stage renal disease requiring renal replacement therapy. Eighty-three per cent of patients were having lower extremity revascularisation due to the presence of tissue loss, whilst 17% of patients had severe rest pain.

Following lower extremity endovascular intervention, the mean ABI or TBI improved significantly from 0.33 $\pm$ 0.26 to 0.62 $\pm$ 0.28 ($p < .001$). Analysis of the washout phase parameters showed a significant reduction in time required for contrast to decay to a specified percentage after peak ($T_{90\%}$, $T_{80\%}$, $T_{70\%}$, $T_{60\%}$, and $T_{50\%}$). Correspondingly, the percentage of contrast decay at specified time intervals after peak (I_{1s}, I_{2s}, I_{3s}, I_{4s}, and I_{5s}) was increased significantly. For example, the time required for contrast decay to 80% after peak ($T_{80\%}$) was reduced from 1.68 $\pm$ 0.9 sec to 0.51 $\pm$ 0.3 (p .001) following intervention, whereas the percentage of contrast decay 2 sec after peak (I_{2s}) was increased from 31.09 $\pm$ 17.08% to 57.15 $\pm$ 20.65% ($p < .001$). The mean values of all pre-and post-intervention washout phase parameters are shown in Table 2.

Changes in ABI or TBI before and after endovascular intervention were then correlated to corresponding changes in washout phase parameters. The percentage of

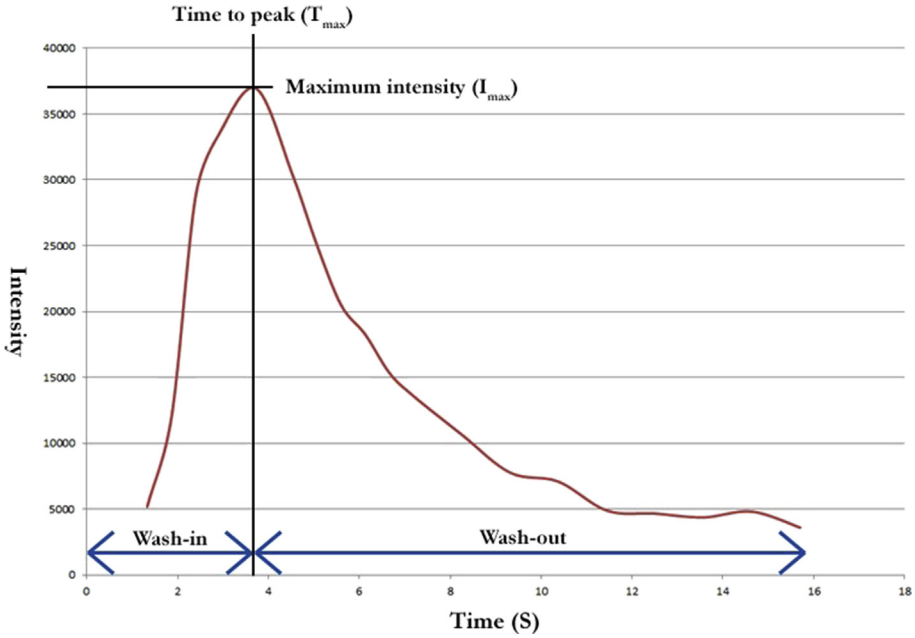

Figure 2. Time attenuation curves were generated from specific regions of interest on digital subtraction angiographic sequences which consisted of basic parameters such as the time to peak, maximum intensity, and comprising of the washin and washout phases.

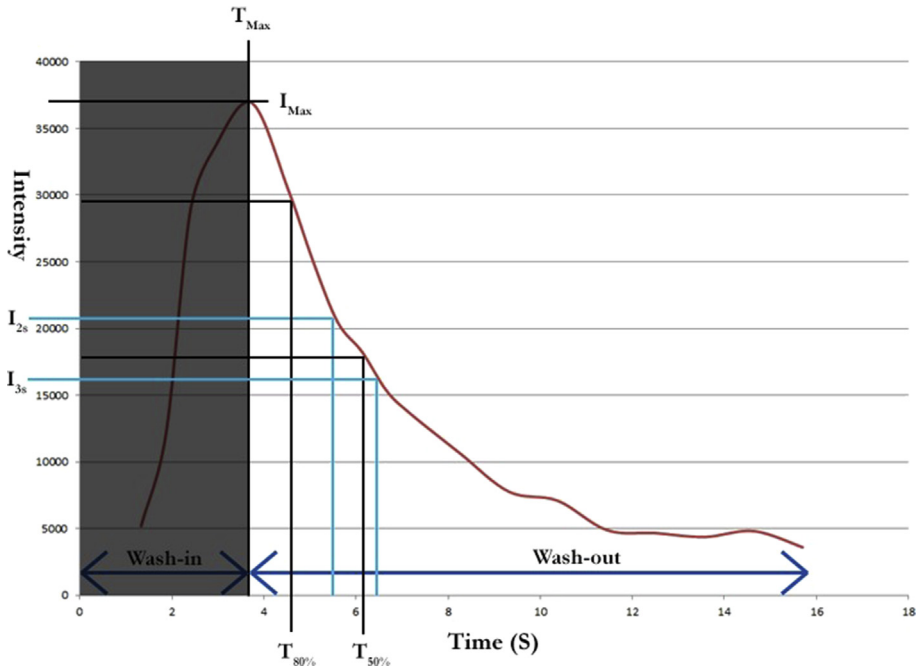

Figure 3. Additional parameters were further derived from the washout segment of the time attenuation curve. For example, the percentage of contrast intensity after 3 sec after peak (I_{3s}), as shown in the light blue lines, is derived as a percentage over the maximum intensity (I_{Max}), whereas, the time required for 50% contrast decay to occur ($T_{50\%}$), as shown in the black lines, is calculated from the time after time to peak (T_{Max}).

contrast decay 4 sec after peak (I_{4s}) demonstrated the highest correlation coefficient ($R = .482$) with improvement in ABI or TBI. The Pearson correlation coefficient for changes in all washout parameters when correlated to changes in ABI or TBI are shown in Table 3.

Table 1. Patient characteristics.

Characteristic	$n = 47$
Age ±SD, years	66.2±11.1
Gender	
Male	24 (51.1)
Female	23 (48.9)
Ethnicity	
Chinese	29 (61.7)
Malay	8 (17)
Indian	8 (17)
Others	2 (4.3)
BMI ±SD (kg/m^2)	25.3±5.6
Comorbidities	
Ischaemic heart disease	25 (53.2)
Cerebrovascular disease	8 (17)
Diabetes mellitus	42 (89.4)
Chronic renal disease	22 (46.81)
Pre-RRT	8 (36.4)
On RRT	14 (63.6)
Treatment indication	
Rest pain	8 (17)
Tissue loss	39 (83)

Data are presented as *n* (%) unless stated otherwise. BMI = body mass index; RRT = renal replacement therapy; SD = standard deviation.

DISCUSSION

Two dimensional DSA is currently the gold standard method used to evaluate the success of lower extremity endovascular intervention. However, despite DSA being an integral part of lower extremity revascularisation procedures, there are still limitations to its use. The assessment of flow or haemodynamic changes using DSA during lower extremity endovascular intervention is routinely conducted using simple visual interpretation or in an "eyeballing" fashion by the operator. As a result, the assessment of the success of revascularisation can be operator dependent and qualitative in nature. Several studies, although not conducted

Table 2. Pre- and post-intervention parameters.

	Pre-intervention (n=47)	Post-intervention (n=47)	p value
Decay time ± SD, s			
$T_{90\%}$	1.03±0.62	0.31±0.19	<.001
$T_{80\%}$	1.68±0.9	0.57±0.21	<.001
$T_{70\%}$	2.24±1.17	0.7±0.22	<.001
$T_{60\%}$	2.53±1.22	0.76±0.16	<.001
$T_{50\%}$	2.89±1.31	0.82±0.14	<.001
Decay intensity ± SD (%)			
I_{1s}	13.66±0.11	31.38±19.32	<.001
I_{2s}	31.09±17.08	57.15±20.65	<.001
I_{3s}	45.38±18.1	69.96±21.89	<.001
I_{4s}	53.58±19.5	76.29±15.6	<.001
I_{5s}	52.18±23.45	82.1±13.74	.02
AUC	2.81±0.9	2.05±0.82	<.001
ABI/TBI	0.33±0.26	0.62±0.28	<.001

ABI/TBI = ankle brachial index/toe brachial index; AUC = area under curve; SD = standard deviation.

Table 3. Correlation of change in washout parameters with ABI/TBI.

	Pearson correlation	*p* value
Contrast decay		
I_{1s}	.34	.02
I_{2s}	.4	.006
I_{3s}	.41	.005
I_{4s}	.48	.002
I_{5s}	.15	.41
Decay time		
$T_{90\%}$	.25	.09
$T_{80\%}$	.29	.05
$T_{70\%}$	.32	.04
$T_{60\%}$	.05	.75
$T_{50\%}$	.16	.34
AUC	.21	.17

ABI/TBI = ankle brachial index/toe brachial index; AUC = area under curve.

exclusively for lower extremity DSA, have shown that simple visual interpretation of angiography is associated with significant intra- and inter-observer variability.[13,14] Simple visual analysis of DSA images has been a widely adopted and established method of haemodynamic assessment since its advent, but the lack of quantitative and volumetric characterisation limits its accuracy in modern day vascular practise.

The implementation of parametric colour coding of DSA sequences before and after lower extremity endovascular intervention allows for a real time quantitative assessment of pedal vessel perfusion. This potentially negates the inaccuracies and subjectivity of simple visual interpretation. In this feasibility study, various parameters associated with the TAC were analysed and correlated with changes in TAC output to changes in ABI and TBI, with the aim of establishing a reliable marker within the TAC that can predict changes in pedal perfusion. Although there are limitations to the use of ABI or TBI, these indices were selected to be a compared with TAC parameters as they have been shown in studies to correspond well to pedal perfusion.[15]

In this study, it was postulated that the washin phase was mainly determined by the volume and velocity of contrast injection, while vessel patency mainly influenced the washout phase which is why only analysis of the washout phase parameters were performed. Washout phase parameters showed a significant reduction in time required for contrast to decay to a specified percentage after peak ($T_{90\%}$, $T_{80\%}$, $T_{70\%}$, $T_{60\%}$, and $T_{50\%}$). Correspondingly, the percentage of contrast decay at specified time intervals after peak (I_{1s}, I_{2s}, I_{3s}, I_{4s}, and I_{5s}) was increased significantly. After correlating the changes in washout parameters with changes in ABI and TBI, it was found that changes in I_{4s} correlated strongest with the changes in ABI or TBI measurements. As such, the change of I_{4s} values after lower extremity intervention could possibly be used as an intra-procedural marker for improvement in pedal perfusion.

At present, the only reliable means of obtaining quantitative data documenting the changes or improvements in pedal perfusion before and after endovascular lower extremity intervention can be achieved by performing before and after measurements such as ABI or transcutaneous oxygen pressure. These tests are conducted at a separate setting from the endovascular intervention and cannot provide any real time information to the operator during the procedure. Quantitative data derived from the TAC can be quickly and easily derived from DSA acquisitions to ascertain tissue perfusion, and hence, enabling the operator to evaluate therapeutic effects in real time, with the objective of improving revascularisation outcomes. Other methods such as indocyanine green angiography or tissue oxygen saturation mapping also allow for real time intra-procedural evaluation of pedal perfusion and flow, but these methods require an additional injection of intravenous drugs and proprietary image capture systems that are separate from the angiography equipment.[16–18] Parametric colour coding of DSA sequences and TAC analysis do not require any additional equipment and are simple to implement.

This clinical study is limited by its small sample size and retrospective nature. However it is meant only to be a feasibility assessment on the use of parametric colour coding and TAC analysis, which have been proven to be useful in the clinical setting. Further validation in a prospective setting and with a larger patient sample size is needed to address the value of parametric colour coding and TAC analysis in daily clinical practice. One of the major drawbacks of this study is the use of hand injection for contrast administration, which can lead to significant variation in initial contrast velocity on the TACs. As the variation in initial contrast velocity could not be controlled or corrected due to inconsistencies and non-standardisation associated with hand injection, the parameters related with the washin phase and time to peak values were not analysed. Instead, the washout phase of the TAC was quantified and analysed, which was less likely to be influenced by contrast injection and flow. Moreover, as the procedures were performed by a single surgeon, this variability is minimised. In future validation studies, an automated contrast injector will be used so that the velocity of contrast injection is uniform throughout all patients. Lastly, in this study, TBI was only performed for patients who had falsely elevated ABI values. Again, in future validation studies, TBI should be performed in all patients as a quantitative indicator of improvement in foot perfusion.

CONCLUSION

Parametric colour coding and TAC analysis using the Syngo iFlow software as a post-processing algorithm of DSA acquisitions in patients undergoing lower extremity endovascular intervention appears to be a helpful tool that can provide real time quantitative data on haemodynamic flow and pedal perfusion during the procedure which is not provided by traditional two dimensional DSA images. This can potentially help limit suboptimal results after lower extremity endovascular intervention and hence improve long term patient outcomes.

CONFLICT OF INTEREST

None.

FUNDING

None.

REFERENCES

1 Aboyans V, Ricco JB, Bartelink MEL, Björck M, Brodmann M, Cohnert T, et al. Editor's choice - 2017 ESC guidelines on the diagnosis and treatment of peripheral arterial diseases. In: *Collaboration with the European Society for Vascular Surgery (ESVS)*, vol. 55; 2018. p. 305—68.
2 Suominen V, Uurto I, Saarinen J, Venermo M, Salenius J. PAD as a risk factor for mortality among patients with elevated ABI–a clinical study. *Eur J Vasc Endovasc Surg* 2010;**39**:316—22.
3 Hoyer C, Sandermann J, Petersen LJ. The toe-brachial index in the diagnosis of peripheral arterial disease. *J Vasc Surg* 2013;**58**:231—8.
4 Wang Z, Hasan R, Firwana B, Elraiyah T, Tsapas A, Prokop L, et al. A systematic review and meta-analysis of tests to predict wound healing in diabetic foot. *J Vasc Surg* 2016;**63**. 29S-36S e1-2.
5 Potier L, Khalil CA, Mohammedi K, Roussel R. Use and utility of ankle brachial index in patients with diabetes. *Eur J Vasc Endovasc Surg* 2011 Jan;**41**:110—6.
6 Gölitz P, Struffert T, Lücking H, Rösch J, Knossalla F, Ganslandt O, et al. Parametric color coding of digital subtraction angiography in the evaluation of carotid cavernous fistulas. *Clin Neuroradiol* 2013;**23**:113—20.
7 Hung SC, Liang ML, Lin CF, Lin CJ, Guo WY, Chang FC, et al. New grading of moyamoya disease using color-coded parametric quantitative digital subtraction angiography. *J Chin Med Assoc* 2014;**77**:437—42.
8 Lin CJ, Hung SC, Guo WY, Chang FC, Luo CB, Beilner J, et al. Monitoring peri-therapeutic cerebral circulation time: a feasibility study using color-coded quantitative DSA in patients with stenoocclusive arterial disease. *AJNR Am J Neuroradiol* 2012 Oct;**33**.
9 Lin CJ, Luo CB, Hung SC, Guo WY, Chang FC, Beilner J, et al. Application of color-coded digital subtraction angiography in treatment of indirect carotid-cavernous fistulas: initial experience. *J Chin Med Assoc* 2013;**76**:218—24.
10 Lin CJ, Chang FC, Tsai FY, Guo WY, Hung SC, Chen DY, et al. Stenotic transverse sinus predisposes to poststenting hyperperfusion syndrome as evidenced by quantitative analysis of peritherapeutic cerebral circulation time. *AJNR Am J Neuroradiol* 2014;**35**:1132—6.
11 Struffert T, Deuerling-Zheng Y, Engelhorn T, Kloska S, Gölitz P, Bozzato A, et al. Monitoring of balloon test occlusion of the internal carotid artery by parametric color coding and perfusion imaging within the angio suite: first results. *Clin Neuroradiol* 2013;**23**:285—92.
12 Saad WE, Anderson CL, Kowarschik M, Turba UC, Schmitt TM, Kumer SC, et al. Quantifying increased hepatic arterial flow with test balloon occlusion of the splenic artery in liver transplant recipients with suspected splenic steal syndrome: quantitative digitally subtracted angiography correlation with arterial Doppler parameters. *Vasc endovascular Surg* 2012;**46**:384—92.
13 Schmittling ZC, McLafferty RB, Danetz JS, Hussain SM, Ramsey DE, Hodgson KJ. The inaccuracy of simple visual interpretation for measurement of carotid stenosis by arteriography. *J Vasc Surg* 2005;**42**:62—6.
14 Guimaraes JA, Victor EG, de Britto Leite MR, Gomes JM, Victor Filho E, Reyes Liveras J. Reliability of the interpretation of coronary angiography by the simple visual method. *Arquivos brasileiros de cardiologia* 2000;**74**:300—8.
15 Caruana M, Bradbury A, Adam D. The validity, reliability, reproducibility and extended utility of ankle to brachial pressure index in current vascular surgical practice. *Eur J Vasc Endovasc Surg* 2005;**29**:443—51.
16 Igari K, Kudo T, Toyofuku T, Jibiki M, Inoue Y, Kawano T. Quantitative evaluation of the outcomes of revascularization procedures for peripheral arterial disease using indocyanine green angiography. *Eur J Vasc Endovasc Surg* 2013;**46**:460—5.
17 Kagaya Y, Ohura N, Suga H, Eto H, Takushima A, Harii K. Real angiosome' assessment from peripheral tissue perfusion using tissue oxygen saturation foot-mapping in patients with critical limb ischemia. *Eur J Vasc Endovasc Surg* 2014;**47**:433—41.
18 Terasaki H, Inoue Y, Sugano N, Jibiki M, Kudo T, Lepäntalo M, et al. A quantitative method for evaluating local perfusion using indocyanine green fluorescence imaging. *Ann Vasc Surg* 2013;**27**:1154—61.