

Quantitative Evaluation of the Outcomes of Revascularization Procedures for Peripheral Arterial Disease Using Indocyanine Green Angiography

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WHAT THIS PAPER ADDS

Indocyanine green angiography (ICGA), has been used in various clinical areas, such as plastic surgery, coronary arterial disease, and peripheral arterial disease. Even though ICGA is useful for assessing tissue perfusion, the quantitative parameters and cutoff level concerning with traditional clinical tests have not been defined. Our clinical data show the quantitative parameters for tissue perfusion with ICGA and first definition of cutoff level of tissue viability.

Objectives: We performed indocyanine green angiography (ICGA) in patients with peripheral arterial disease (PAD), and established a method for the quantitative measurement of appropriate parameters to assess peripheral perfusion and the applicability of ICGA tests.

Methods: Twenty-one patients with PAD underwent revascularization procedures with pre- and postinterventional ICGA tests. The ICGA parameters, which included the magnitude of intensity of indocyanine green, the time to maximum intensity, and the time from fluorescence onset to half the maximum intensity ($T_{1/2}$) were compared with the ankle-brachial pressure index, toe-brachial pressure index, and toe pressure. We evaluated these parameters for regions of interest (ROIs).

Results: $T_{1/2}$ was the strongest parameter among all parameters of the ICGA tests. ROI 3, which included the distal region of the first metatarsal bone, correlated more significantly with the traditional measurements than the other ROIs. A value of $T_{1/2} > 20$ seconds for ROI 3 was significantly correlated with a toe pressure of < 50 mmHg (sensitivity: 0.77, specificity: 0.80).

Conclusions: ICGA can be used to assess peripheral tissue perfusion. By measuring the value of $T_{1/2}$ in ROI 3, ICGA tests can be used to evaluate the outcomes of revascularization procedures.

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INTRODUCTION

The introduction of noninvasive vascular laboratory tests arose from the need to obtain more accurate differential diagnoses, assessments of disease localization, and measurements of severity in addition to documenting the progression of peripheral arterial disease (PAD) and the effects of treatment. Several measurements can be used to assess the severity of ischemia, such as the ankle-brachial pressure index (ABI), absolute toe systolic pressure (TP), toe-brachial pressure index (TBI), and transcutaneous oxygen tension ($tcPO_2$). However, clinical tests measuring limb perfusion and hemodynamics are often limited by a variety of issues, including the presence of open and/or infected wounds,

previous toe or forefoot amputation, and media sclerosis causing false elevation of the systolic pressure.¹

Indocyanine green (ICG) has been clinically used as a type of near infrared (NIR) fluorophore for intravital imaging, a marker of the liver function,² and a sensitizer for photodynamic therapy.^{3,4} ICG angiography (ICGA) has the potential to provide information about regional perfusion and has recently been used to assess the viability of flap perfusion.⁵⁻⁷ Previous reports have demonstrated its use in the subjective assessment of tissue perfusion in patients with PAD.^{8,9} ICGA can provide excellent and informative images of tissue perfusion; however, it offers little quantitative information.¹⁰ Furthermore, even though the quantitative data may change according to the settings of the region of interest (ROI), in which parameters of the fluorescence intensity and time are evaluated, there have been no reports referring to the establishment of an ideal ROI.

The aim of this study was to establish a protocol for ICGA and to develop quantitative parameters of peripheral tissue perfusion, including the settings of ROIs. Furthermore, we

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assessed the applicability of ICGA tests as alternatives to traditional clinical tests, including ABI measurement.

METHODS

Patients

All protocols, surveys, and consent forms were approved by the Institutional Review Board of Tokyo Medical and Dental University Hospital. Written informed consent was obtained from all patients. Between November 2012 and February 2013, 36 patients underwent 43 revascularization procedures for PAD. Because ICG contains sodium iodide, we did not perform ICGA tests in patients with previous allergic reactions to iodinated contrast agents. Patients without both pre- and postintervention ICGA tests were also excluded from this study. We performed both pre- and postintervention ICGA tests in a total of 23 limbs in 21 patients. According to the Rutherford classification,¹¹ there was one limb in category 2, 17 limbs in category 3, and five limbs in category 4.

ICGA tests

The ICGA test protocol is shown in Table 1. A 0.1-mg/kg dose of ICG (Diagnogreen; Daiichi-Sankyo Pharmaceutical, Tokyo, Japan) was intravenously injected via a peripheral venous line. Immediately after the injection of ICG, fluorescence images were obtained using an infrared camera system (Photodynamic Eye, Hamamatsu Photonics K.K., Hamamatsu, Japan), which activated the ICG with emitted light at a wavelength of 760 nm and filtered out light with a wavelength of <820 nm. The light source for the emission of ICG consisted of 760 nm light-emitting diodes, and the detector was a charge-coupled device camera. Real-time fluorescence images were displayed on a monitor and recorded using a digital image processing method of the

Audio Video Interweave system. ICG is nontoxic and has a very low incidence of adverse reactions (1/40,000 doses).¹² Pre-interventional ICGA tests were performed before the interventional procedures, and postinterventional ICGA tests were performed within 7 days of the interventional procedures (Fig. 1A and B).

ICGA image analysis

For the comparative measurements, we set three types of ROIs: (1) from the Chopart joint (the tarsal joint that comprises the talonavicular and calcaneocuboid articulations) to the Lisfranc joint (the articulation between the tarsal and metatarsal bones); (2) at the metatarsal bones; and (3) in the distal region of the first metatarsal bone (Fig. 2). In order to evaluate the ICGA tests, multiple parameters were obtained and analyzed to assess perfusion. These parameters included the magnitude of intensity from ICG onset to maximum intensity (I_{max}), the time from ICG onset to maximum intensity (T_{max}), the slope of the intensity increase from ICG onset to maximum intensity (S), the time elapsed from the fluorescence onset to half the maximum intensity ($T_{1/2}$), and the fluorescence intensity measured 10 seconds after the onset of fluorescence (PDE_{10}) (Fig. 3). Image processing and data analysis were performed using the ROIs version U11437 software program (Hamamatsu Photonics K.K., Hamamatsu, Japan).

The obtained parameters were also compared with traditional measurements, including the ABI, TBI, and TP, measured using the VasoGuard P84 system (SciMed Ltd, Bristol, UK). In all cases, hemodynamic parameters, such as the pulse rate and blood pressure, were within the normal ranges. In this study, clinical success was defined as a more

Table 1. Indocyanine green (ICG) angiography protocol.

- Clear the patient of contraindications
- Supine positioned of patients
- Position the camera over the foot at 20 cm from the skin
- Remove any dressings and extinguish overhead lights
- A 0.1 mg/kg of 0.1% ICG solution administrated intravenously with bolus infusion, and push 10 mL normal saline to flush intravenous route
- After the injection, start capturing and recording for 5 min

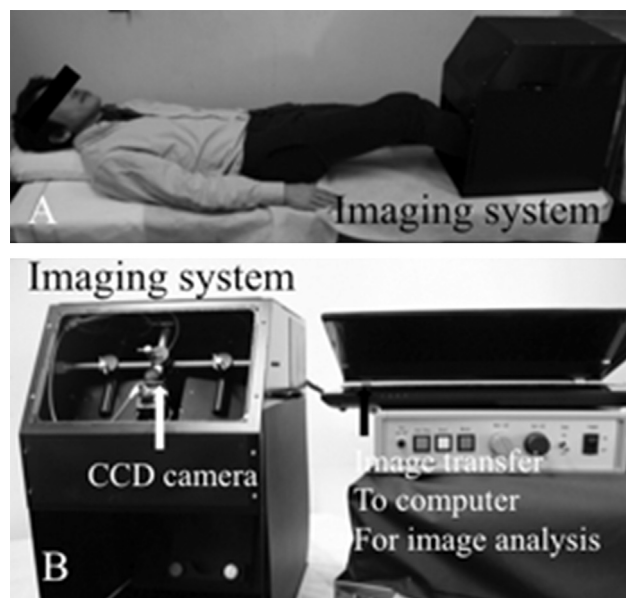


Figure 1. A diagram of the imaging system. (A) Capturing the indocyanine green imaging. (B) The system contains the imaging system, which has a charge-coupled device (CCD) camera (white arrow) with near-infrared light-emitting diode arrays, and a computer system for the image analysis (black arrow).

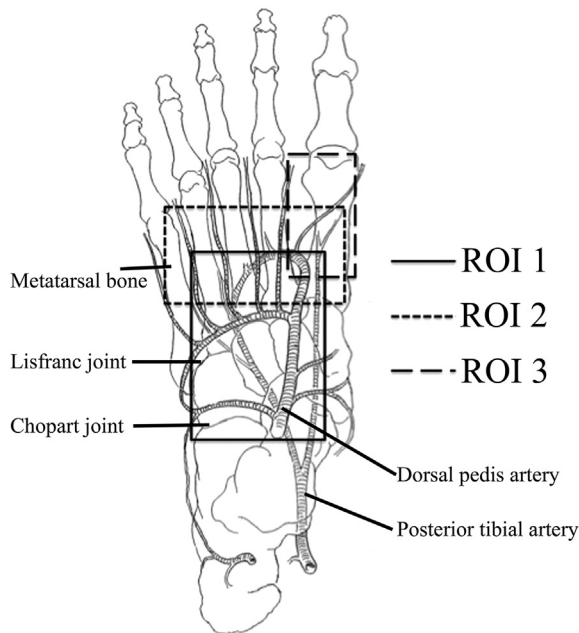


Figure 2. The settings of the regions of interest (ROI). ROI 1: from the Chopart joint to the Lisfranc joint; ROI 2: at the metatarsal bones; ROI 3: at the distal region of the first metatarsal bone.

than 0.1 increase in the ABI following the revascularization procedures, with an upward shift of at least one Rutherford clinical category, except in patients with actual tissue loss (categories 5 and 6), who were required to move up at least two categories.¹¹

Statistical analysis

The data are expressed as the mean \pm SD. Statistical significance was assessed using the Mann–Whitney *U* test for continuous variables, and Spearman’s rank correlation coefficients were used to reflect the degree of relationships

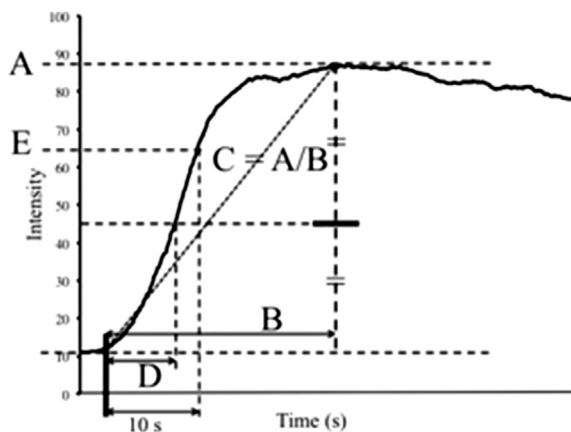


Figure 3. Indocyanine green angiography test parameters were defined graphically. (A) I_{\max} ; (B) T_{\max} ; (C) $S = I_{\max}/T_{\max}$; (D) $T_{1/2}$; (E) PDE_{10} . *Note.* I_{\max} = magnitude of intensity from ICG onset to maximum intensity; T_{\max} = time from ICG onset to maximum intensity; S = slope of intensity increase from ICG onset to maximum intensity; $T_{1/2}$ = time elapsed from fluorescence onset to half the maximum intensity; PDE_{10} = fluorescence intensity measured 10 seconds after the onset of fluorescence.

Table 2. Ankle-brachial pressure index (ABI), toe-brachial pressure index (TBI), absolute toe systolic pressure (TP), and indocyanine green angiography (ICGA) parameters values pre- and postintervention.

	Pre-intervention	Postintervention	<i>p</i>
ABI	0.632 \pm 0.283	0.959 \pm 0.215	<.0001
TBI	0.354 \pm 0.185	0.642 \pm 0.206	<.0001
TP	49.8 \pm 26.0	85.9 \pm 25.6	<.0001
ROI 1			
I_{\max}	26.6 \pm 10.6	43.2 \pm 12.8	<.0001
T_{\max}	99.5 \pm 31.1	68.1 \pm 29.4	.001
<i>S</i>	0.293 \pm 0.149	0.792 \pm 0.476	<.0001
$T_{1/2}$	34.0 \pm 10.5	23.7 \pm 11.7	.0005
PDE_{10}	1.43 \pm 1.53	6.07 \pm 5.05	.0001
ROI 2			
I_{\max}	23.7 \pm 11.4	42.9 \pm 14.1	<.0001
T_{\max}	89.3 \pm 39.1	53.0 \pm 26.5	.0011
<i>S</i>	0.325 \pm 0.210	1.08 \pm 0.724	<.0001
$T_{1/2}$	31.4 \pm 13.1	18.3 \pm 7.42	.0001
PDE_{10}	1.98 \pm 2.27	10.1 \pm 8.91	.0001
ROI 3			
I_{\max}	23.3 \pm 12.3	45.5 \pm 17.2	<.0001
T_{\max}	85.1 \pm 57.5	47.5 \pm 27.7	.0048
<i>S</i>	0.404 \pm 0.300	1.37 \pm 1.02	<.0001
$T_{1/2}$	31.4 \pm 17.5	15.1 \pm 7.07	.0001
PDE_{10}	3.42 \pm 3.48	15.9 \pm 11.7	<.0001

Note. Other ICGA parameters were seen in the “Methods” section. ROI = region of interest; I_{\max} = magnitude of intensity from ICG onset to maximum intensity; T_{\max} = time from ICG onset to maximum intensity; *S* = slope of intensity increase from ICG onset to maximum intensity; $T_{1/2}$ = time elapsed from fluorescence onset to half the maximum intensity; PDE_{10} = fluorescence intensity measured 10 seconds after the onset of fluorescence.

between variables. Statistical analyses were performed using Stat View v. 5 (Abacus Concept, Berkley, CA, USA).

RESULTS

Patient characteristics

During the study period, 21 patients underwent 23 revascularization procedures, and both pre- and postinterventional ICGA tests. We performed three open surgeries: two cases of thromboendarterectomy at the common femoral artery and one case of femoropopliteal bypass surgery. Eighteen of the 23 revascularization procedures were endovascular procedures: 10 aortoiliac lesions, nine femoral and popliteal lesions, and two infrapopliteal tibioperoneal lesions. Two procedures were hybrid procedures, including simultaneous open surgery and endovascular treatment. One procedure was simultaneous thromboendarterectomy at the common femoral artery and endovascular treatment of aortoiliac stenotic lesions, and the other was simultaneous femoropopliteal bypass surgery and endovascular treatment of aortoiliac stenotic lesions. The average age of the patients was 72.7 years (range: 59–88 years) and 17 patients were men. The documented comorbidities were hypertension (76%), dyslipidemia (57%), diabetes mellitus

Table 3. Correlation of ankle-brachial pressure index (ABI), toe-brachial pressure index (TBI), and absolute toe systolic pressure (TP) with indocyanine green angiography (ICGA) parameters on regions of interest (ROI) 1, 2, and 3.

Variable	ABI	ρ (Spearman)	p	TBI	ρ (Spearman)	p	TP	ρ (Spearman)	p
ROI 1									
I_{\max}		0.288	.0530		0.424	.0045		0.373	.0122
T_{\max}		-0.330	.0268		-0.475	.0014		-0.427	.0041
S		0.366	.0140		0.522	.0005		0.462	.0020
$T_{1/2}$		-0.437	.0034		-0.495	.0009		-0.494	.0009
PDE_{10}		0.442	.0030		0.529	.0004		0.508	.0007
ROI 2									
I_{\max}		0.358	.0163		0.486	.0011		0.462	.0019
T_{\max}		-0.439	.0032		-0.546	.0003		-0.495	.0009
S		0.491	.0010		0.599	<.0001		0.551	.0002
$T_{1/2}$		-0.489	.0010		-0.577	.0001		-0.563	.0002
PDE_{10}		0.413	.0056		0.537	.0003		0.535	.0003
ROI 3									
I_{\max}		0.469	.0016		0.469	.0016		0.482	.0012
T_{\max}		-0.360	.0158		-0.549	.0002		-0.580	.0001
S		0.513	.0006		0.590	<.0001		0.621	<.0001
$T_{1/2}$		-0.530	.0004		-0.614	<.0001		-0.627	<.0001
PDE_{10}		0.520	.0005		0.581	<.0001		0.616	<.0001

Note. Other ICGA parameters were seen in the "Methods" section. ROI = region of interest; I_{\max} = magnitude of intensity from ICG onset to maximum intensity; T_{\max} = time from ICG onset to maximum intensity; S = slope of intensity increase from ICG onset to maximum intensity; $T_{1/2}$ = time elapsed from fluorescence onset to half the maximum intensity; PDE_{10} = fluorescence intensity measured 10 seconds after the onset of fluorescence.

(47%), chronic obstructive pulmonary disease (42%), coronary artery disease (23%), and chronic kidney disease requiring hemodialysis (10%). All procedures resulted in improvement of the ABI postoperatively; however, clinical success was achieved in only 19 limbs (82%).

Evaluation of the revascularization procedures using ICGA tests

In this study, all procedures were evaluated based on the results of pre- and postinterventional ICGA tests. With respect to the measurements of ROI 1, 2, and 3, the values of I_{\max} , T_{\max} , S, $T_{1/2}$, and PDE_{10} were all significantly different between the pre- and postinterventional ICGA tests. We also evaluated the interventional outcomes using the traditional measurements of ABI, TBI, and TP, all of which exhibited statistically significant improvement from the pre-interventional measurements to the postinterventional measurements (Table 2).

We compared the ICGA test parameters and traditional parameters measured with the ABI, TBI, and TP. The ABI exhibited a statistically significant correlation with the T_{\max} , S, $T_{1/2}$, and PDE_{10} in ROI 1, while the I_{\max} , T_{\max} , S, $T_{1/2}$, and PDE_{10} demonstrated significant correlations with each other in ROI 2, and the I_{\max} , T_{\max} , S, $T_{1/2}$ and PDE_{10} showed significant correlations with each other in ROI 3. The TBI exhibited a statistically significant correlation with the I_{\max} , T_{\max} , S, $T_{1/2}$ and PDE_{10} in all three ROIs. The TP also showed a statistically significant correlation with the I_{\max} , T_{\max} , S, $T_{1/2}$ and PDE_{10} in all ROIs (Table 3).

Evaluation of the ROIs

The $T_{1/2}$ of ROI 3 demonstrated the most statistically significant correlation with the TP; this was the strongest correlation observed for any parameter in any ROI. After setting the value of the $T_{1/2}$ in ROI 3 as a cutoff (20 seconds), the ICGA test predicted that 50 mmHg was the borderline value for TP, with a sensitivity of 0.77, a specificity of 0.80, and an area under the receiver operating characteristic curve of 0.862 (Fig. 4).

DISCUSSION

Perfusion imaging tools used to visualize the structure of the vasculature or obtain functional perfusion information are useful and have several clinical applications. Although computed tomography angiography is widely used, it provides only structural information, not functional information, about the blood flow. Because the prognosis of vascular insufficiency is directly coupled with the functional perfusion level, rather than the vascular structure,¹³ functional perfusion imaging is superior to structural vascular imaging.

ICGA has been a focus of research owing to its convenience and effectiveness for imaging the vasculature and allowing for estimation of tissue perfusion.¹⁰ Previous studies that have used ICGA tests to estimate blood perfusion failed to provide the quantitative information required for interindividual comparisons,¹⁴ and ICGA has been primarily applied for flow assessment.^{15,16} In this article, we demonstrated that ICGA tests are useful for the quantitative measurement

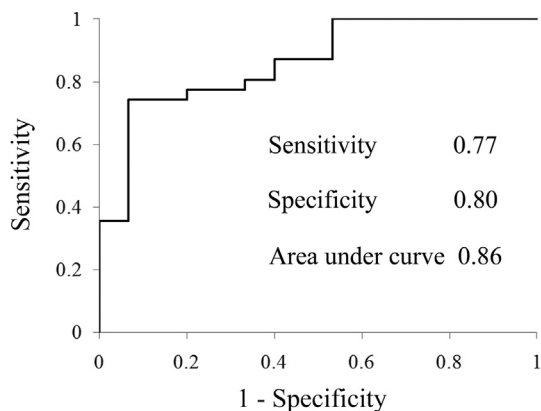


Figure 4. The receiver operating characteristic curve of the value of $T_{1/2}$ for region of interest 3 for an absolute toe systolic pressure value of 50 mmHg, with a sensitivity of 0.77, a specificity of 0.80, and an area under the curve of 0.86. Note. $T_{1/2}$ = time elapsed from fluorescence onset to half the maximum intensity.

of perfusion in peripheral tissue. The quantitative data of ICGA tests can be quickly and reliably derived from the images to determine the degree of tissue perfusion and evaluate the therapeutic effects of revascularization procedures. Kang et al.¹⁷ reported encouraging preliminary data using the time to maximum intensity as an indicator in patients with Raynaud's phenomenon. Braun et al.¹⁸ reported that both fluorescence intensity and time parameters are significantly correlated with the outcomes of revascularization procedures and can be used as novel parameters. However, the intensity of ICG depends on the distance from the camera to the skin, the patient's skin color, and the ambient light in the testing room, as reported in a prior study.¹⁸ Therefore, we believe that the intensity of ICG is not a good parameter for assessing tissue perfusion using ICGA tests. In the present study, although the parameters related to the intensity of ICG, including the I_{max} , S , and PDE_{10} , were correlated with the ABI, TBI, and TP, the T_{max} and $T_{1/2}$ were more significantly correlated than the other parameters. Parameters influenced based on the time after ICG injection may be the best parameters. Furthermore, until recently, there have been no reports concerning the settings of ROIs. We therefore evaluated the accuracy of different settings of ROIs and found that ROI 3 was most highly correlated with the ICGA parameters. With respect to ROI 3, the ICGA tests primarily measured the perfusion of the toe arteries; therefore, the TBI and TP correlated more significantly with the parameters than did the ABI. Furthermore, we defined the value of $T_{1/2}$ on ROI 3 as the cutoff value and evaluated the accuracy of the borderline (50 mmHg) TP value. The Trans-Atlantic Inter-Society Consensus¹⁹ requires a finding of a TP of <50 mmHg in order to confirm a diagnosis of critical limb ischemia (CLI), and a $T_{1/2}$ of >20 seconds may also predict the presence of CLI. We believe that the present study is the first attempt to propose quantitative parameters, suitable settings for ROIs, and a cutoff value of CLI for ICGA tests.

Furthermore, ICGA tests are useful as minimally invasive tools for determining the tissue viability in patients who lack toe pulses due to ulceration or amputation of the toes,

and patients with an abnormal ABI due to medial calcification. Further studies of ICGA testing should be performed to assess its ability to predict the optimal treatment for PAD, including the need for revascularization procedures, and to evaluate the outcomes of revascularization procedures intra-operatively. This may help to determine whether further procedures are needed to improve tissue perfusion and wound healing.

There are several limitations to this study, the foremost being the small sample size. Although only a small number of patients were enrolled, our study demonstrated that ICGA tests provide highly reliable and quantitative estimates of peripheral tissue perfusion. There are additional variables that may affect the specificity of ICGA tests, including the presence of open wounds and inflammation, which can change the tissue perfusion, resulting in over-estimation of the degree of actual perfusion. Although these limitations will need to be examined in future studies, the advantages of ICGA tests could help in selecting treatments for PAD.

In conclusion, our results indicate that ICGA tests rapidly provide qualitative and visual information regarding the regional perfusion of the foot, and can be used to quantitatively evaluate the degree of perfusion in peripheral tissues. Moreover, ICGA tests can be used to predict wound healing. A value of $T_{1/2}$ in ROI 3 of >20 seconds predicts a TP of <50 mmHg. Although further studies are needed to evaluate the reliability of these parameters, especially in defining and grading the severity of PAD, we believe that our results obtained using the quantitative analysis of ICGA tests will contribute to the development of new clinical diagnostic tools for assessing PAD.

CONFLICT OF INTEREST

None.

FUNDING

None.

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