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Blood volume measurement with indocyanine green pulse spectrophotometry: dose and site of dye administration

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Abstract
Background (1) To determine the optimal administration
site and dose of indocyanine green (ICG) for blood volume
measurement using pulse spectrophotometry, (2) to assess
the variation in repeated blood volume measurements for
patients after subarachnoid hemorrhage and (3) to evaluate
the safety and efficacy of this technique in patients who
were treated for an intracranial aneurysm.
Methods Four repeated measurements of blood volume
(BV) were performed in random order of bolus dose (10 mg
or 25 mg ICG) and venous administration site (peripheral or
central) in eight patients admitted for treatment of an
intracranial aneurysm. Another five patients with subarach-
noid hemorrhage underwent three repeated BV measure-
ments with 25 mg ICG at the same administration site to
assess the coefficient of variation.
Findings The mean ± SD in BV was 4.38 ± 0.88 l (n=25)
and 4.69 ± 1.11 l (n=26) for 10 mg and 25 mg ICG,
respectively. The mean ± SD in BV was 4.59 ± 1.15 l (n=
26) and 4.48 ± 0.86 l (n=25) for central and peripheral
administration, respectively. No significant difference was
found. The coefficient of variance of BV measurement with
25 mg of ICG was 7.5% (95% CI: 3–12%).
Conclusions There is no significant difference between
intravenous administration of either 10 or 25 mg ICG, and
this can be injected through either a peripheral or central
venous catheter. The 7.5% coefficient of variation in BV
measurements determines the detectable differences using
ICG pulse spectrophotometry.

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Introduction

The majority of patients with an aneurysmal subarachnoid
hemorrhage (SAH) have a poor prognosis, with mortality
rates as high as 45% and significant morbidity among the
survivors [1]. The major causes of morbidity are the initial
bleed, a rebleed, hydrocephalus and delayed ischemic
neurological deficits (DIND). Delayed ischemic neurological
deficits (DIND) are presumably related to cerebral vaso-
spasm and have a large impact on outcome after SAH [3, 17,
18]. This ischemic complication occurs in 17–40% and
carries a risk of 10–20% of permanent disability or death
[12, 18]. A hallmark of current therapy includes induction of
hypervolemia, hemodilution and hypertension (triple-H
therapy) aiming to restore cerebral perfusion [12]. This
aggressive treatment is controversial, however, and its
efficacy has not been proven in prospective studies.
Additionally, it has considerable morbidity, such as pulmo-
nary edema and cardiac failure [4, 12]. In a recent study
performed by Hoff et al. [7], no association between daily or
cumulative fluid balance and actual circulating blood volume

was seen. So, to increase therapeutic efficacy of triple-H therapy and decrease morbidity, monitoring of circulating blood volume (BV) prior to and during treatment for symptomatic cerebral vasospasm may be of value [11, 16].

Blood volume can be determined using dye dilution [5, 9]. Determination of BV using indocyanine green (ICG) administration and detection with pulse spectrophotometry has several advantages. It can be performed in several minutes at the bedside [5, 10, 15], allowing multiple measurements on a daily basis, limited only by the short washout time of the ICG dye [2]. This technique has been validated in healthy volunteers and is comparable in accuracy to the gold standard isotopic dilution techniques [6, 8]. Furthermore, ICG pulse spectrophotometry has been safely applied in critically ill patients in the ICU and perioperatively [9, 13, 14]. In our opinion, this technique could be used to optimize the BV status of patients after SAH. However, for the reliable clinical application of this technique in patients with intracranial pathology, several issues need to be addressed. First, the optimal ICG dose site of venous administration (central vs. peripheral) has to be determined, and second, the variation in repeated BV measurements should be assessed to determine the detectable differences.

The aims of this study were (1) to determine the optimal dose and venous administration site for ICG for measurement of BV, (2) to establish the coefficient of variation for repeated BV measurements with pulse spectrophotometry and (3) to evaluate the safety and efficacy of this technique in patients who were treated for an intracranial aneurysm.

Methods and materials

Patient population

Adult patients (≥18 years) admitted for treatment of an intracranial aneurysm, with or without recent subarachnoid hemorrhage (confirmed on computer tomography scan or by lumbar puncture positive for xanthochromia), were recruited for this study. All patients had a medical indication for both a central and a peripheral venous catheter and were admitted to the intensive care. Exclusion criteria were iodine allergy or increased baseline liver enzymes (AST > 150 U/l or ALT > 150 U/l or AF > 150 U/l or γ-GT > 150 U/l) because ICG is cleared hepatically. The Medical Ethical Committee of the University of Amsterdam approved the study protocol (02/203 no. 02.17.1017), and informed consent was obtained from all participants.

Indocyanine green dilution procedure

The Dye Densitogram 2501 A/K analyzer (Nihon Kohden, Tokyo, Japan) was used for registration of the spectrophoto-metrical absorption of ICG and calculation of the BV. After an intravenous bolus of ICG (Infracyanine®, S.E.R.B. laboratories pharmaceutiques, Paris, France) in glucose 5% solution, the decay curve in the peripheral tissue was assessed spectrophotometrically with a light probe attached to the nasal wing for 10 min. Because ICG does not leave the intravascular compartment, the diluting volume for ICG equals the BV. The diluting volume can be calculated from the decay curve by regression [5], and measurements can be repeated after 30 min when all ICG has been cleared by the liver [6]. Further details have been described elsewhere [8, 9].

Study protocol

In this study two successive protocols were used. The first was to determine the optimal dose and administration site, followed by the establishment of the coefficient of variation.

In the first protocol, ICG powder was dissolved in glucose 5% to a concentration of 5 mg/ml, from which either 5 ml (25 mg ICG) or 2 ml (10 mg ICG) was used as bolus. The bolus was manually infused within 5 s through either a peripheral or central venous catheter followed by 20 ml or 23 ml glucose 5% flush, respectively. Using the pulse spectrophotometer probe attached to the nasal wing, dye absorption was instantaneously measured for the following 10 min. All patients received every single combination between dose and administration site with 30-min intervals. The order of combinations was randomized in advance.

The four measurements consisted of two paired observations of 10 mg ICG versus 25 mg ICG and two paired observations of central versus peripheral venous administration site. Patients who were eligible for more than one series of four repeated measurements participated to a maximum of three separated series. Because of the admission of 25 ml of the study agent in four repeated BV measurements reduced by continuous diuresis, the net result in fluid balance was assumed to be constant during the experiment.

To determine the coefficient of variance, three repeated BV measurements using 25 mg ICG through the same venous administration site were performed in a period with 30-min intervals. For this protocol, five different patients with recent SAH were included who had not participated in the first part of this study.

Statistics

The BV difference between low- and high-dose ICG and between central and peripheral venous administration was hypothesized to be less than 5%. Assuming a standard deviation of 5%, a power of 0.90 and an α-level of 0.05, a minimum of 23 paired observations were required. A linear mixed model was used to establish differences in BV

Table 1 Patients characteristics and interval between hemorrhage and BV measurement of first study population (see text)

Patient	Gender	Age (years)	Weights (kgs)	Hunt and Hess	Localisation of aneurysm	Treatment	Triple-H	Hyponatriaemia	Days between SAH and measurement(s)
1	F	40	62.0	I	ACM	Clip	Yes	No	10
2	M	39	70.0	0	PICA	Clip	No	No	n.a.
3	F	41	70.0	II	P.comm.	Clip	No	Yes	3
4	F	42	60.0	III	ACM	Clip	Yes	No	(1) 21
									(2) 22
5	F	54	79.0	II	ACM	Clip	No	No	(1) 2
									(2) 3
									(3) 6
6	F	66	66.0	III	P.comm.	Clip	No	Yes	(1) 15
									(2) 16
7	M	51	80.0	II	Ant.chor.	Clip	Yes	No	(1) 7
									(2) 8
8	F	38	60.0	II	ACM	Clip	No	No	36

ACM: middle cerebral artery; PICA: posterior inferior cerebellar artery; p.comm.: posterior communicating artery; Ant.chor.: anterior choroideal artery

between low and high dose ICG and central and peripheral administration site.

Data analysis was performed using SPSS 16.0.1 (SPSS Inc, Chicago, IL) with the restricted maximum likelihood estimation method using BV as independent variable. ICG dose, administration site and the interaction of these were included as fixed effects, and patient and repeated measurement series identification as random effects.

Results

The first study population consisted of two males and six females with a mean age of 46.4 ± 9.8 years. Seven patients presented with a ruptured aneurysm and one with an incidental aneurysm discovered by computer tomography angiography. Five aneurysms were situated in the anterior circulation, and there were two posterior communicating artery and one posterior inferior cerebellar artery aneurysms; all were treated surgically. Three patients had been treated for DIND with triple-H therapy, and during the repeated BV measurements none of the patients was suspected of having symptomatic cerebral vasospasm, evaluated by neurological examination. Two patients had a mild hyponatriaemia (130–135 mmol/l) during measurements; these had not been previously treated with triple-H therapy (see Table 1).

In 8 patients, 51 BV measurements were done resulting in 25 paired observations. One patient completed three series of the four repeated measurements on separate days, three patients completed two series, and four patients completed one series. An ICG dose of 10 mg and 25 mg was administered in 25 and 26 measurements, respectively. A central venous catheter and a peripheral venous catheter were used for administration in respectively 26 and 25 measurements. One

Fig. 1 Results of blood volume measurements. On x-axis the combination of dose and site administration with means ± standard deviation: 1= central 10 mg: 4.28 ± 0.94 l (n=13); 2= central 25 mg: 4.90 ± 1.28 l (n=13); 3= peripheral 10 mg: 4.49 ± 0.84 l (n=12); 4= peripheral 25 mg: 4.47 ± 0.91 l (n=13)
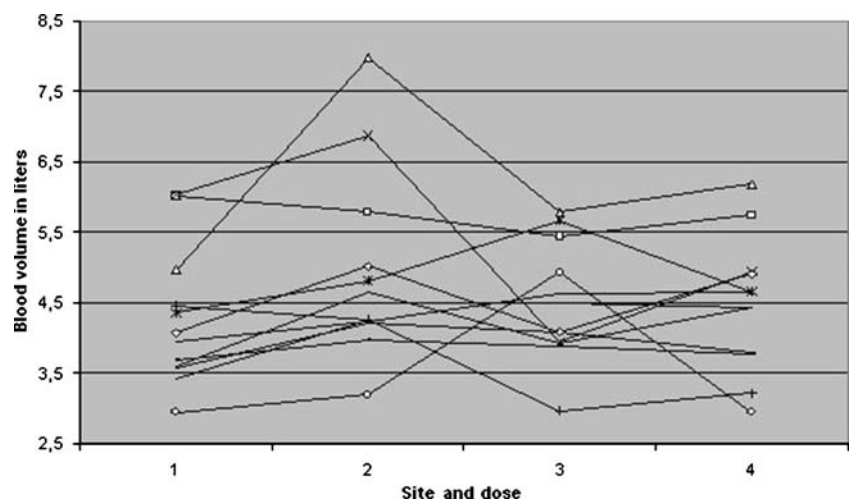
Table 2 Patients characteristics and interval between hemorrhage and BV measurement of second study population (see text)

Patient	Gender	Age (years)	Hunt and Hess	Localisation	Treatment	Triple-H	Hyponatriaemia	Days between SAH and measurements
a	F	74	II	P.comm.	Clip	No	No	11
b	M	70	II	-	-	No	No	7
c	M	61	I	A.comm.	Coil	No	Yes	13
d	F	69	III	A.comm.	Clip	Yes	Yes	22
e	M	57	II	Bas.top	Coil	No	No	6

ACM: middle cerebral artery; PICA: posterior inferior cerebellar artery; p.comm.: posterior communicating artery; a.comm.: anterior communicating artery

measurement of 10 mg ICG bolus through a peripheral venous catheter was not completed, because the patient withdrew from further participation due to pain at the injection site at bolus injection. No other adverse events were observed.

The mean ± SD of the BV measured by 10 mg and 25 mg ICG was 4.38 ± 0.88 l (n=25) and 4.69 ± 1.11 l (n=26), respectively. At central and peripheral administration, it was 4.59 ± 1.15 l (n=26) and 4.48 ± 0.86 l (n=25), respectively (Fig. 1). Using the linear mixed model, we calculated comparable BVs in the two sites of administration (estimate=0.43 l, SE=0.27, p=0.126), as well in the two different doses (estimate=0.02 l, SE=0.28, p=0.953). With these results we could not determine a significant difference between the ICG dose nor the administration site.

Subsequently, the coefficient of variance was measured in three repeated BV measurements in five patients, two females and three males with a mean age of 64 ± 9 years (patients a to e; see Table 2). Calculated BVs of the three measurements in every patient (a to e) are plotted in Fig. 2. The mean ± SD of the coefficient of variation for a 25 mg ICG bolus in five patients was 7.5% ± 3.6% resulting in a 95% CI between 3% and 12%.

Discussion

For determination of BV by ICG pulse spectrophotometry in patients being treated for an intracranial aneurysm, there is no significant difference between a bolus ICG dose of 10 or 25 mg through either a central or peripheral venous catheter. Earlier reports using ICG spectrophotometry in critically ill patients describe varying dosages of ICG between 10 and 25 mg [5, 6, 8–11, 14, 15]. It seems reasonable to use a standardized ICG bolus dose; in the calculation for variance, we have chosen 25 mg to minimize the error of spilling ICG at injection. As can be concluded from these data, the theoretical delay to mean transit time from peripheral injection does not substantially affect BV measurements in adult patients with average weight. This is in contrast with He et al. [6], who suggested that the mean transit time depends on the size of the subject. As they drew their conclusion after comparison

between adults and children with diverse body surface areas, no conclusive statement can be made concerning this issue.

When evaluating the larger than average BV measurements, no direct relation was seen between previous triple-H therapy or hyponatriemia during the measurement except for one patient. His BV was larger than the standard deviation in three of four measurements, explained by the preceded triple-H therapy 2 days before. The absence of a relation is in accordance with the conclusion of a recent study of Hoff et al. [7] who "…raises doubt whether fluid management guided by fluid balances is effective…."

During the inclusion period also one patient without a recent SAH was treated. Theoretically, this could confound the results because BV in a presumed healthy patient could be different as compared with patients with a recent SAH. But in our opinion, measurements in this patient did not influence the results because treatment of this patient was identical to patients with SAH and an uncomplicated course.

With the standard 25-mg dose injected through either venous administration site, the coefficient of variance of BV measurements appears to be 7.5%. Taking the 95% confidence
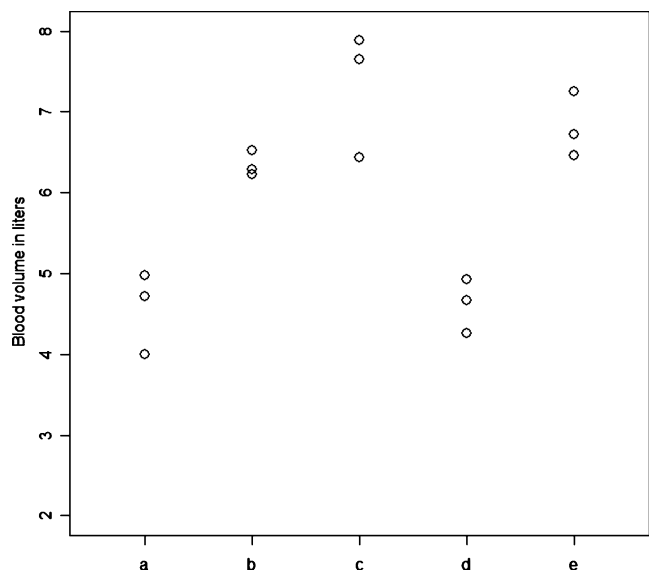
Fig. 2 Repeated blood volume measurements in separate patients (**a** to **e**) with 25 mg ICG through the same administration site

interval into account, it seems reasonable to assume that the mean differences in BV of more than 12% can be detected significantly using this technique. This percentage is an important baseline parameter for planning further studies.

One study using repeated BV measurements with ICG pulse spectrophotometry in healthy volunteers determined a variation of 3.94% [6]. The larger variation in our data can be explained by the different measurement circumstances and smaller number of patients. The measurements in our study were performed when the patient was awake, contrary to the patients who were under general anesthesia in the study of He et al. Apparently, awake patients induce more measurement artifacts, probably by probe movement or changes in cardiac output during the 10-min pulse spectro-photometry or between successive measurements. Nevertheless, our results show that reliable BV measurements can also be performed in awake patients with recent SAH.

Our percentage of coefficient of variance is an important baseline parameter for planning further studies concerning patients with SAH.

Blood volume can be determined in a safe and reproducible manner in patients after SAH using ICG pulse spectrophotometry. Administration of a bolus of either 10 or 25 mg ICG through a central or peripheral catheter results in no significant differences in measured BV. To minimize the error of spilling during injection, we recommend 25-mg boluses for repeated BV measurements. The coefficient of variation of repeated measurements with 25 mg is estimated at 7.5%. These results are considered important premises for planning further clinical studies.

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Comment

The authors provide a means for easy and consistent measurement of BV in patients with SAH. The further perspective is to validate in due time the use of triple-H therapy in these patients by having a measurement tool to know whether "volume" interventions really do increase circulating blood volume. The authors have adopted an existing technique and have standardized this in a sensible matter: one place for infusion of dye, one concentration for all. The results prove rather adequately that this is possible. The neurosurgical community will look forward to further studies with the use of this technique that may prove or disprove that "single-," "double-" or "triple"-H therapy has a physiological basis and effect in the treatment of secondary ischemia after SAH!

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