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Original article

# When to assess the DIEP flap perfusion by intraoperative indocyanine green angiography in breast reconstruction?

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ABSTRACT

*Background:* Although the indocyanine green angiography (ICGA) has been used for years in the assessment of Deep Inferior Epigastric Perforator (DIEP) perfusion, it has not yet been established when it should be performed during the surgery. The aim of this study is to evaluate whether it is better to perform the test on the donor or recipient sites.
*Methods:* Intraoperative perfusion of 46 DIEP flaps was assessed twice, on the donor and recipient sites. Differences between both ischemic areas of each flap were statistically analyzed. In addition, perforator location and risk factors were evaluated in order to assess whether they are associated with changes in the perfusion of the flap between both sites.
*Results:* Differences between ischemic areas on the donor and recipient sites were statistically significant ($p = 0.012$). However, in most cases (82.6%) the ischemic area was the same on both sites, and the final flap design only changed in two cases (4.3%) because of the ICGA findings on the recipient site. Besides, performing the ICGA on the donor site facilitated the identification of the best perfused areas, allowed a better planning of its placement into the recipient site, and also can be useful to choose the best perforator. Bilateral DIEP flap, lateral location of the perforator and tobacco use had a statistically significant association with lower probability to increase the perfusion area between both sites.
*Conclusions:* several advantages have been found in performing the ICGA on the donor site to assess the perfusion of the DIEP flap.



## 1. Introduction

The indocyanine green (ICG) is a tricarbocyanine dye that binds strongly to plasma proteins remaining in the intravascular space and emits fluorescent light following excitation with near infrared light [1]. It has been used for years in the evaluation of the vascularization with worthy results in several medical and surgical specialties [2–7]. It is useful in the assessment of the perfusion of the flaps, and it could reduce the skin and fat necrosis [8–11]. However, it has not yet been established when is the best moment to assess the perfusion of the Deep Inferior Epigastric Perforator (DIEP) flap during the surgery.

The main aim of this study is to compare the perfusion of the flap by ICG angiography (ICGA) on the donor site (before pedicle section) and on the recipient site (after performing the anastomosis) during DIEP flap breast reconstruction surgery, in order to determine the best timing to assess the perfusion of the flap. The secondary objective is to evaluate whether the location of the perforator in the flap and the risk factors for complications in free flaps for breast reconstruction are associated with changes between the perfusion of the flap on the donor and recipient sites.

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### 1.1. Patients and methods

All patients who underwent breast reconstruction by single-perforator DIEP flap anastomosed to the internal mammary artery (IMA) between November 2017 and January 2019 in our institution (Hospital Germans Trias i Pujol, Barcelona, Spain) were prospectively included. A written informed consent was obtained from each patient prior surgery. This study was approved by the Ethics Committee of Hospital Germans Trias i Pujol, and it was performed in accordance with the Declaration of Helsinki.

Patient variables collected included age, body mass index (BMI), hypertension, hyperlipidemia, diabetes mellitus, tobacco use, previous radiotherapy and number of previous pregnancies. Postoperative complications (fat necrosis, skin flap necrosis, hematoma and infection) were registered during the follow-up.

### 1.2. Surgical procedure and measurement protocol

All surgeries were performed by two teams, one of them harvesting the flap and the other one preparing the internal mammary artery and vein as recipient vessels. The perforator was chosen according to the preoperative computed tomography angiography (CT angiography), hand-held Doppler and intraoperative direct visualization [12–17]. We prefer the larger caliber perforator in the ipsilateral side of the breast for reconstruction, with less intramuscular course according to the CT angiography and the best Doppler signal [18,19]. When there are two or more perforators with similar characteristics, we clamp them alternatively and perform an ICGA for each one in order to assess their capability to perfuse the flap [19].

Intraoperative perfusion of the flap was assessed by laser-assisted indocyanine green angiography (ICGA). The ICGA was performed once the perfusion of the flap was based on only one perforator vessel. A bolus of 1 ml of an ICG solution of 2.5 mg/ml with sterile water was introduced through to peripheral venous line (ICG-Pulsion, Pulsion Medical System AG, Munich, Germany). The perfusion of the flap was assessed by the same surgeon with a near-infrared camera system (PDE Near infrared fluorescence imager C9830, Hamamatsu Photonics, Hamamatsu, Japan) (Fig. 1). The borders of the areas with no fluorescence or very low fluorescence signal detected (ischemic areas) were marked on the skin by the surgeon. After the anastomosis to the internal mammary artery and vein, it is verified that there is no residual fluorescence in the flap from the previous ICGA, and then the test was repeated with the same technique. Both times, the ischemic areas were assessed with similar blood pressure and after a stabilization period of 10 min [20–22]. Each ischemic area was intraoperatively photographed with a sterile ruler at the side of the flap to calibrate the photographs, taking care that the flap was flat, and the photograph was taken parallel in order to avoid future measurement mistakes (Fig. 2).

The ischemia time, the diameter of the flap, the location of the perforator, the thickness of the flap and the impact of the perfusion assessment by ICGA on the final flap design were also registered during the surgery. The location of the perforator was measured in both planes, horizontal (medial or lateral) and vertical (upper, middle or lower thirds).

### 1.3. Data analysis and statistics

The ischemic areas were postoperatively calculated measuring the calibrated photographs by an image analysis program based on the NIH Image software (ImageJ 1.52e, Wayne Rasband National Institutes of Health, USA), which has been widely used in research [23–28]. The paired sample *t*-test was used to compare the differences between both measurements of the ischemic areas of each flap, at the donor and at the recipient sites. The analysis included all the DIEP flaps, the unilateral flaps and the bilateral flaps separately.

In addition, the differences between the ischemic area on the donor and recipient sites depending on the horizontal and vertical location of the perforator in unilateral DIEP flaps, were also analyzed using the Chi-squared test.

The following preoperative demographics were considered as potential risk factors for complications in autologous breast reconstruction: nulliparity [29,30], obesity [31–36], tobacco use [32–35,37,38], previous radiotherapy [35,39–42], diabetes mellitus [36,43], hypertension [36,43] and hyperlipidemia [36]. The Mann-Whitney *U* test and the multiple linear regression were used to determine whether there was an association between the ischemic area variation between both sites and these variables separately and combined, respectively.

Data analysis was performed using IBM SPSS Statistics software,

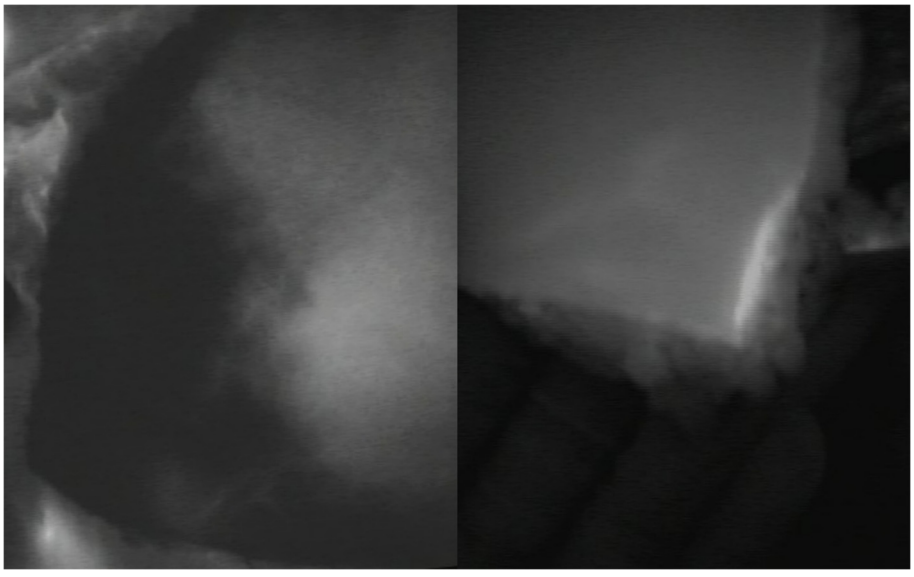
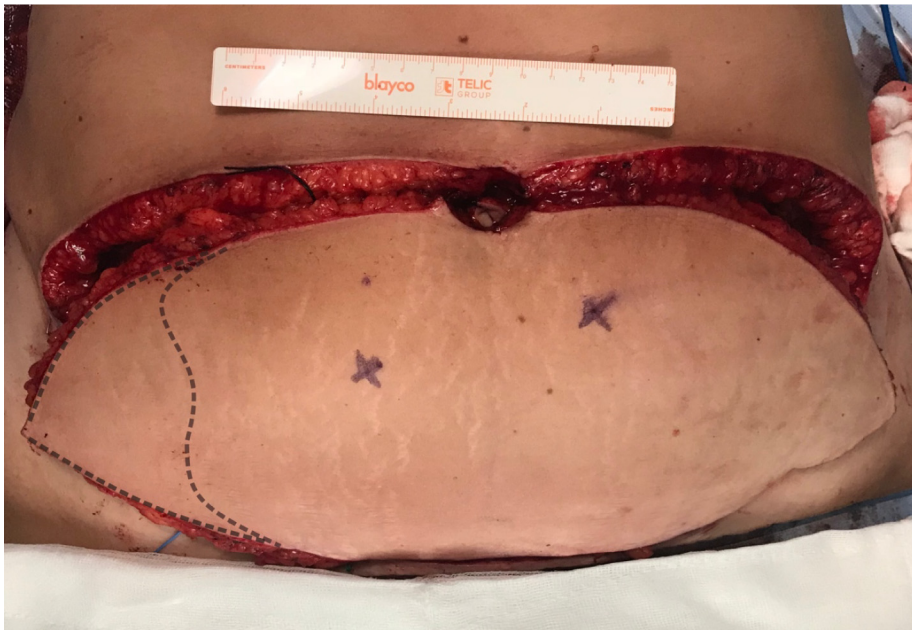


**Fig. 1.** Assessment of the perfusion of the DIEP flap by near-infrared camera system.




TABLES

**Fig. 2.** Intraoperative calibrated photograph of the DIEP flap on the donor site. The crosses mark the two perforators that were assessed by the ICGA. The final flap was based on the left side perforator, and its ischemic area is marked with a discontinued line.

version 22.0 (SPSS, Chicago, IL). Differences with *p value* less than 0.05 were considered statistically significant.

## 2. Results

A total of 46 DIEP flaps in 41 consecutive patients were included (26 immediate and 20 delayed reconstruction; 36 unilateral and 10 bilateral flaps). The overall mean age was 52.9 years (range, 36–68) and the BMI was 26.5 (range, 21.1–40.7).

The mean diameter and midline thickness of the flap were 25.9 cm (range, 22–38.2 cm) and 3.6 cm (range 2.2–4.9 cm), respectively. The mean ischemia time of the flap was 56.4 min (range 48–72 min). All incisions of donor site were closed by primary suture.

The average of ischemic areas on the donor and recipient sites were 40.3 $cm^2$ and 38 $cm^2$, respectively, and the difference was statistically significant in the paired sample *t*-test ($p = 0.012$). Other differences between the ischemic areas according to the ICGA on both sites are shown in Table 1.

No differences were found between the measures of ischemic areas at both sites in 82.6% of the total cases (77.7% of the unilateral flaps and 100% of the bilateral flaps) (Table 2). In the rest of the cases (8 patients, 17.4%), the areas with fluorescence were larger at the recipient site and included all the well perfused areas according to the ICGA at the donor site. The extra fluorescent area at the recipient site was located at the edges of the well perfused area on the donor site.

The non-perfused areas were completely removed from the final flap in all cases. Besides, part of the well perfused area according to the ICGA on the donor site was removed in 30 unilateral DIEP flaps (83.3%). Well perfused area was completely included in all bilateral DIEP flaps and in 6 unilateral DIEP flaps (16.6%). The ischemic areas in these 6 cases were over 30% of the total flap. However, the design of the final flap only changed in two cases (4.3%), and the differences in the area were 4% and 5% of the total area of the flap, respectively.

The results of the analysis of the location of the perforator and the perfusion assessment between both sites were shown in Table 3.

The prevalence and the statistical analyses of the risk factors for complications in autologous breast reconstruction were shown in Table 4.

Postoperative complications included 7 cases (15.2%) of fat necrosis, 1 case (2.1%) of skin flap necrosis, 2 cases (4.3%) of infection that were treated with oral antibiotics and 1 hematoma (2.1%) that required surgical revision. The mean follow-up was 9 months (range, 5 months–1 year).

## 3. Discussion

The ICGA is a useful intraoperative test that have been used for many years in reconstructive surgery. It provides information about the perfusion of the flap; its safety has been demonstrated and there is no significant increase in the surgical time [44–53].

However, there is controversy in the best timing for assessing the perfusion of the flap. In previous published studies, some authors performed the ICGA on the donor site, others after the anastomosis, and other times it is not mentioned when it has been

**Table 1**
Comparison of the ischemic area of the flaps according to the ICGA on the donor and recipient sites. The differences were analyzed using the paired sample *t*-test. Relative values of the ischemic areas were expressed as percentage of the total area of each flap. Note: *: the statistical analysis was not carried out because there were no differences between the two samples.

| | Ischemic area according to the ICGA | | | |
|---|---|---|---|---|
| | Donor site | Recipient site | Difference | *p* value |
| All DIEP flaps (n = 46) | | | | |
| Mean $cm^2$ [range] | 40.3 [0–129.8] | 38 [0–129.8] | 2.3 | **0.012** |
| Mean % [range] | 13.9 [0–42.4] | 13.1 [0–42.4] | 0.8 | **0.012** |
| Unilateral DIEP flaps (n = 36) | | | | |
| Mean $cm^2$ [range] | 50.3) [10–129.8] | 47.4 [9–129.8] | 2.9 | **0.011** |
| Mean % [range] | 17.2% [3.7–42.4] | 16.1% [3.7–42.4] | 1.1 | **0.011** |
| Bilateral DIEP flaps (n = 10) | | | | |
| Mean $cm^2$ [range] | 4.2 [0–15] | 4.2 [0–15] | 0 | * |
| Mean % [range] | 2.1% [0–6.9] | 2.1% [0–6.9] | 0 | * |

**Table 2**
Cases with differences in the ischemic areas according to the ICGA on the donor and recipient sites. Relative values of the ischemic areas were expressed as percentage of the total area of each flap.

| | Ischemic area according to the ICGA | | | | | |
|---|---|---|---|---|---|---|
| | Donor site | | Recipient site | | Change | |
| | Absolute ($cm^2$) | Relative (%) | Absolute ($cm^2$) | Relative (%) | Absolute ($cm^2$) | Relative (%) |
| 1 | 105 | 41.6 | 97 | 38.4 | 8 | 3.2 |
| 2 | 25.8 | 9.4 | 16.6 | 5.8 | 9.2 | 3.6 |
| 3 | 85.8 | 31.5 | 75 | 27.5 | 10.8 | 4 |
| 4 | 65.2 | 27.3 | 44.1 | 18.4 | 21.1 | 8.9 |
| 5 | 15 | 6.3 | 9 | 3.8 | 6 | 2.5 |
| 6 | 115 | 36.5 | 98.5 | 31.2 | 16.5 | 5.3 |
| 7 | 45 | 16.1 | 18 | 6.4 | 27 | 9.7 |
| 8 | 70 | 24.1 | 64 | 22.1 | 6 | 2 |
| Total | | | | | | |
| Mean | 65.8 | 24.1 | 52.7 | 19.2 | 13.1 | 4.9 |
| [range] | [15–115] | [6.3–41.6] | [9–98.5] | [3.8–38.4] | [6–27] | [2–9.7] |

**Table 3**
Comparison of the ischemic area of unilateral DIEP flaps on the donor and recipient sites depending on the location of the perforator. The differences were analyzed using the Chi-squared test.

| | No differences in the ischemic area | Differences in the ischemic area | *p* value |
|---|---|---|---|
| Horizontal | | | **0.044** |
| Lateral, n (%) | 13 (100%) | 0 | |
| Medial, n (%) | 15 (65%) | 8 (35%) | |
| Vertical | | | 0.571 |
| Upper third, n (%) | 18 (75%) | 6 (25%) | |
| Middle third, n (%) | 10 (83%) | 2 (17%) | |
| Lower third, n | 0 | 0 | |

**Table 4**
Comparison of the ischemic area according to the ICGA on the donor and recipient sites, depending on the risk factors for complications in autologous breast reconstruction.

| | Total cases (n = 46) | | Cases with differences in the ischemic area between the donor and recipient sites (n = 8) | | U Mann-Withney | Multiple linear regression |
|---|---|---|---|---|---|---|
| | n | % | n | % | *p* value | *p* value |
| Obesity (BMI>30) | 12 | 26.1 | 2 | 25 | 0.970 | 0.995 |
| Hypertension | 10 | 21.7 | 1 | 12.5 | 0.627 | 0.184 |
| Hyperlipidemia | 8 | 17.4 | 1 | 12.5 | 0.765 | 0.627 |
| Diabetes mellitus | 2 | 4.3 | 0 | 0 | 0.698 | 0.708 |
| Smokers | 15 | 32.6 | 0 | 0 | **0.033** | **0.039** |
| Nulliparity | 6 | 13 | 0 | 0 | 0.453 | 0.348 |
| Previous radiotherapy | 21 | 45.6 | 4 | 50 | 0.894 | 0.410 |

performed [8,45,48,54–56]. The main aim of this study is to determine when it is the best intraoperative moment to assess the perfusion of the DIEP flap by the ICGA. For this purpose, the ischemic area according to the ICGA on the donor site (before pedicle section) and on the recipient site (after performing the anastomosis) were compared.

Due to the half-life of the ICG in the plasma is 3–5 min [57,58], it is possible to repeat the ICGA in a short time. In our study, there is a period of 10 min after performing the anastomosis for perfusion stabilization and for complete elimination of the dye of the previous ICGA [20–22].

The results of the study showed that there were statistically significant differences in the ischemic area between performing the ICGA on the donor and recipient sites ($p = 0.012$). However, the mean difference was small (2.3 $cm^2$, 0.8% of the flap) and there was no difference between the areas in both sites in most cases (82.6%).

The IMA has higher blood flow than the deep inferior epigastric artery, so it could be expected that the perfusion of the flap on the recipient site must always improve. However, Lorenzetti et al. [59] shown that the flow rate in the IMA decreased after anastomosis in free TRAM flaps, falling to the same level as the donor artery. That means that the flow adapts to the flap not to the recipient artery, as previous studies had also indicated [59,60]. This corresponds with our results: there were no relevant clinical changes in the ischemic areas in most cases.

Besides, it was not necessary to include all the well perfused area in the final design of most unilateral DIEP flaps (83.3%); part of this area was removed in order to improve shape and symmetry. In fact, the final flap design only changed in two cases because of the ICGA findings on the recipient site. The maximum perfused areas were preserved in those two cases because of the body proportions of the patients.

In summary, the differences in the ischemic area between both sites had not enough clinical repercussion in the final flap in most cases, and in addition, several advantages in performing the ICGA on the donor site were found.

First of all, it was easier to identify the best perfused areas at the donor site. When there were differences in the perfused areas between the donor and recipient sites (17.4%), the ischemic area was always smaller at the second site. Therefore, an area that was poorly perfused at the donor site may be considered as well perfused at the recipient site. Although the difference was not excessively large, the new fluorescent area at the recipient site was probably not as properly perfused as the rest of the flap with fluorescence. This increase in the well perfused area according to the ICGA is due mainly to the opening of the choke-vessels, which are mostly located in the subdermal layer [61,62]. The fluorescence can be detected at a maximum of depth of 1–2 cm [63–66], so it is possible to assess the subdermal layer and the superficial choke vessels. However, because of the thickness of the DIEP flap (in our study up to 4.9 cm), deeper layers which are probably more poorly perfused cannot be evaluated by the ICGA. In addition, in most cases there was no need to include all the fluorescent area in the final flap, and therefore the design can be more adjusted to the best perfused area in each flap. For all these reasons, performing the ICGA on the donor site is more reliable to identify the best perfused areas and it is easier to optimize the design of the final flap.

Another advantage of performing the ICGA on the donor site is that it is also useful to choose the best perforator vessel [8,66,67]. It is not unusual to find two or more adequate perforators in the preoperative CT angiography or during the surgery. In those cases in which there are doubts about which perforator to choose because of their similar characteristics, performing the ICGA on the donor site allows assessing which one provides better perfusion for the flap.

Furthermore, we found that it is more effective to perform the ICGA on the donor site, due to the possibility to design the flap in advance and to take into account its size and shape before the anastomosis. It allows a better planning of the placement and adaptation to the recipient site.

For all these reasons, the authors consider that in order to assess the perfusion of the DIEP flap, it is better to perform the ICGA on the donor site. A second assessment on the recipient site may be useful when a unilateral DIEP flap has not enough well perfused area according to the ICGA on the donor site; if there is a decrease in the ischemic area, it will be possible to include more volume to the final flap (4.3% of the cases in our study). We did not find benefit in performing the test again on the recipient site in unilateral DIEP flaps that have enough perfused area at the donor site or in bilateral DIEP flaps.

The second objective of the study was to assess the potential causes of the occasional change of the ischemic area according to the ICGA on the donor and recipient sites. For this purpose, the location of the perforator and the risk factors were analyzed.

The location of the perforator vessel in the flap was assessed horizontally and vertically. According to our results, perforators located in the central zone of the flap (medial perforators in the middle vertical third) have more tendency to have less ischemic area after the anastomosis to the IMA. The results were statistically significant for the medial perforator-based flap ($p = 0.044$). That is in accordance to an anatomical cadaver study that showed that the vascularity of lateral row-based perforator flaps rarely cross midline, probably due to a higher number of choke vessels needed to cross the midline, compared with a medial perforator-based flap [61].

The risk factors of perfusion-related complications were also analyzed. The relative prevalence of most of them (obesity, hypertension, hyperlipidemia, diabetes mellitus, nulliparity and tobacco use) was lower in the 8 patients with differences between the ischemic areas according to the ICGA on the donor and recipient sites (Table 4). The largest differences were found in relation to tobacco use and nulliparity.

Many studies have suggested a correlation between cigarette smoking and vascular complications [32,68–72]. Tobacco induces oxidative stress and development and progression of atherosclerosis, which causes endothelial dysfunction [73–78]. In addition, nicotine inhibits capillary blood flow through its direct cutaneous vasoconstrictive effect [68] and the sympathetic nervous system activation [79,80]. It also induces vasoconstriction by stimulating the activity of the thromboxane A2 [81, 82], and interfering with production of prostaglandin I2, a potent vasodilator [79]. Moreover, it is also thought that may play a role in fibrosis and calcification in the media of the vessel wall [83].

In our study there was a statistically significant association between non-smoking and higher probability to improve the perfused area of the flap after the anastomosis to the IMA, in both the Mann-Whitney *U* test and multiple linear regression (Table 4). The previously commented negative effects of smoking in the microvascular circulation and the dysfunction in the choke vessels of the flap could explain these results.

Nulliparity had also been described as a risk factor for complications in DIEP flaps for breast reconstruction [30], as partial fat necrosis [29]. During pregnancy the growth of the intraabdominal volume causes progressive stretching and expansion of the abdominal wall. It is thought that it causes reorganization in arterial and venous hemodynamics, the perfusion via perforators increases and new connections between adjacent perforasomes are created by activation of the linking vessels. The final consequence is a change in the pattern of perforators and angiosomes becoming both larger in women with previous pregnancies than nulliparous

ones [30,84]. That means that previous pregnancies may be associated to an improvement in the perfused area of the flap. In our study, although there was a tendency for nulliparous to have less probability of improving the perfusion of the flap after the anastomosis (13% vs 0%), the results were not statistically significant (Table 4). Further studies with larger sample sizes are required to confirm this possible association.

A limitation of our study was the ischemia time. It was demonstrated that ischemia time longer than 99.5 min increases postoperative perfusion-related complications risk as fat necrosis [85]. Our results were limited to a shorter ischemia time (mean 56.4 min, range 48–72 min) and then, further studies assessing if there are differences between the flap perfusion on both sites with longer ischemia time are needed.

## 4. Conclusions

Differences between ischemic areas according to the ICGA on the donor and recipient sites were statistically significant ($p = 0.012$). However, in most cases (82.6%) these areas did not change between both sites. Moreover, it was not necessary to include all the well perfused area in the final flap of most unilateral DIEP flaps (83.3%), and the flap design changed only in two of the total cases (4.3%) because of the ICGA findings on the recipient site.

Performing the ICGA on the donor site facilitates the identification of the best perfused areas of the flap and it also can be useful to choose the best perforator. Besides, knowing the flap design in advance allows a better planning and management of its placement and adaptation into the recipient site before the anastomosis. The authors conclude that it is better to assess the perfusion of the DIEP flap by performing the ICGA on the donor site.

A second assessment on the recipient site may be useful when a unilateral DIEP flap has not enough well perfused area at the donor site; if there is a decrease in the ischemic area, it will be possible to include more volume to the final flap (4.3% of the cases in our study). We did not find benefit in performing the test again on the recipient site in bilateral DIEP flaps or when there is enough perfused area in unilateral DIEP flaps according to the ICGA on the donor site.

Finally, the results of the study also showed that bilateral DIEP flaps, location of the perforator (lateral vs medial) and tobacco use had a statistically significant association with lower probability to increase the perfusion area between both sites.

## Confilct of interest statement

The authors have no declarations of interest. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

## Ethic committee

This study was approved by the Ethics Committee of Hospital Germans Trias i Pujol, and it was performed in accordance with the Declaration of Helsinki. A written informed consent was obtained from each patient prior surgery.

## Declarations of interest

None.

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