EXHIBIT 1008
Assessment of Microcirculation of an Axial Skin Flap Using Indocyanine Green Fluorescence Angiography

Serdar Eren, M.D., Albert Rübhen, M.D., Rainer Krein, M.D., Grahame Larkin, M.D., and Rolf Hettich, M.D.

Cologne, Germany

In many cases the complexities of skin-flap microcirculation are difficult to assess despite all the subjective and objective examination techniques available today. Adequate microcirculation is essential for tissue viability, so any method employed for studying microcirculation should provide an accurate assessment of the prevailing conditions as possible. Of all the clinical methods, the fluorescence technique using the dye sodium fluorescein has so far provided the most reliable results. However, the pharmacokinetic properties of this tracer have prevented the technique from becoming established in clinical practice. The fluorescent dye indocyanine green (Cardio Green), on the other hand, has far more favorable pharmacokinetics.

In an experimental animal model, the fluorescence technique using indocyanine green (indocyanine green angiography, ICGA) was used to study postoperative changes in the microcirculation of a skin flap. On the day of operation, indocyanine green angiography revealed a state of hemodynamic imbalance for which the organism was able to compensate in the postoperative phase with the aid of humoral, physical, and metabolic factors. With indocyanine green angiography, it was possible to quantitatively observe the new hemodynamic equilibrium. Basically, microcirculation may be quantified in temporal and spatial terms. The significant objectivity of indocyanine green angiography and short intervals between each examination favor its possible and meaningful use in clinical practice and give cause for continuing studies. (Plast. Reconstr. Surg. 96: 1636, 1995.)

The microcirculation of the skin is a very complex chain of events which, even under physiologic conditions, is characterized by its heterogeneous behavior. Of the total blood flow through the skin, functional circulation plays a greater role than nutritive circulation. The heterogeneity of resting perfusion is, on the one hand, dependent on anatomic factors and, on the other, adapts itself to local conditions and requirements. Adequate microcirculation is, however, essential for tissue viability and functionality. Autoregulatory mechanisms over time and space control the basic demands of the skin. These mechanisms include first and foremost the neural regulation of the vascular system. In addition, humoral, metabolic, and physical factors exert their influence on the microcirculation.

Similarly, adequate microcirculation is essential for the viability of a skin flap. With regard to the physiologic conditions of skin perfusion, even the dissection of the flap has a significant effect on its microcirculation, as well as on its autoregulatory mechanisms, leading to a hemodynamic imbalance in its circulatory system. The organism tries to compensate for this by humoral, metabolic, and physical mechanisms. The otherwise dominant neural regulation of the microcirculation is disrupted by flap dissection. If the organism is not able to restore an adequate microcirculation, then necrosis of the skin flap will occur. Skin perfusion is complex even under physiologic conditions; with a skin flap, one is confronted with even more difficulty when assessing microcirculation.

McCarthy describes various subjective and objective methods of examination to assess microcirculation, the most common being the clinical examination. Inspection of skin color and capillary blanching on pressure gives clues to the current state of microcirculation. Monitoring skin temperature also can be very helpful. Stabbing with a cannula or a no. 11 scalpel...
blade to induce capillary bleeding is another effective test for judging flap circulation. Interpretation of these examination results, however, requires a sufficient degree of clinical experience. On the whole, these tests are easy to apply yet must be considered unreliable.

These purely subjective tests are contrasted by objective procedures for assessing microcirculation that are employed in clinical practice and research with varying degrees of success and significance. These methods include measuring transcutaneous $P_{O_2}$ ($tcP_{O_2}$), vital capillaroscopy, photoplethysmography, laser Doppler flowmetry, thermography, isotopic clearance, dermofluorometry and dermofluorography, and measurements using radioactively labeled corpuscular blood components.

Measuring $tcP_{O_2}$, a selective technique, has so far not produced the expected results with regard to the complexities of skin circulation, and because of its susceptibility to interference, it is now rarely used. Vital capillaroscopy is an excellent method for recording local mechanisms of microcirculation (flow distribution, erythrocyte flow rate, capillary diameter, etc.). Furthermore, qualities of transcapillary and interstitial diffusion can be determined by injecting a fluorescent dye. Despite modifications of the method, photoplethysmography has so far not produced unequivocal results in the assessment of skin-flap circulation, so this technique is now seldom used. Great expectations were placed on the laser Doppler flowmeter. As a noninvasive method, it is simple and can be repeated several times in succession. Serial monitoring allows registration of local autoregulatory fluctuations of skin perfusion. Plastic surgery in particular can look back on a number of interesting studies. The disadvantages of this procedure are its susceptibility to artifacts due to movement and its inability to provide an overall picture of the microcirculation. Extensive data are provided by thermography, which, despite its good approach, however, is not particularly popular. The most exact study results have so far been provided by the clearance method using Xe, H, and Te and by the process using radioactively labeled corpuscular blood components. But for reasons of time and cost, these tests are used principally in research.

The fluorescence technique currently provides the most accurate information on the microcirculatory state of skin. It was first used by Lange and Boyd to study circulation time, capillary permeability, and tissue circulation in peripheral vascular diseases. They used the dye sodium fluorescein to gain an impression of the conditions of microcirculation from the intensity, rate, and homogeneity of the appearance of fluorescence in the tissue.

Sodium fluorescein is a water-soluble fluorescent dye with a molecular weight of 376. In plasma and whole blood it displays an absorption maximum at 495 nm and an emission maximum at 515 nm. Approximately 50 percent of systemically applied sodium fluorescein is bound primarily to albumin, as well as to the surface of erythrocyte membranes. Fluorescein is freely dissolved in plasma and, as a result of its low molecular weight, can diffuse into the interstitium by a transcapillary route.

It was Myers who in 1962 used sodium fluorescein in operations to predict skin necrosis by differentiating between fluorescent and nonfluorescent areas. By using the dermofluorometer, Silverman et al. quantified the uptake of sodium fluorescein in the skin and correlated it with flap viability. Since then, various studies have shown good correlations of the fluorescence technique with blood flow and the viability of tissues.

Although dermofluorometry is commonly used by various authors, it only allows a punctate registration of tissue fluorescence. This is why Lund employed a rapid-sequence photographic recording of dye distribution to gain a spatial analysis of skin perfusion. This technique was modified further by Rieger and Scheffler using a digital image processing system. However, the pharmacokinetic properties of sodium fluorescein have until now prevented this method from becoming further established in clinical practice. Its routine use for assessing blood circulation of skin or a skin flap was unsuccessful, not least because of the long intervals (7 to 8 hours) between examinations.

The vital dye indocyanine green (ICG) was first introduced into clinical medicine by Fox et al. in 1957. Indocyanine green is used primarily in hepatology as a liver function test and in cardiology diagnostics. In 1973, Flower and Hochheimer introduced it into the fluorescence technique. They used the dye for fluorescence angiography of the choroid. Indocyanine green has a molecular weight of 775 and is almost completely bound to plasma proteins following intravenous application, with alpha-lipoproteins and albumin being the principal binding partners. Tight binding to plasma proteins guarantees that the fluorescent...
dye will remain intravascular. During its elimination from the blood, indocyanine green undergoes biphasic plasma clearance. In the initial phase, \( t_{1/2} \) amounts to 3 to 4 minutes at a dose of 0.5 mg/kg of body weight, with a \( t_{1/2} \) of 66 minutes in the second phase. More than 90 percent of the applied dye is eliminated in the first phase. These pharmacokinetic properties offer a considerable advantage over the behavior of the dye used hitherto. Further studies on the choroida, as well as those using fluorescence videomicroscopy, have produced good results with indocyanine green, so it would seem reasonable to use this dye in a broader model using skin or a skin flap. The rapid elimination of the dye also makes the possibility of a time-oriented analysis of skin perfusion more likely. The present animal study provides data on the microcirculatory state of an axial-pattern flap by means of a computer-assisted analysis of the influx and efflux dynamics of the dye and its fluorescent intensity.

**Materials and Methods**

**The Test**

A total of seven Sprague-Dawley rats (weighing approximately 300 gm) (Central Laboratory for Experimental Animal Studies, Aachen, Germany) were anesthetized with a subcutaneous injection of 0.4 ml Hypnorm (Jansen GmbH, Neuss, Germany). After complete removal of abdominal hair, axial-pattern skin flaps, modified according to a model by Vidas et al., were raised. Measuring 2 X 8 cm², they were based on the left inferior epigastric neurovascular bundle (Fig. 1). Before returning the flaps to their wound beds, collagen sheets were sutured in to delay revascularization from the wound bed and its edges. The right femoral vein was punctured for injection of indocyanine green. An in vitro study demonstrated maximum fluorescence at plasma dye concentrations that indicated a dose of 0.5 mg/kg of body weight. The animals were divided into two groups. Group I was studied on the day of operation and on the first and third postoperative days. The operation day and days 2 and 4 were selected for studying group II. On the seventh postoperative day, the viability of the skin flap was assessed clinically in all the study animals. Room temperature was maintained at 25°C during the entire study period, and standardized conditions (focusing of the camera, distance of the object from the camera or the light source, etc.) were strictly adhered to.

**Indocyanine Green Angiography**

For indocyanine green angiography, a 2000-W halogen lamp was used to excite the dye (Strand Lighting GmbH, Wolfenbüttel, Germany). Because of the considerable development of heat, a water filter was included to protect the excitation filter 750-FS 40 (LOT, Darmstadt, Germany). A long-pass filter RG 850 (LOT, Germany) was used as a barrier filter. The emission of the excited fluorescent dye was then recorded with a Sanyo CCD camera, a videotimer (VTG-33, FOR A), a Sony U-Matic videorecorder, and a high-resolution monitor. The signal was entered into a digital image processing system, where it was further evaluated. The test construction is depicted in Figure 2.

**Digital Image Processing and Evaluation of Indocyanine Green Angiography**

The pictures received from indocyanine green angiography were digitalized by a 768 X 512 pixel, 8-bit image processor (VP 1100-768-E-AT; OFG). A series of images was stored at a rate of two per second during the first 25 seconds. Subsequent rates were slower as a result of computer capacity. Processing of the digitized images was then undertaken with a Software Bisc Optimas (Stemmer, Puchheim, Germany). Ten different regions of interest were defined on the skin flap, and a mean fluorescent intensity was measured over time (see Fig. 1). The regions of interest were numbered 1 to 10 from proximal to distal to facilitate evaluation. The evaluation of indocyanine green angiography was then performed with a model that took into account influx and efflux as well as lag time, which allowed for the dye to spread from the injection site to the region of interest. The formula for the time course of the mean intensity \( f(t) \) is as follows:

\[
 f(t) = f_{\text{max}} (1 - e^{-(t-t_{\text{lag}})/C_{\text{inf}}}) e^{-(t-t_{\text{lag}})/C_{\text{eff}}} 
\]

where

- \( f_{\text{max}} \) = maximum intensity
- \( t \) = \( t - t_{\text{lag}} \)
- \( t_{\text{lag}} \) = influx lag time
- \( C_{\text{inf}} \) = influx time constant
- \( C_{\text{eff}} \) = efflux time constant

To determine the time constants, \( f_{\text{max}} \) was set at \( f_{\text{max}} - \max[f(t)] \) under the assumption that
Fig. 1. A 300-gm Sprague-Dawley rat with a skin flap (2 × 8 cm²) based on the left inferior epigastric artery, vein, and nerve. Beneath the flap is a synthetic collagenous sheet.

*C*ₐ is considerably larger than *C*ᵢᵦ, that is, *C*ₐ > *C*ᵢᵦ. Calculation of the influx constant *C*ᵢᵦ results from

\[ g(t) = \log[I(t) - f_{max}] \quad t < t_{max} \]

After finding the logarithms of the data up to the peak of the curve at \( t = t_{max} \), a straight line is drawn by linear regression. The slope of the straight line provides the influx time constant.

The efflux time constant is calculated in a similar fashion. In this case, however, \( f_{max} \) is not subtracted because these data follow the peak. The time constants thus calculated (\( C_{i,th}, C_{eff} \)) and the maximum intensity (\( f_{max} \)) then allow conclusions to be drawn on the state of blood circulation. The quality of the calculated data was confirmed by determining the correlation coefficients.

**The Dye: Indocyanine Green (Cardio Green)**

Indocyanine green is supplied in 25- and 50-mg single packs (Paesel Company, Frank-
As a finished solution, indocyanine green contains 5.0 to 9.5 percent sodium iodine. For this reason, the manufacturer recommends caution when applying it in patients with iodine allergy or thyroid disease. Similarly, administration during pregnancy or lactation is not guaranteed free of risk. The incidence of untoward reactions to indocyanine green is low. The literature cites a rate of 1 in 42,000. An article by Carski et al. mentions a case number of 4 reactions in over 240,000 applications. These reactions usually take a mild and harmless course with symptoms such as nausea, hot flushes, headache, and urticaria. On the other hand, exceptional cases also have been described with more severe side effects such as dyspnea, edema, fall in blood pressure, and tachycardia. Michie et al. report an increased incidence of reactions to indocyanine green in patients with chronic uremia. On the whole, side effects from indocyanine green are not considered genuinely allergic but rather a pseudoallergic reaction. The lack of eosinophilia and no significant IgE increase support this view. When using the fluorescent dye indocyanine green in clinical practice, however, the possibility of a reaction should be kept low or even excluded, so preventative measures or a reliable test to initiate prophylaxis deserves consideration. As a rule, atopic individuals and patients belonging to these groups (those with hay fever, allergic eczema, etc.) are considered at risk. A positive intracutaneous test provides reliable results, while a negative result would not exclude a later reaction. The intravenous injection of a small test dose would be the safest method of excluding sensitization, although it could interfere with the subsequent examination.

Before the examination, an antihistamine or a cortisone preparation could be applied as a direct form of prophylaxis. An important prerequisite for using this dye for fluorescence is an exact knowledge of its spectral properties. In serum, indocyanine green displays an absorption maximum at 805 nm and an emission maximum at 835 nm.

**Results**

After intravenous injection of the dye, a rapid inflow was observed by means of the afferent vessel of the axial-pattern skin flap. The first fluorescence was registered after 1.20 s (SD = 0.54 s). Comparing the individual test days, vascularity was sparse on the operation day, while the following postoperative days showed clear...
Fig. 3. Indocyanine green angiography. (Above, left) Second postoperative day, the axial skin flap after 1.45 s. (Above, right) Second postoperative day, the axial skin flap after 1.98 s. (Below, left) Second postoperative day, the axial skin flap after 4.06 s. (Below, right) Second postoperative day, the axial skin flap after 1.00 min.
vascular structures during the influx phase (Fig. 3, above, left and right). In the postoperative course, the size of the structures visible in the skin flap also increased. Depending on the size of the vascular network, the proximal part of the flap very rapidly became homogeneously fluorescent (see Fig. 3, below, left). The distal part was subject to a slower distribution of the dye. After the flap was completely stained (see Fig. 3, below, right), additional vascular structures appeared during the efflux phase that differed from those seen during the influx phase. This vascularity persisted for a much longer time.

Evaluations of indocyanine green angiography for the operation days showed a very conspicuous microcirculatory state. On the whole, a retarded influx was registered that manifested itself particularly in the proximal and distal parts of the flap (Fig. 4). With varying degrees of expression, the efflux pattern was visible over longer periods of time across the entire flap. The maximum fluorescence intensities showed low values. The development in the postoperative course produced a homogenization of the flow dynamics, allowing an increasing improvement in influx and, in particular, in efflux dynamics in indocyanine green angiography. On the first postoperative day, a very clear rise in
the efflux constants was shown from the proximal to the distal part of the flap (Fig. 5). This tendency, which increased toward the tip of the flap, declined over the following days and was only slightly pronounced by day 4. In the same way, the efflux constant took on a course similar to the rising tendency of the influx (see Fig. 4). The reverse was true for the behavior of the maximum fluorescence intensity. The fluorescence values that declined toward the flap tip on the first postoperative day rose over time, displaying only a slight gradient by day 4 (Fig. 6). A final examination at the end of the trial revealed clinically viable skin flaps in all animals.

**DISCUSSION**

When assessing the microcirculation of skin or a skin flap, its complexity demands the use of a technique that will provide as objective and reliable a result as possible. The technique of the fluorescein test described by Lange and Boyd is fundamentally simple to use for examining the microcirculation of tissue. The excellent studies by these authors using the dye sodium fluorescein showed a good correlation
with the circulation in skin flaps. The pharmacokinetic properties of sodium fluorescein, however, render it only partially suitable for clinical use. The possibility of its application is particularly limited by the diffusion of the dye into the interstitium and its remaining in the perivascular tissue for some time. After the introduction of indocyanine green, however, a vital dye has made its entry into the fluorescence technique that promises an improved clinical usage on the grounds of its physiologic properties. A primary aspect of its excellent behavior is its almost complete binding to plasma proteins. This guarantees the fluorescent dye remaining intravascular, allowing conclusions to be drawn on the existence of a perfused vessel.

Furthermore, the short half-life of indocyanine green is enormously advantageous for its clinical application. According to Meijer et al., 32 indocyanine green is subject to biphasic elimination from plasma. Over 90 percent of the applied dose of 0.5 mg/kg of body weight is washed out during the initial phase with a half-life of 3 to 4 minutes. This allows short intervals between each examination for assessing the microcirculation of the tissue. Changes in circulation occurring acutely, such as arterial occlusion, vascular thrombosis, or torsion of the

---

**Fig. 6.** Maximum fluorescence intensity in the axial skin flap during the postoperative course.

---

### Table: SD (standard deviation)

<table>
<thead>
<tr>
<th>ROI</th>
<th>Operation day</th>
<th>1.post OP</th>
<th>2.post OP</th>
<th>3.post OP</th>
<th>4.post OP</th>
</tr>
</thead>
<tbody>
<tr>
<td>ROI 1</td>
<td>15.6</td>
<td>5.9</td>
<td>3.2</td>
<td>6</td>
<td>2.5</td>
</tr>
<tr>
<td>ROI 2</td>
<td>19.1</td>
<td>5.4</td>
<td>8.4</td>
<td>8.3</td>
<td>3.6</td>
</tr>
<tr>
<td>ROI 3</td>
<td>12.1</td>
<td>5.4</td>
<td>4.1</td>
<td>7.4</td>
<td>6.3</td>
</tr>
<tr>
<td>ROI 4</td>
<td>16.6</td>
<td>5.3</td>
<td>6.9</td>
<td>6.7</td>
<td>9.2</td>
</tr>
<tr>
<td>ROI 5</td>
<td>14.7</td>
<td>5.9</td>
<td>5</td>
<td>8.7</td>
<td>5.3</td>
</tr>
<tr>
<td>ROI 6</td>
<td>18.4</td>
<td>7</td>
<td>2.9</td>
<td>10.9</td>
<td>5.4</td>
</tr>
<tr>
<td>ROI 7</td>
<td>25</td>
<td>7.7</td>
<td>2.3</td>
<td>6.9</td>
<td>4.7</td>
</tr>
<tr>
<td>ROI 8</td>
<td>23.4</td>
<td>10.1</td>
<td>2.1</td>
<td>8.9</td>
<td>3.9</td>
</tr>
<tr>
<td>ROI 9</td>
<td>17.7</td>
<td>10.1</td>
<td>7.2</td>
<td>7.6</td>
<td>4.5</td>
</tr>
<tr>
<td>ROI 10</td>
<td>14.3</td>
<td>4.6</td>
<td>10.1</td>
<td>2.9</td>
<td>2.9</td>
</tr>
</tbody>
</table>
pedicle, can therefore be detected shortly after a previous negative examination. With sodium fluorescein, the dye used until now, short-term controls would be useless because of the persistence of the dye in the tissue. A fluorescent area might in actual fact be less perfused or even not perfused at all.

Indocyanine green offers another advantage for assessing the dynamics of microcirculation. The analysis of dye distribution over time with a dye that remains exclusively intravasal will allow reliable conclusions to be drawn on the dynamics of blood flow. With sodium fluorescein, the additional dimension of transcapillary diffusion complicates any such conclusions and makes assessment more difficult.

The spectral properties of indocyanine green are also considered a positive factor. The absorption and emission maxima of indocyanine green are to be found in the near-infrared area. It is in just this range that human skin has its “optic window.” The literature cites a penetration depth of approximately 3 mm for this wavelength.

The indocyanine green angiography examinations in the present study demonstrated perfusion of the skin flap by means of the afferent inferior epigastric artery immediately after operation. The time lag before the first appearance of fluorescence gives an impression of the microcirculatory state of the organism. Here initial fluorescence was demonstrated after 1.20 s (SD = 0.54 s)—a value that may well be interpreted as a good macrocirculatory state of the study animals. On further evaluation of the postoperative days, a state of hemodynamic imbalance was noted in the microcirculatory system of the flap. The disturbed microcirculation might well be due mainly to the loss of sympathetic innervation following flap dissection. Adrenergic afferences control vessel diameter and the effective flow pressure gradient. Both factors, together with the viscosity of the blood, represent the most important parameters in
capillary circulation. Sympathectomy subsequently causes dilatation of the vessels and a reduction in the perfusion pressure gradient. However, further interpretation of the postoperative days would seem, at the moment at least, very difficult. Nevertheless, the influx and efflux constants, as well as the maximum intensity, show values that are quite plausible from a theoretical physiologic point of view. It is essential, however, that the efflux constant is not confused with the outflow rate by means of the efferent vascular system. The efflux constant contains information that includes the recirculation of the dye, possible adhesion to the vessel wall, and the small proportion of transcapillary penetration. For this reason, $C_{\text{eff}}$ is many times larger than $C_{\text{int}}$. To a certain degree, the influx constant is related to the flow rate of the afferent vascular system.

As McCarthy states, the skin at this point of time can no longer be regarded as a thermoregulatory organ but rather as tissue that is just trying to survive by humoral, metabolic, and physical mechanisms. If the organism does not succeed in establishing a new hemodynamic equilibrium, then within a certain period of time the tissue will die. In the further postoperative course, the effects of this compensation become apparent, effects that lead to changes in perfusion and were then detected by indocyanine green angiography. Adaptation of the hemodynamics to the new situation created a microcirculatory state that became more homogeneous during the first postoperative day. Initially, however, the distal part of the flap still demonstrated reduced perfusion. This is reflected in the increase in the influx and efflux constants and the fall of the maximum intensity values. Situated furthest from the base of the flap, this region is usually one of the most critical areas as far as blood supply is concerned.

From day 3 to 4 onward, anatomic changes then exert their influence on the microcirculation. Long years of experience support this fact, which again was recognized in the present study by the increasing vascularity during the influx phase. Blood circulation is improved, on the one hand, by the growth of new capillaries from the surrounding tissue and, on the other hand, by the dilatation of already available anastomoses between vessels running in a transverse direction. An increase in the actual density of the vessels does not occur. Revascularization from surrounding tissue was prevented in our model by a synthetic collagenous sheet. The further improvement in flap circulation up to day 4 ought therefore to be due to increased perfusion through already present anastomoses. The fact that another type of vascular structure becomes visible during the efflux phase is possibly due to the appearance of the venous system. This conclusion is reached by the fact that the structure of the vessels differs from that of the arterial influx phase. Why the venous system is depicted for a much longer time than the arterial system is still unexplained. Binding of indocyanine green to glycocalix or directly to endothelial cells is one of the possible explanations offered by Bollinger et al. with respect to fluorescence videomicroscopy. Phagocytosis of the protein-bound dye in endothelial cells has not yet been excluded. The influence of the non-protein-bound component of indocyanine green certainly deserves consideration. The literature cites a proportion of 3 to 5 percent.

Prognoses based on the present study regarding viability should only be made with caution. Marginal or normative values cannot be determined because of the small number of cases. The time interval between each examination was probably too long. Determining the optimal point of time for examination must be the object of a further study; the ischemic time of the tissue necessitates shorter intervals during the first postoperative hours. A larger animal study or clinical trials should be considered here.

**Conclusions**

Indocyanine green angiography is an excellent method for recording the microcirculatory state of a given tissue. Computerized analysis of the distribution pattern of the tracer, which is almost completely bound intravasally, offers the best possible correlation with the actual pattern of perfusion. The distribution of perfusion in the dimension of space is also guaranteed by the macroscopic recording technique. Guaranteeing the dimension of time is certainly more difficult. In order to capture the sensitive regulation of the microcirculatory system, the procedure should offer the possibility of continuous analysis over time, something that indocyanine green angiography is most probably unable to fulfill. A quick repetition of the examination, however, is guaranteed by the short half-life of indocyanine green. The first of a number of further studies suggests a minimal time interval between examinations of approximately 30 to 45 minutes. If the microcirculation is grossly disturbed, however, the intervals can be length-
ened further. As with all other procedures, a prognosis about the development of the microcirculation or the viability of the tissue is difficult and can only be made with great caution. At the moment of examination, the state of the microcirculation is registered, and this result should form a basis for a prognostic statement. If an insufficient microcirculation is the result, and should this inadequate state persist, then one would conclude that the viability of the tissue is at risk. It is therefore necessary to determine an optimal point of time for the examination. In flap surgery, this should depend on the particular point in question. With regard to postoperative prognoses of viability, it would most probably not be possible to perform indocyanine green angiography immediately postoperatively because regulatory mechanisms of the microcirculatory system are strongly activated and the sensitive balance of regulation shows considerable fluctuations. The present study demonstrates this fact, despite being unrepresentative because of its low number of cases. The most certain indication for indocyanine green angiography is in cases of a critical state of circulation or when a clinical assessment does not provide a clear result. In this case, indocyanine green angiography can produce a good quantitative result.

With an appropriate further development and sufficient experience with the procedure, the clinical application of indocyanine green angiography is certainly justified. The spectrum of disturbances and illnesses dependent on the microcirculation runs through the whole field of medicine. A whole number of possible uses of this technique are conceivable, especially in the field of plastic surgery. Depending on the point in question, indocyanine green angiography can be applied for the preoperative, intraoperative, or postoperative assessment of flaps. Indocyanine green angiography also would be helpful for reaching decisions in re plantation surgery or even for determining levels of amputations. Indocyanine green angiography would prove its worth particularly in the assessment of burn wounds. Many areas of indication will doubtlessly be found in other specialties. Peripheral vascular disease, for example, is one of society’s most common ailments. The diagnostic value of the procedure would then have to be established for each of these indications before deciding whether to apply indocyanine green angiography. In each case, the possibility of an allergic reaction, however slight, should be taken into consideration.

REFERENCES

17. Silverman, D. G., La Rosa, D. D., Barlow, D. H., Bering, T. G., Pobky, L. M., and Smith, Th. C. Quantifica-


