Snapshot Multispectral Imaging Is Not Inferior to SPY Laser Fluorescence Imaging When Predicting Murine Flap Necrosis

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Background: Objective assessment of tissue viability is critical to improve outcomes of cosmetic and reconstructive procedures. A widely used method to predict tissue viability is indocyanine green angiography. The authors present an alternative method that determines the relative proportions of oxyhemoglobin to deoxyhemoglobin through multispectral reflectance imaging. This affordable, hand-held device is noninvasive and may be used in clinic settings. The authors hypothesize that multispectral reflectance imaging is not inferior to indocyanine green angiography in predicting flap necrosis in the murine model.
Methods: Reverse McFarlane skin flaps measuring 10 × 3 cm were raised on 300- to 400-g male Sprague-Dawley rats. Indocyanine green angiography and multispectral reflectance imaging was performed before surgery, immediately after surgery, and 30 minutes after surgery. Clinical outcome images acquired 72 hours after surgery were evaluated by three independent plastic surgeons. Objective data obtained immediately after surgery were compared to postsurgical clinical outcomes to determine which method more accurately predicted flap necrosis.
Results: Nine reverse McFarlane skin flaps were evaluated 72 hours after flap elevation. Data analysis demonstrated that the 95 percent confidence intervals for the sensitivity of postoperative multispectral reflectance imaging and indocyanine green angiography imaging to predict 72-hour tissue viability at a fixed specificity of 90 percent for predicting tissue necrosis were 86.3 to 91.0 and 79.1 to 86.9, respectively.
Conclusions: In this experimental animal model, multispectral reflectance imaging does not appear to be inferior to indocyanine green angiography in detecting compromised tissue viability. With the advantages of noninvasiveness, portability, affordability, and lack of disposables, multispectral reflectance imaging has an exciting potential for widespread use in cosmetic and reconstructive procedures. (*Plast. Reconstr. Surg.* 145: 85e, 2020.)

Accurate and objective assessment of skin flap viability in reconstructive surgery at all phases of the wound healing continuum has been a critical goal of reconstructive surgeons for decades. Aesthetic and reconstructive surgical procedures require extensive dissection, tailoring, elevation, advancement, transpositions, and free tissue transfer, all of which introduce the risk of vascular compromise and complications.[1–3] Advanced warning with a clinically significant endpoint for decision-making allows precise interventions to be implemented in an effort to thwart devastating complications and restore or enhance perfusion and tissue oxygenation.[4]

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Clinical assessment (dermal bleeding, capillary refill, temperature, color, and turgor) and judgment remain the standard of care, and was the primary method of assessment for overall tissue quality intraoperatively until the turn of the century.[3–10] One adjunct, fluorescein imaging with ultraviolet light, was introduced in the latter part of the twentieth century as a method for perfusion assessment.[4,11] Fluorescein as a technique was not ideal, however. It is invasive, prone to adverse drug reactions, diffuses rapidly into the interstitium, is not immediately repeatable, and there is no widely accepted means for quantitative evaluation of the florescence.[3,4,9,12–16] It has been surpassed in recent years by SPY laser fluorescence near-infrared angiography using indocyanine green (Stryker Corp., Kalamazoo, Mich.).[3,6,9,10,12–14,16–23] Although the technology was slightly more accurate than fluorescein, it still requires intravenous injection of the dye, which remains intravascular, and may tend to overpredict necrosis.[3,24] The imaging equipment required for use of indocyanine green remains bulky and is extremely costly, limiting its availability. Multispectral near-infrared reflectance imaging is another adjunct originally developed in tandem with indocyanine green fluorescence angiography. The technology is now commercially available as the Snapshot KD203 device from Kent Medical Imaging (Calgary, Alberta, Canada), which uses near-infrared technology, or as the OxyVuTM-2 from HyperMed Imaging, Inc. (Memphis, Tenn.), which uses visible spectrum technology.[25] The Snapshot device is handheld, portable, and easily used in the operating room, hospital floors, or outpatient clinics. It is highly affordable, with no injected material or disposables required for use. The Snapshot KD203's U.S. Food and Drug Administration–indicated use is for the determination of oxygenation levels in superficial tissues for patients with potential circulatory compromise. Unlike SPY imaging, which requires separate processing of the image to acquire any quantification of the recorded fluorescence values, Snapshot provides an almost instantaneous measure of tissue oxygenation. SPY generates a grayscale image that can be colorized. Interpretation then relies on the use of either an absolute or relative fluorescence value to determine tissue perfusion. With a single recording, the Snapshot device generates a red, green, and blue image, and three sets of hemoglobin reflectance images (mixed venous capillary bed, oxyhemoglobin and deoxyhemoglobin). No additional processing is required and values are absolute.

In this study, we used an experimental animal model of ischemic necrosis to compare the accuracy of both indocyanine green angiography and multispectral near-infrared reflectance imaging in assessing tissue perfusion, with both of these devices using near-infrared technology. It is our hypothesis that multispectral near-infrared reflectance imaging is not inferior to laser fluorescence near-infrared angiography using indocyanine green in assessing tissue viability intraoperatively.

MATERIALS AND METHODS

Tissue Model

After approval by the Institutional Animal Care and Use Committee of the University of Illinois College of Medicine Peoria was obtained, nine Sprague-Dawley rats weighing 300 to 400 g with prearranged jugular vein access were acclimatized for a minimum of 3 days before use. Animals were anesthetized with general anesthesia by means of induction chamber with 4 to 5% isoflurane in 1.5 to 2 liters/minute oxygen. After induction, maintenance for the surgical procedures used 1.5 to 2.0% isoflurane delivered by 100% oxygen, 1.0 liter/minute.

The back of each rat was shaved with a clipper, and a depilatory agent (Nair; Church & Dwight, Ewing, N.J.) was applied. A 10 × 3-cm reverse McFarlane flap, consisting of skin and the panniculus carnosus along the dorsum of the rat, was raised as described in a previous study with the incorporation of an inferiorly based pedicle containing parasacral vessels.[26,27] The lateral edges of the wound were approximated to close the defect with 5-0 polypropylene sutures. Buprenorphine 0.01 to 0.05 mg/kg was provided to the animals every 12 hours after surgery for analgesia.

Indocyanine Green Angiography

Intraoperative indocyanine green angiography was performed immediately after surgery on each flap using the Novadaq/Stryker SPY Elite system. The SPY system uses a low-power infrared laser (806 nm) to stimulate fluorescence of the indocyanine green dye immediately following intravenous injection; the resulting fluorescence, which is emitted at 830 nm, is captured in video format. One bolus of 0.05 ml of indocyanine green (4.16 mg/ml) was administered through a jugular venous access.[28] The flow of dye into the flap was captured at a rate of 30 frames/second over a 90-second duration with a 15 × 15-cm area of view. This indocyanine green protocol is similar to the protocol used on human patients during skin flap reconstruction.[6]

Tissue Hemoglobin Oxygenation Imaging

The Kent KD203 Snapshot near-infrared system was used to image the tissue hemoglobin oxygen saturation of the flap. These measurements were acquired by holding the camera parallel to the flap surface at a distance of 30 cm. The focus distance is indicated by the alignment of two central pinpoint laser markers. The field-of-view is 15 × 20 cm, and imaging takes less than 3 seconds to perform. The oxygen saturation measurements reported by the device are weighted toward the smaller arterioles, venules, and capillaries of the vascular bed being imaged.[29] This gives an indication of the local oxygen available to the surrounding tissue and thus is termed tissue hemoglobin oxygen saturation. The KD203 automatically takes digital color photographs that are spatially registered with the tissue hemoglobin oxygen saturation image. These color images were used to record the visual appearance of the flap at the time of imaging, and the 72-hour color image was used to document the outcome of the flap.

Processing Color Images and Indocyanine Green and Tissue Hemoglobin Oxygen Saturation Images

For each flap, the postoperative color image, indocyanine green, and tissue hemoglobin oxygen saturation image were resized to have the same pixel dimensions. The postoperative photographs were then spatially registered to the 72-hour postoperative color photograph (Fig. 1). Images were co-registered to the 72-hour outcome color photograph using a piecewise linear transformation based on seven to 10 pairs of invariant anatomical or other physical landmarks on the flap. The 72-hour outcome photographs were supplied to three clinical evaluators, blinded to the immediate postsurgical images. Each evaluator traced the demarcation of the flap into ischemic and viable regions. This segmentation could then be automatically superimposed onto the corresponding spatially registered immediate postoperative images. Figure 2 shows a pair of registered digital photographs of the same flap taken immediately postoperatively and 72 hours after surgery, followed by images showing the segmentation of flap into viable and necrotic areas. Based on the evaluated outcome of the flap overlaid onto the registered immediate postoperative photograph, the co-registered indocyanine green and tissue hemoglobin oxygen saturation could be compared and analyzed on a pixel-by-pixel basis.

Statistical Analysis

Nonparametric methods were used in the receiver operating characteristic curve analysis of the data.[30–32] Receiver operating characteristic curves provide a graphic comparison of the diagnostic performance of indocyanine green fluorescence angiography and tissue hemoglobin oxygen

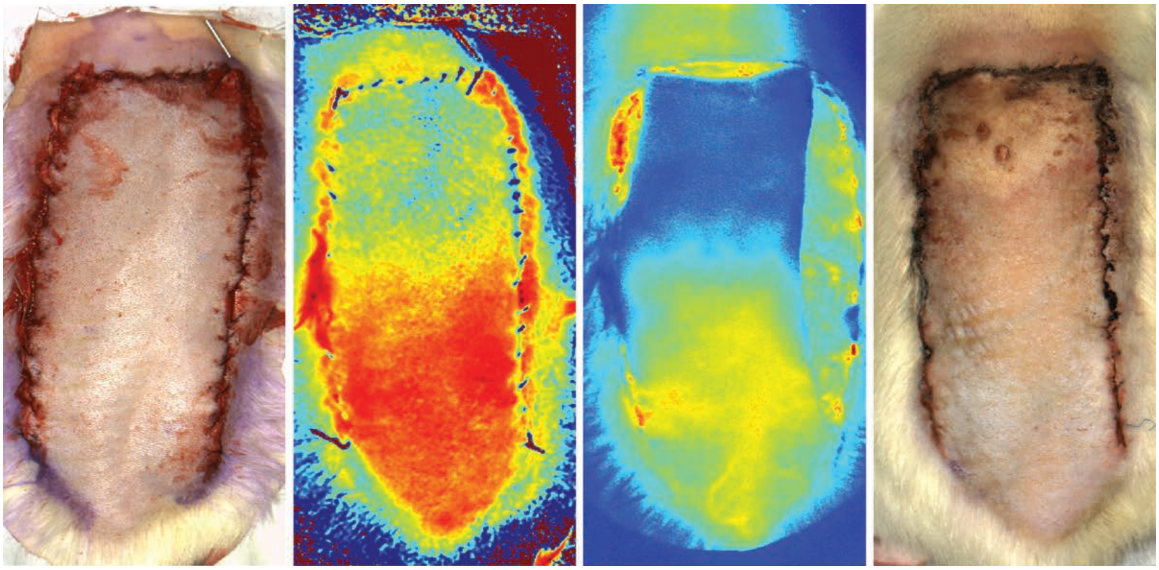

Fig. 1. (*Left*) Color digital photograph of the flap immediately postoperatively. (*Second from left* and *second from right*) Tissue hemoglobin oxygen saturation and indocyanine green images of the same flap taken immediately postoperatively. (*Right*) A 72-hour postoperative image.

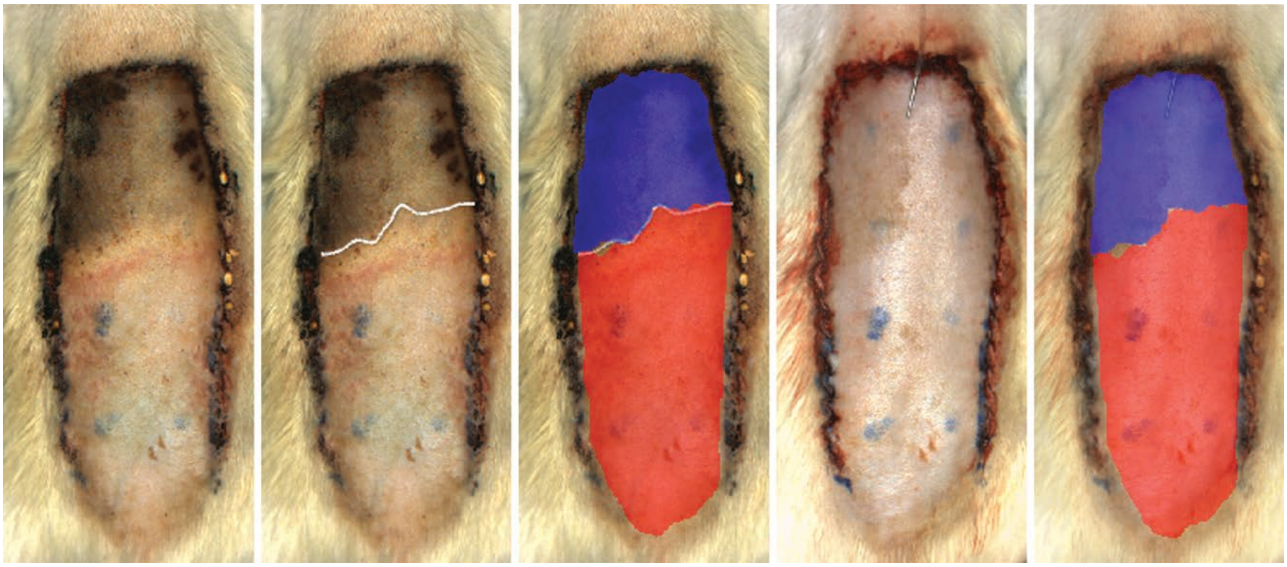

Fig. 2. (*Left*) A 72-hour postoperative outcome digital color image. (*Second from left*) Line drawn by clinical evaluator demarking the viable and necrotic zones on the 72-hour outcome image. (*Center*) Segmentation of the flap into viable (*red*) and necrotic (*blue*) zones based on the demarcation provided by the expert evaluator. (*Second from right*) Immediate postoperative digital photograph spatially matched (registered) to the 72-hour outcome image. (*Right*) Registered immediate postoperative image with the outcome segmentation of the flap overlaid.

saturation imaging measured immediately postoperatively to predict the 72-hour outcome of the flap. The area under the receiver operating characteristic curve is a commonly used metric of the diagnostic accuracy of a test.[33] Receiver operating characteristic curves and the corresponding areas under the receiver operating characteristic curve were calculated for the postoperative indocyanine green and tissue hemoglobin oxygen saturation images over the study population of nine flaps using the outcomes determined by each clinical evaluator. The sensitivities of the two postoperative imaging methods to predict 72-hour tissue viability of the flap at a fixed specificity (90 percent) for tissue necrosis were determined using the method reported by Zhou and Qin.[34] The difference in the sensitivities of the two imaging methods at a specificity of 90 percent were compared using the method outlined for paired dependent samples by Qin et al.[35]

Each pixel in the registered postoperative indocyanine green and tissue hemoglobin oxygen saturation images correspond to a pixel in the binary image of the flap where regions that were viable 72 hours after surgery were assigned a true value (Figs. 2 and 3), whereas dead regions were assigned a false value (Figs. 2 and 3). Because of the high degree of spatial correlation between nearby pixels, a random sampling of 100 pixels from the viable and necrotic regions were selected from each flap to form a single bootstrap draw. Confidence intervals for the area under the receiver operating characteristic curve, sensitivity at a fixed specificity and the difference in areas under the receiver operating characteristic curve, and the difference in sensitivities at a fixed specificity were determined from 2000 such bootstrap draws. The predictive ability of postoperative indocyanine green and tissue hemoglobin oxygen saturation imaging to predict 72-hour flap outcome in terms of area under the receiver operating characteristic curve and sensitivity at 90 percent specificity was compared. Given that the same flaps were imaged in close temporal proximity using indocyanine green and tissue hemoglobin oxygen saturation, the data from the two tests were treated as paired dependent measurements. Differences in area under the receiver operating characteristic curve or sensitivity were considered statistically significant if their confidence intervals did not include 0.

RESULTS

Outcome Evaluation

Flap outcome was assessed independently at 72 hours postoperatively by three clinical experts, blinded to the immediate postoperative indocyanine green and Snapshot images. Table 1 compares the assessed viable areas of each flap for each of the evaluators. Viable area ratio, defined as the viable

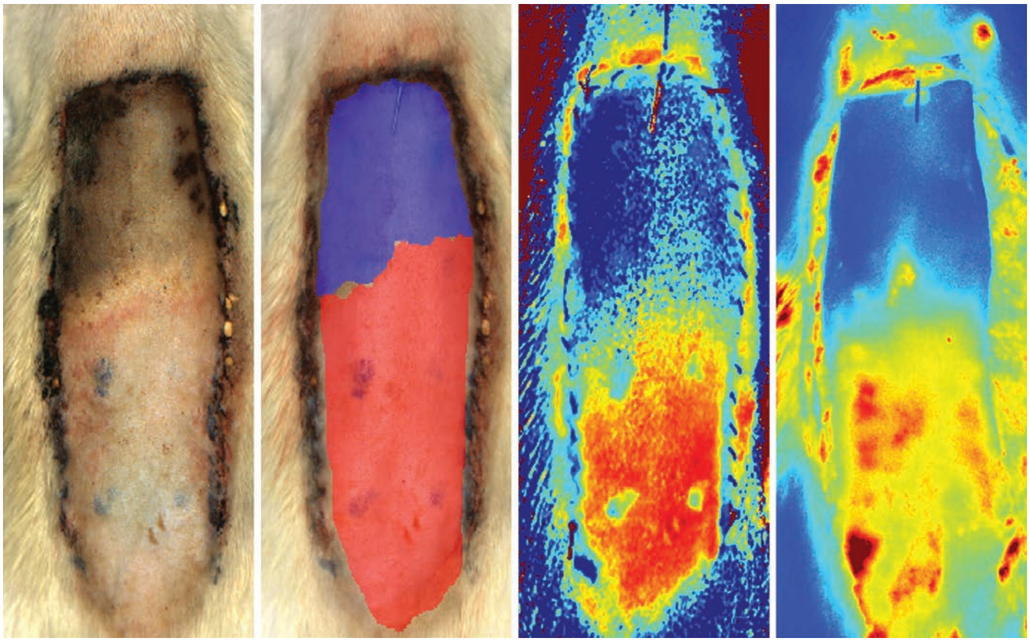

Fig. 3. (*Left*) Image showing outcome at 72 hours. (*Second from left*) Overlay of the 72-hour outcome image; registered postoperative image with the outcome segmentation of the flap. (*Second from right*) Registered tissue hemoglobin oxygen saturation image acquired immediately postoperatively. (*Right*) Registered indocyanine green image acquired immediately postoperatively. The pixel-by-pixel correlation between the tissue hemoglobin oxygen saturation and indocyanine green images over the area of the flap is $\rho = 0.85$.

area divided by the total viable and necrotic area of the flap, was based on the evaluator's demarcation of the 72-hour flap digital color image into dead and viable zones. The differences in assessed viable area ratios between the evaluators were not statistically significantly different. Immediate postoperative indocyanine green and Snapshot images were compared to 72-hour flap outcome based on the assessment of each evaluator. Analysis of the outcomes was based on the consensus of the three evaluators. In this case, consensus means including only those pixels in the image where all three evaluators agreed on outcome.

Diagnostic Accuracy

Figure 4 presents the receiver operating characteristic curves for the immediate postoperative Snapshot tissue hemoglobin oxygen saturation measurement for each of the three clinical evaluators, and Figure 5 presents the corresponding receiver operating characteristic curves for the immediate postoperative indocyanine green measurements. Table 2 reports the 95 percent confidence interval for the area under these curves. Table 3 reports the 95 percent confidence interval of the sensitivity of immediate postoperative measurements for predicting viable tissue at 72 hours postoperatively at a fixed specificity of 90 percent for predicting 72-hour necrosis. The last columns of Tables 2 and 3 report the 95 percent confidence intervals in the difference between the two diagnostic tests based on the 72-hour flap assessment from the three clinical evaluators. The last rows of these tables report the 95 percent confidence intervals when using the 72-hour

Table 1. Independent Assessments of the 72-Hour Flap Outcome from Three Clinical Evaluators*

	Evaluator		
Flap	1 (%)	2 (%)	3 (%)
1	74.5	76.2	74.5
2	70.8	70	74.1
3	73.8	74.1	80.3
4	66.5	65.6	65.7
5	89.6	88.1	84.3
6	69.5	70.5	74
7	94	93.1	88.6
8	58.6	58.2	56.3
9	60.3	61.7	61.7

*The percentage viable area was defined as the assessed viable area divided by the total area of the flap. The viable area was determined independently by each evaluator by marking the viable zones on the 72-hr digital color photograph of the flap using a standard drawing program. These clinical evaluators were blinded to the postoperative tissue hemoglobin oxygen saturation and indocyanine green images. There was no statistically significant difference in the assessed percentage viable area between the evaluators.

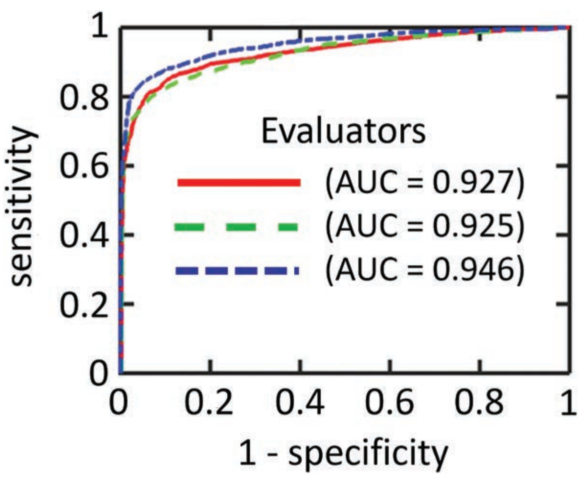

Fig. 4. Postoperative tissue hemoglobin oxygen saturation receiver operating characteristic curves. Receiver operating characteristic curve immediately postoperatively of tissue hemoglobin oxygen saturation imaging predicting 72-hour flap outcome based on the evaluation by three independent clinical reviewers. *AUC*, area under the receiver operating characteristic curve.

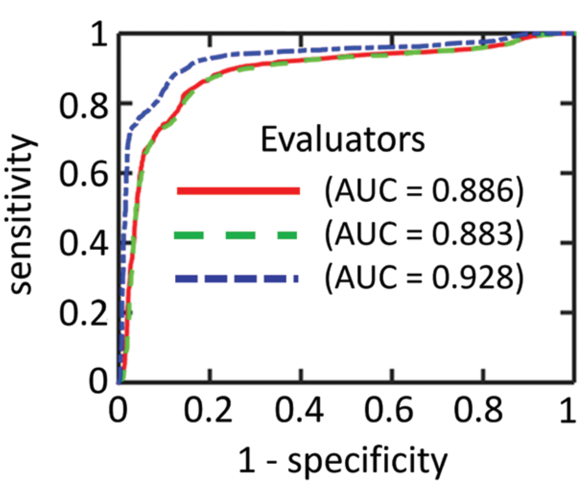

Fig. 5. Postoperative indocyanine green receiver operating characteristic curves. Receiver operating characteristics curve immediately postoperatively of indocyanine green imaging predicting 72-hour flap outcome based on the evaluation by three independent clinical reviewers. *AUC*, area under the receiver operating characteristic curve.

outcome assessment based on the consensus of the three evaluators. Figure 6 graphically reports the receiver operating characteristic curves associated with the immediate postoperative indocyanine green and Snapshot measurements using the consensus 72-hour flap outcome assessment.

Raw Data

Table 4 reports the mean and standard deviation of the percentage tissue hemoglobin oxygen saturation (Table 4) and indocyanine green fluorescence intensity counts (Table 5) from the viable and necrotic zones over the study population based on the consensus flap outcome assessment.

Table 2. Area Under the Receiver Operating Characteristic Curve*

Evaluator	Sto_2	ICG	Sto_2 – ICG
1	0.92–0.94	0.87–0.90	0.03–0.06
2	0.91–0.94	0.87–0.90	0.03–0.06
3	0.94–0.96	0.92–0.94	0.01–0.04
Consensus	0.94–0.96	0.92–0.94	0.01–0.04

Sto_2, tissue hemoglobin oxygen saturation; ICG, indocyanine green.
*The 95% CI for the area under the receiver operating characteristics curve for postoperative tissue hemoglobin oxygen saturation and indocyanine green imaging to predict 72-hr flap outcome are shown. The column on the right reports the 95% CIs the difference in area under the receiver operating characteristic curve of postoperative tissue hemoglobin oxygen saturation and indocyanine green imaging to predict 72-hr flap outcome. The first three rows report the results for each clinical evaluator, whereas the last row presents the results using the consensus outcome assessment from all three clinical evaluators. Tissue hemoglobin oxygen saturation and indocyanine green imaging are treated as paired dependent tests when determining the difference in area under the receiver operating characteristic curve.

Table 3. Percentage Sensitivity at Fixed Specificity of 90 Percent

Evaluator	Sto_2 (%)	ICG (%)	Sto_2 – ICG (%)
1	81.0–86.9	71.1–77.4	6.4–13.0
2	80.5–86.3	70.8–77.4	5.8–12.8
3	86.0–90.7	78.3–86.0	2.1–10.4
Consensus	86.3–91.0	79.1–86.9	1.6–9.9

Sto_2, tissue hemoglobin oxygen saturation; ICG, indocyanine green.
*The 95% CI for the sensitivity of postoperative tissue hemoglobin oxygen saturation and indocyanine green imaging to predict 72-hr tissue viability at a fixed specificity of 90% for predicting tissue necrosis are shown. The column on the right reports the 95% CIs for the difference in sensitivity of postoperative tissue hemoglobin oxygen saturation and indocyanine green imaging to predict 72-hr tissue viability at a fixed specificity of 90% for predicting tissue necrosis. The first three rows report the results for each clinical evaluator and the last row presents the results using the consensus outcome assessment from all three clinical evaluators. The reported differences treat the tissue hemoglobin oxygen saturation and indocyanine green imaging as paired dependent tests to account for the matched experimental design used to image the flaps.

DISCUSSION

In November of 2017, our practice started using both the Novadaq/Stryker SPY Elite and Kent KD203 Snapshot near-infrared systems in tandem in the clinical setting. Our preliminary experience with 19 patients revealed that both systems correlate well overall.[36] Although not yet peer reviewed, we have now performed dual-image assessments on an estimated 60 clinical flaps to date. We have had nine cases where Novadaq/Stryker SPY Elite system overpredicted necrosis relative to the Kent KD203 Snapshot near-infrared system.[3,24]

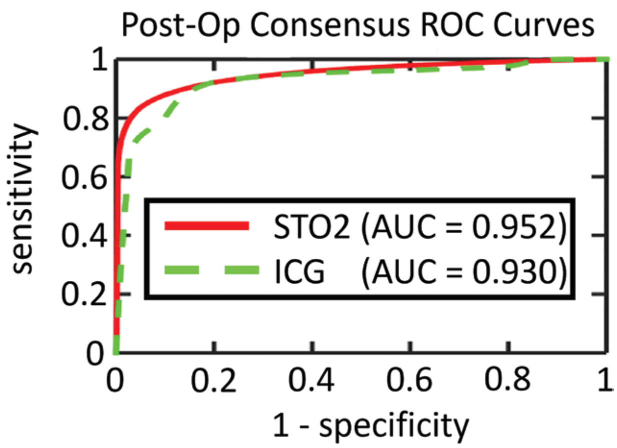

Fig. 6. Receiver operating characteristic (*ROC*) curves of immediate postoperative tissue hemoglobin oxygen saturation (*Sto₂*) and indocyanine green (*ICG*) imaging to predict 72-hour flap outcome based on the consensus evaluation from three independent clinical reviewers. *AUC*, area under the receiver operating characteristics curve.

Table 4. Summary of Percentage Tissue Hemoglobin Oxygen Saturation over the Two Groups of the Study Population*

Viable Zone		Necrotic Zone	
Mean (%)	**SD (%)**	**Mean (%)**	**SD (%)**
57.7	17.3	26.2	16.5

*Using the consensus diagnosis of three clinical evaluations of the flaps 72 hr postoperatively that divided (grouped) each flap into viable and necrotic zones, the mean and standard deviation of percentage tissue hemoglobin oxygen saturation is reported for the two groups over the study population.

Table 5. Summary of Indocyanine Green Measurements over the Two Groups of the Study Population

Viable Zone		Necrotic Zone	
Mean	**SD**	**Mean**	**SD**
133.8	45.3	52.8	26.0

*Using the consensus diagnosis of three clinical evaluations of the flaps 72 hr postoperatively that divided (grouped) each flap into viable and necrotic zones, the mean and standard deviation of indocyanine green fluorescence intensity are reported for the two groups over the study population.

Multispectral reflectance imaging–based devices have been commercially available for many years in localized probe format, exemplified by the T.Ox by ViOptix, Inc. (Newark, Calif.). Two recent analyses of such multispectral reflectance imaging platforms presented evidence indicating near-infrared spectroscopy may be better able to detect vascular compromise in postoperative flap evaluations earlier than conventional methods, such as physical examination or Doppler monitoring, leading to higher salvage rates.[5,37] However, these probe-based devices have a narrow field of view and require continuous direct application on the patient. The Kent KD203 Snapshot near-infrared system incorporates similar multispectral reflectance imaging technology, but this camera-based platform allows instantaneous assessment of tissue oxygen saturation over a much wider field of view, similar in area to that of SPY imaging. This translates into a device more suitable for intraoperative assessment and surgical decision-making because there is no probe to clutter the surgical field, and one can view differential tissue oxygen saturations of an entire region/flap and intervene as necessary.[27,29,38–40]

Previous studies evaluating multispectral reflectance imaging over a wide field are restricted largely to the basic science realm using noncommercial devices.[27,41] In 1998, Stranc et al. found that regions of tissue imaged 1 hour after flap elevation with an oxygen saturation index remaining below 1 went on to necrosis in Sprague-Dawley rats.[41] Sowa et al. later performed principal component analysis in another Sprague-Dawley rat model. This study found multispectral reflectance imaging within the near-infrared spectrum only to be more sensitive than multispectral reflectance imaging, including both visible and near-infrared wavelengths together.[27] Payette et al. found wide-field multispectral reflectance imaging to have less variability in predicting arterial insufficiency when compared to laser Doppler flux measurements in a Sprague-Dawley rat model.[42] In 2012, Sowa et al. specifically looked at the predictive capabilities of multispectral reflectance imaging in predicting tissue necrosis. Sowa and colleagues found specificities and sensitivities exceeding 85 percent in the early postoperative period.[29] Most recently, the predictive capability of the OxyVuTM-2 from the HyperMed commercial platform was evaluated in a naked mouse model. This study found that the clinically significant time threshold for measurements of deoxygenated hemoglobin that correlates with tissue becoming necrotic is present within 30 minutes postoperatively.[25]

The present study differs from those mentioned previously in that we aim to show multispectral reflectance imaging is not inferior to the most widely available and used tissue assessment technology currently on the market. Review of the receiver operating characteristic curves and final columns of Tables 2 and 3 indicate that the immediate postoperative tissue hemoglobin oxygen saturation measurements were better predictors of McFarlane flap outcome compared with indocyanine green imaging. Immediate postoperative tissue hemoglobin oxygen saturation measurements yielded a larger area under the curve for each of the three clinical evaluators and a higher sensitivity to predicting 72-hour tissue viability as a 90 percent specificity for predicting 72-hour flap necrosis. Data were reanalyzed only including pixels where all three clinical evaluators agreed on the 72-hour diagnosis. The receiver operating characteristic curves for indocyanine green and tissue hemoglobin oxygen saturation consensus diagnosis imaging are compared in Figure 6. The area under the receiver operating characteristic curve for tissue hemoglobin oxygen saturation imaging was slightly greater than indocyanine green imaging. The sensitivity of immediate postoperative tissue hemoglobin oxygen saturation imaging for predicting 72-hour tissue viability with the specificity for predicting 72-hour necrosis fixed at 90 percent was between 1.5 to almost 10 percent higher than for immediate postoperative indocyanine green imaging, and statistically significant.

Extrapolation of our results is limited. First, our data are based on a murine model. Second, our statistical power is low, with only nine flaps being assessed. However, power analysis deemed the use of more animals unjustifiable. Further analysis will also be required to determine whether the statistically significant difference in predictive capability between the two modalities translates into a clinically significant difference. More data are needed to draw definitive conclusions both in animals and in humans.

CONCLUSIONS

Multispectral reflectance imaging is an exciting and affordable new technology with the potential to make tissue viability assessment widely available, cost-effective, and portable. Our Sprague-Dawley experimental model found multispectral reflectance imaging's predictive capability of tissue necrosis to be greater than or equal to that of indocyanine green angiography. Further compilation of human clinical data is pending.

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