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Hypoperfusion following the injection of epinephrine in human forearm skin can be measured by RGB analysis but not with laser speckle contrast imaging

Rafi Sheikh[a], Josefine Bunke[a], Rannveig Linda Thorisdottir[a], Jenny Hult[a], Kajsa Tenland[a], Bodil Gesslein[a], Nina Reistad[b], Malin Malmsjö[a,*]

[a] Lund University, Skane University Hospital, Department of Clinical Sciences Lund, Ophthalmology, Lund, Sweden
[b] Department of Physics, Lund University, PO Box 118, SE-22100 Lund, Sweden

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ABSTRACT

Background: The time taken for epinephrine to achieve its optimal effect during local anesthesia has recently become the subject of debate. The time from injection to commencement of surgery is traditionally quoted to be 7 to 10 min, while recent reports claim that it may take 30 min to achieve maximum hypoperfusion, which would prolong the time required for surgical procedures. The discrepancy may be related to difficulties associated with the techniques used to measure blood perfusion. The aim of this study was to test two methods of determining the time to maximum hypoperfusion.

Methods: Laser speckle contrast imaging (LSCI) and red, green, blue (RGB) analysis of images obtained with a commercial digital camera, were used to monitor the effect of infiltration with commonly used local anesthetic preparations: lidocaine (20 mg/ml) + epinephrine (12.5 μg/ml), lidocaine (10 mg/ml) + epinephrine (5 μg/ml), and lidocaine (20 mg/ml) alone, in healthy subjects.

Results: LSCI showed a paradoxical increase in signal after the injection of local anesthetics containing epinephrine, probably due to a change in the laser penetration depth resulting from blanching of the skin. However, RGB analysis of digital photographs gave more reliable results, showing skin blanching that corresponded to the expected effect of epinephrine in local anesthetics. The time to maximum effect was found to be 7 (range 5–10) minutes for 12.5 μg/ml epinephrine, and 9 (range 7–13) minutes for 5 μg/ml epinephrine in lidocaine.

Conclusions: RGB analysis of digital images proved to be a valid technique for monitoring the effect of local anesthetics with epinephrine in human skin. The technique requires only a commercial digital camera and constitutes a cheap, simple method. The optimal delay between epinephrine injection and incision, to minimize bleeding, was found to be 7 to 9 min, which is in good agreement with common surgical practice.

1. Introduction

The optimal delay between the injection of local anesthetics containing epinephrine and incision, to ensure vasoconstriction and minimize bleeding, has recently become the subject of debate. The time commonly given in textbooks is around 7 to 10 min (Collin and Rose, 2001). However, in a study by McKee et al. (2013), who measured the relative hemoglobin concentration over time in the arm skin of healthy volunteers using oxygen spectroscopy, the lowest cutaneous hemoglobin level was not observed until 26 min after injection (McKee et al., 2013). In another study, McKee et al. measured the blood loss from the skin of patients undergoing carpal tunnel release surgery, and found a significant reduction after 30 min, compared to 7 min (McKee et al., 2015). However, when bleeding was measured during oculoplastic surgery procedures, we observed minimum bleeding after only 7 min (Hult et al., 2017). Furthermore, laser Doppler velocimetry (LDV) studies have shown maximal vasoconstriction to occur after about 8 to 10 min in the forearm and face of healthy volunteers (Ghali et al., 2008), and after 3 to 4 min in the neck of patients undergoing head and neck surgery (O'Malley et al., 1995). Similarly, short times have also been found in previous LDV and laser speckle contrast imaging (LSCI) studies in pigs (Larrabee Jr et al., 1987; Sheikh et al., 2017b; Sheikh et al., 2017a). We believe that these apparently conflicting results could be explained by difficulties associated with the techniques used for

* Corresponding author: Kioskgatan 1B, Skåne University Hospital, SE-221 85 Lund, Sweden.
E-mail address: malin.malmsjo@med.lu.se (M. Malmsjö).

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blood flow measurements. The use of LDV to measure blood perfusion in humans has been reported not to be as reliable as invasive techniques such as microdialysis (Farnebo et al., 2011).

The most common tools available today for monitoring perfusion and oxygenation include spectrometry, LDV and LSCI. Spectrometry determines the degree of oxygenation by irradiating the tissue with light in the wavelength range of 500 nm to 650 nm, in which the absorption changes upon oxygenation of hemoglobin (Kasler et al., 1990). The imaging depth in spectrometry is dependent on the wavelength, from a few micrometers in the ultraviolet part of the spectrum to several millimeters in the near infrared. In the red part of the spectrum the penetration depth in tissue is typical 3–5 mm (Randeberg, 2005). LDV is based on the change in frequency, i.e., the Doppler shift, that occurs when laser light is scattered by moving objects (in this case, erythrocytes) (Fredriksson et al., 2009). LDV has been applied extensively to measure blood flow in flaps during plastic surgery procedures (Pietila et al., 1987), and the measurement depth in forearm skin is about 1 mm (Fredriksson et al., 2009). The high spatial variability in blood flow in the skin limits the accuracy of the single point measurements that are possible with LDV (Allen and Howell, 2014). LSCI measures the interference pattern created when laser light is scattered from an illuminated surface (Yamamoto et al., 1993). LSCI is a fast, full-field technique for the imaging of microvascular perfusion (Allen and Howell, 2014), and the imaging depth is approximately half that for LDV (0.5 mm). Laser-based techniques measure motion in the tissue and are affected by movement artifacts. There is therefore considerable interest in developing new techniques that do not suffer from these problems for non-invasive monitoring of perfusion. In a previous report, Leahy described a method of visualizing red blood cell content in the microcirculation with a RGB camera and reported a measurement depth of approximately 350 μm to 490 μm (Leahy et al., 2006). Jakovels et al. has showed that RGB-analysis with a simple camera can be used to quantify hemoglobin distribution and perfusion dynamics (Jakovels et al., 2011). Radioisotope clearance was previously considered the gold standard for measuring skin perfusion However, the method is no longer widely used due to the need to inject radionuclides, and the complexity of the procedure (Pan et al., 2018). To the best of our knowledge, no other method has replaced radioisotope clearance as the gold standard for skin perfusion measurements.

The aim of the present study was to compare the ability of red, green, blue (RGB) image analysis to LSCI in monitoring skin perfusion. The techniques were used to examine the change in skin perfusion upon administration of epinephrine in local anesthetics, which is known to cause vasoconstriction in the subcutaneous vascular plexus. The time to maximum response was evaluated.

2. Materials and methods

2.1. Ethics

The protocol for this experimental study was approved by the Ethics Committee at Lund University, Sweden. The research adhered to the tenets of the Declaration of Helsinki as amended in 2008. All the patients participating in the study were given information about the study and informed of the voluntary nature of participation. All patients gave their informed written consent.

2.2. Study subjects

The study subjects were adult volunteers. The exclusion criterion was the presence of any medical condition that would contraindicate the administration of local anesthesia with epinephrine, such as heart conditions or previous allergic reaction to local anesthetics, about which the subjects were particularly asked. Two participants were excluded from the study before analysis: the first due to large movement artifacts making RGB analysis difficult, and the second due to too deep administration of the anesthetic agent, resulting in insufficient anesthesia and the suspicion of unreliable results. The subject excluded because of movement artifacts was taking medication for hypertension, while the others had no known medical conditions, and were considered healthy. The subjects were classified according to the Fitzpatrick scale for skin pigmentation (Fitzpatrick, 1988). One subject was type I, eleven subjects type II, one type III and one type IV. The subject with skin type IV was the one excluded due to too deep administration of the anesthetic agent. The characteristics of the subjects are given in Table 1.

Table 1
Subject characteristics.

Total number of subjects	14
Total number of subjects included in the analysis	12
Gender women/men	8/6
Median age (y) (range)	53 (31–72)
Median resting pulse before surgery, range (BPM)	60 (56–86)
Median maximum pulse during surgery, range (BPM)	65 (63–91)
Median pulse 30 min after infiltration, range (BPM)	61 (60–70)
No. of patients with diabetes	0
No. of patients using antihypertensives	1 (excluded)
No. of patients Fitzpatrick type I	1
No. of patients Fitzpatrick type II	11
No. of patients Fitzpatrick type III	1
No. of patients Fitzpatrick type IV	1 (excluded)

2.3. Local anesthetics

The following three anesthetics were chosen as they are often used for local anesthesia in plastic surgery.

1. Lidocaine (20 mg/ml) + epinephrine (12.5 μg/ml) (Xylocaine Dental® Adrenaline, Dentsply Ltd., York, PA, USA), denoted LIDO (20.0) + EPI (12.5)
2. Lidocaine (10 mg/ml) + epinephrine (5 μg/ml) (Xylocaine Adrenaline®, AstraZeneca, Södertälje, Sweden), denoted LIDO (10.0) + EPI (5.0), buffered to pH ≈ 7.4 with a 5:1 solution of sodium bicarbonate (50 mg/ml) (Natriumbikarbonat Fresenius Kabi®, Fresenius AG Bad Homburg, Germany)
3. Lidocaine (20 mg/ml) (Xylocaine®, AstraZeneca, Södertälje, Sweden), denoted LIDO (20.0)

2.4. Experimental procedure

The light sources in the room were turned off and the windows were covered to achieve a controlled light environment before the perfusion measurements were started. The studies were performed in a draft controlled room, at a temperature of 20 °C, in which the equipment had been placed at least 24 h before starting the experiments. All subjects rested in the supine position for 10 min, after which their heart and lungs were auscultated. Heart rate was then monitored continuously 10 min before and during the perfusion experiments. The subject's arm was stabilized using a vacuum pillow (Germa Protec, Germa AB, Kristianstad, Sweden). The anesthetic solutions were preheated to 37 °C before injection, and 0.5 ml was injected into the subcutaneous tissue on the volar side of the forearm, at least 8 cm apart. The volume used was 0.5 ml as this represents a clinically significant amount, without the risk of “interference” between the injection locations. The anesthetics were infiltrated as uniformly as possible by the same surgeon within a 1.5 cm^2 area in order to achieve standardized anesthesia. The response of perfusion to local anesthetics was imaged with LSCI or a digital camera for RGB analysis.

2.5. Laser speckle contrast imaging

Perfusion was measured with LSCI using the PeriCam PSI NR System