

Retraction

The article "A review of the clinical applications and performance of laser speckle contrast imaging" is retracted by the Editor-in-Chief, due to violation of the policies and practices of International Journal of Scientific Reports.¹ Some portions of the article is overlapping with an article published in the Journal of Biomedical Optics (J of Biomedical Optics. 2019;24(8):080901. DOI: <https://doi.org/10.1117/1.JBO.24.8.080901>), which violates publication ethics and academic practice.

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Review Article

A review of the clinical applications and performance of laser speckle contrast imaging

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ABSTRACT

Laser speckle contrast imaging (LSCI) is a useful tool for visualizing full-field blood flow images. Speckle pattern is formed when a coherent light illuminates a rough object, and the backscattered radiation is transformed into images and be shown on a screen. Movement within the object results in the fluctuation of patterns over time. The same data can be obtained by employing the Doppler effect, yet producing a two-dimensional Doppler map needs scanning; speckle imaging renders the same information without the requirement to scan. Nowadays, LSCI has gained expanded consideration, in part because of its accelerated adoption for blood flow studies in the different surgical departments. Here we represent and review the application of laser speckle contrast methods to the field of perfusion visualization as clinical studies from various medical fields and discuss the limitations hindering clinical acceptance.

Keywords: Laser speckle contrast imaging, Reconstructive surgery, Microcirculation, Flap monitoring

INTRODUCTION

Measuring the tissue perfusion is vital in microsurgery as it helps clinicians to determine the viability of a tissue flap. Recently, there are several optical imaging techniques have been established to analyze tissue perfusion. Nowadays, most of the clinicians want a noninvasive, noncontact, easy handle, quick as well as cheap procedure.¹ Laser speckle contrast imaging (LSCI) is comparatively a cheap, quick, noncontact, full-field, and relatively simple imaging method that produces two dimensional perfusion maps.² LSCI works basing on the principle that a detector's spontaneous interference pattern. The so-called speckle pattern is created by the backscattered light from a tissue illuminated by coherent laser light. Thus, when the particle moves within the tissue, provokes a variation in this speckle pattern causing the blurring of speckle patterns.³ When the variations are triggered by the moving red blood cells (RBCs), this blurring can be accompanied by the blood

flow. Starting as a slow, analog research tool, LSCI systems nowadays have gained rapid popularity to record blood flow in (near) real-time. This reason has made LSCI be approved by more clinicians into clinical practice to evaluate perfusion of different kinds of tissue, i.e., different kinds of free flaps, during replantation as well as reconstruction surgeries. LSCI has been used to image burn scalds, to check perfusion of the retina, cerebral blood flow (CBF), microvasculature of the skin, liver, esophagus, and the large intestine.⁴⁻¹⁰ Even though many studies have been done using laser speckle, clinical applications are still very uncommon. This review presents a summarizes the clinical applications of LSCI currently applied by clinicians.

BRIEF IDEA ABOUT LSCI SYSTEM

Fercher and Biers informed the earliest biomedical application.² Fercher and Briers proposed a procedure that was non-real-time and had practical restrictions due

to the use of systems that were not digital, which hindered the use clinically. The earliest real speed rises to quasi-real-time image attainment and processing were done in the 1990s with the primer of digital photography.^{11,12} As stated previously, most of the fundamental developments in the usage of LSCI as a tool to use clinically took place in the past 15 years with the massive expansion in cheap computing power. For example, Richards et al built an LSCI system for spending only 90 USD with image quality as good as a 2000 USD setup machine. Usually, the modules required are a laser diode of low-power, a digital camera, a diffuser, and data analyzing software. The entire setup is very simple but effective. Presently, several corporations have been commercializing LSCI. There are some other names for the same principle as LSCI as well. The first users named it laser speckle contrast analysis (LASCA), and another name is laser speckle imaging (LSI).

The primary principles of LSCI

Visualization of blood vessels is an essential task in the assessment of the health and biological integrity of transferred tissue. LSCI is a non-invasive method to determine the blood flow of superficial or exposed vasculature. However, the tissue hinders the visualization of deep vascular structures. When a scattering medium backscatters coherent light, the random interference patterns called speckle patterns to arise. Here scattering medium is usually the biological tissue. The slightly dissimilar optical wavelengths result in the waves to reach the observer at random mutual periods, following in bright and dark spots, correspondingly.¹³ The principle of the measurement technique of the PeriCam PSI system is done by an advanced charge-coupled device camera that records these changes in the speckle pattern. The speckle image consists of both static and dynamic speckles. Static speckles are the result of the speckles that do not alter over time; on the other hand, dynamic speckles change over time as a result of the optical Doppler effect. The dynamic speckles are consisting of information about the movement of the particle or motion of particles inside the object. When the speckle pattern is produced on a moving object such as blood cells, the flow of the blood in the vessels causes fluctuations in the speckle pattern on the detector. In fluid mechanics, the phenomenon where an optical wave propagates through a medium experience intensity fluctuation is referred to as optical turbulence. In the LSCI technique, blood flow causes blurriness of image pixels, which leads to gleaming of the intensity. The result is an instant image of the microcirculation. Blood perfusion is displayed in the arbitrary units, perfusion units. It is this blurring that is used to calculate the speckle contrast K using the following formula: $K = \sigma / \langle I \rangle$, where σ is the standard deviation of the intensity I over the mean intensity $\langle I \rangle$ calculated over a window in space or time

Multi-exposure speckle imaging

As stated above, the amount of blurring depends on the movement of particles within the object and the exposure

time. The initial applications of LSCI were single-exposure procedures, which means that the exposure time is kept constant with every measurement. Single exposure has the drawback that the measured perfusion it is hard to quantify since the sensitivity and quantitative accuracy are highly related to the exposure time.¹⁴ Parthasarathy et al. developed the first multi-exposure laser speckle imaging system in an attempt to make the technique stronger and to upsurge the reproducibility of results.¹⁵ While maintaining a constant intensity, this new setting can vary the exposure time. Additionally, to the multi-exposure setup, by considering the presence of static scattered light, they derived a new as well as a broader, mathematical model for speckle imaging. The single-exposure setup is less accurate for more substantial variations compared to the multi-exposure setup as it shows linearity with relative changes in speed over a broader range of velocities, allowing for semi quantitative measurements. Based on the Lorentzian velocity distribution, the proposed speckle model can be used to obtain the fraction of dynamically scattered light ρ , the systems noise, and the correlation time τ_c .¹⁵

LSCI IN CLINICAL APPLICATIONS

This review is comprised of preclinical and clinical LSCI literature. The reviewed articles are selected based on the authors' interests. The formal review was done of all published literature from the last 30 years related to the application of LSCI clinically in internet-based scientific journals.

Application in neuroscience

The determination of CBF during neurosurgery is fundamental in confirming that blood perfusion levels are at pre-operative levels and to examine post-operative tissue morbidity.¹⁶ The CBF was initially studied in rodents, which are considered small animals.¹⁷ Subjects of studies were gone through not only some artificial stimulations, such as cortical spreading depressions, electrical stimulation, and hypercapnia but also physiological stimulations such as hyperthermia, hyperoxia, and vascular occlusions.¹⁸ There is some studies report on the successful clinical application of LSCI, although the real interpretation from the experimental recruiting to clinical recruiting as a standard of care has yet to come. Hecht et al. described the first clinical study that comprised three patients experiencing extracranial-intracranial bypass methods.¹⁹ The results they provided were promising as they recorded an increase in relative baseline after finishing the vascular anastomosis. They were able to confirm adequate blood flow replacement via the bypass following the obstruction while Richards et al and Parthasarathy et al established a microscope laser speckle contrast imager that was used mainly for neurosurgical approaches.^{6,20} In another study by Hecht et al, thirty patients recruited to have direct surgical revascularization were comprised of giving some similar promising outcomes concerning the

application of LSCI clinically.²¹ Nomura et al in their research compared LSCI to 123 I-iodoamphetamine photon emission computed tomography and described a reasonable success.²² Other related uses of LSCI are the estimation of infarction the malignant stroke and functional brain mapping.²³ The integration in neurosurgical operation causes least interruption, mainly using the microscope setup reported by Parthasarathy et al.⁶ Future studies should include an accumulation of a large number of data on CBF evaluation to resolve different limits of interest based on blood flow alterations, in which the clinicians can make their decision for further treatment. As a result, LSCI may be taken as a standard of neurosurgical approaches within neurosurgery.

Application in rheumatology

LSCI is applied in rheumatology to define the state of systemic sclerosis (SSc) by assessing perfusion. Della Rossa et al., in their study, reported on the application of LSCI to monitor the dynamic vascular response and perfusion changes in patients affected by Raynaud's phenomenon, including SSc patients.²⁴ A distinction between primary Raynaud's phenomenon and SSc could be made just only basing on qualitative blood flow measures such as post-ischemic hyperemic area and peak flow area after an ischemic test under the curve. Others later confirmed this.²⁵

LSCI and laser Doppler flowmetry (LDF) are currently used to measure the peripheral blood perfusion (PBP). In rheumatology, Nailfold video capillaroscopy is considered as the standard of care to determine the state of SSc by providing information on the morphological aberrations of the capillaries. The PBP values reported using LSCI and LDF were found to have a direct relationship between dissimilar nonviolent communication patterns. Lesser PBP values were recorded for SSc patients compared to subjects with no complication, which is connected to the findings of others using LDF and laser Doppler imaging (LDI).^{24,26,27} Compared to a previous study, it was reported that is considered as a good potential in comparison to thermography.²⁵ With these results considered, LSCI is a reliable technique for detecting PBP in humans. LSCI is yet an entirely new method in this field; however, it is gaining popularity over the more frequently accepted LDF because of its accuracy, shorter acquisition time, simplicity of use, and the fact should be noted that LSCI provides an image which is promising rather than a single-point measurement.²⁴ Arthritis is a prevalent disease in rheumatology. An inflammatory reaction causes arthritis affecting joints that can be illustrated by locally increased perfusion. Early detection of arthritis might help to delay or inhibit further damage to patients if the characteristic new vasculature can be measured using LSCI. By using their so-called transmissive LSI technique, Dunn et al. reported that depth could be gained upto 15 mm into tissues, which is satisfactory to monitor

finger joint synovial blood flow.³¹ Recently we are doing a pilot study on replanted fingers to measure the perfusion value and predict the tissue viability. Lastly, a report on a new endoscopic apparatus was done by Forrester et al. that was used to image the joint capsule tissue of a rabbit in vivo.³² Changes in microvascular perfusion is a character of many diseases in, which suggests that LSCI could become a key tool for the rheumatologist for assessment of disease activity.

Application in reconstructive surgeries

Free tissue transfer has become a popular surgical procedure in reconstructive surgeries of the limbs as well as the head and neck. The success rate of reconstructive surgeries is high; however, there are occasional failures as well. Furuta et al used the LSCI method to investigate on twenty patients having that needed excision of their head and neck tumors and microvascular free tissue flap transfers for repair and was able to find out low vascular perfusion in the edge of the tissue flap.⁴⁹ In some recent studies, Zötterman et al on an animal model monitored partial and full venous outflow obstruction in a porcine flap model using LSCI.⁵⁰ They showed clear benefits in favor of LSCI, in terms of variability and reliability. They also used the LSCI technique to predict flap necrosis on the procaine model, which seemed to be useful for many surgeons.²³ In oral and maxillofacial surgery. Currently, our group is also doing two pilot studies on free flaps and replanted fingers to determine a threshold of the perfusion under which there will be the possibility of tissue morbidity. In reconstructive surgeries, nowadays, the application of LSCI procedure is gaining popularity.

Application in plastic and burns surgery

A burn surgeon deals on delicate tissues such as skin or superficial muscle tissue in most situations, unlike the rheumatologist. An example is the assessment of burn wounds. Only in about 70 percent to 80 percent of the time, the clinical assessment based on visual and tactile knowledge of burn wound severity by professional burn surgeons is appropriate.⁴⁵ For most clinicians, the two extremes, red, painful, non-blistering superficial burns, and pale, leathery, deep burns, are easy to detect. Failure to diagnose deep partial-thickness wounds may result in unnecessary hospitalization, excision, and grafting. Therefore, there is a vital therapeutic need for a rigorous analytical process. Microcirculatory blood flow control is an indication of healing capacity, and visualization modalities that can image the blood circulation can be of excellent help to the plastic and burn surgeon. LSCI; otherwise, it can achieve parallel outcomes while maintaining the advantage of being minimal-invasive and non-contact with the additional benefit of being inexpensive, simple and with short acquisition times.⁴⁶ LSCI is essential for the treatment of patients who cannot remain still or because it concerns infants.

The first to write on the use of LSCI to evaluate superficial blood flow in burn surgery is by Stewart et al.⁴⁶ The group evaluated the perfusion of burn scar and compared LDI to LSCI, finishing with a positive note to LSCI. In a mouse burn model, Crouzet et al used LSCI to record perfusion.⁴⁷ Both superficial partial and deep partial-thickness burns were induced. The findings show that LSCI can differentiate the statistical significance between the induced superficial-partial and deep-partial burns. Such findings are auspicious even though, because of the massive biological differences in the skin, for example, thickness and structure conversion to clinically relevant evidence could be difficult. Lindahl et al conducted a study using LSCI on pediatric scald injuries that attempted to predict the burn consequences at 14 days after burning.⁴⁸ Due to the short processing time, LSCI is well adapted for pediatric burns. The group reported a significant difference from those who received treatment after one day for wounds that recovered within two weeks. LSCI allows with simply understandable images to predict wound healing. A single perfusion calculation is adequate to determine the need for surgery with greater accuracy when an additional measurement is made after burning between 0 and 24 hr. Together with the experience of the surgeon, LSCI should be used as perfusion measures do not preclude deep or superficial burns. Furthermore, because of the need for treatment, it can be a useful tool for the surgeon to make critical decisions in superficial wounds.

Application in ophthalmology

LSCI is widely used in ophthalmology in recent times and is the main field of research. Generally, two kinds of laser diodes are used in ophthalmic researches; one is used for measuring deep perfusion; another one is a blue module argon laser for measuring superficial perfusion depending on the application is used. Two separate blood supplies supply the retina by a feature of the high metabolic activity. The circulation of choroid supplies the choroidal tissues and the outer layer of the retina, and the retinal circulation supplies the inner serving of the retina. The earliest digital application of LSCI was made by Tamaki et al. to measure the blood flow of retina, blood flow dynamics of the choroid, and optical nerve head (ONH).³³ The group applied the technique suggested by Fercher and Briers by following alterations in blood flow in ONH tissue.² This was later developed to evaluate the choroid and ONH of the human eye in real-time.³⁴ Separable characteristics such as sex, glaucoma, changes in atherosclerosis, and hemodynamic values are said to be associated with the factors that pulse waveform provides.³⁵ Numerous studies using LSCI are existing within the field of ophthalmology since this way, the consequence of the circulatory system can be studied in detail, such as diabetes.³⁷ Although the contrast of interpatient qualitative methods of blood flow dynamics has not yet been reported in any other field, however, these parameters consequence in more comprehensive

clinical applicability varying from ocular disease to systemic hemodynamic examination.

Application in dermatology

Port-wine stain (PWS) marks are examined using the LSCI technique recently in dermatology. PWS is progressive and associated with abnormalities of blood vessels causing increased blood flow locally. The outcome of pulsed dye laser treatment on the blood flow was first examined by Huang et al.³⁸ They reported a significantly decreased perfusion in treated areas; on the other hand, the untreated areas remained natural. This implies that LSCI is a promising guidance method for the surgeons to reduce the number of periods needed for the complete blanching of PWS.³⁹ LSCI could be used in examining the diabetic foot ulcers that might go through local morbidity was stated by Mennes et al.⁴⁰ LSCI has gained feasibility to be clinically recruited both in burn surgery and dermatology.⁴

Other application of LSCI

There are some other interesting uses of LSCI are applicable in dentistry and reconstructive surgeries. In dentistry and oral science LSCI has been applied to image the gingival blood flow, dental pulp flow.^{41,42} In cardio vascular studies there are numerous uses of LSCI. A study was published regarding the evaluation of the forearm endothelium presenting notably impaired vasodilatory response with type I diabetic patient.⁴³

CURRENT LIMITATIONS OF LSCI

As explained above in a plenitude of forms, there are still constraints that hinder the clinical application of LSCI. First of all, most investigations are restricted to qualitative estimations and shallow interpatient contrast. This appears to be a difficulty for recording the tissues with the motion, for example, intraabdominal perfusion analyses as well as patients such as Parkinson's disease patients who cannot remain still. However, recent reports propose that a reference zero flow patch may be favorably used to get rid of movement artefacts in LSCI recordings.⁴⁴

CONCLUSION

It is obvious that there is a considerable number of activities around the globe involving LSCI procedure. Notwithstanding, LSCI has been applied in different sectors for above 25 years; the basic method has remained comparatively unchanged. LSCI has several strong points, such as simplicity and inexpensiveness; however, the main weakness is the relatively low real-time spatial resolution. However, a significant amount of work is still required to improve our understanding of the complex physics underlying speckle imaging.

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