International Journal of Innovative Research in Engineering
Volume 3, Issue 5 (September-October 2022), PP: 132-142.
www.theijire.com
ISSN No: 2582-8746

Potential Non-Invasive Techniques to Track Inflammation in vivo - A Review

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How to cite this paper: V. Marasinghe[1], D.V.S. Kalubowila[2], "Potential Non-Invasive Techniques to Track Inflammation in vivo - A Review", IJIRE-V3I05-132-142.

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Abstract: *Inflammation is a reaction of the immune system to the removal of foreign stimuli from the body. A clinical need exists for noninvasive tools capable of tracking inflammation levels continuously for patients with inflammatory diseases. This review aims to demonstrate devices and methods that can be utilized to test and quantify inflammation noninvasively in vivo. The methods are categorized based on five main cardinal signs related to inflammation; pain, swelling, redness, heat, and loss of function related to inflammation. The paper also explores possible techniques to detect and monitor related physiological changes such as inflammatory biomarkers, and oxygen deficiency.*

Key Word: *Inflammation; Foreign stimuli; Noninvasive; Cardinal signs; Bio-markers.*

I.INTRODUCTION

Inflammation is a reaction of body's defense system to eliminate physiological and pathological foreign stimuli which are harmful to the body. The steps include recognition the threats, removing agent and healing and restoring tissue structure to recover from infectious, post-ischemic, autoimmune injuries, traumatic or toxic pathogens [1], [2]. Inflammation is linked with metabolic disorders, cardiovascular diseases, stress, cancer, diabetes, respiratory and skin diseases [2]. Inflammation is adaptive and makes unique changes in anatomy and functionality and is more generalized depending the region. For example, inflammation associated with meaning and appendix are called meningitis and appendicitis. Inflammation can be categorized as acute or chronic based on the inflammatory process , microbes involve and duration. [3].

Considering visual observation, five main symptoms associated with inflammation are characterized. by five cardinal signs, namely pain(dollar), swelling (tumour), redness (rubor), heat (calor, in body extremeties only), pain (dolor) and loss of function (functiolaesa) [4]. However, those five symptoms can be found in any inflammation more or less.

Frequent monitoring of cardinal reaction levels is essential as a guidance for medical treatments, understanding related disease progression toward optimal management of the disease. Inflammation can be detected by clinical methods and relevant investigations in a clinical setting. Monitoring of the inflammation continuously is not permitted in currently and available detecting techniques have certain drawbacks associated with cost, time, accessibility, safety, patient comfort, and reliability. A non-invasive sensing system is are volutionary solution for these limitations and to put traditional health care in to a more timely, remote and portable path [5],[6].

Bio sensors are devices which are lightweight, capable to bind to skin of human and able to tolerate mechanical deformation. Therefore, bio sensors are emerging technique which is powerful and flexible to detect and measure biological signals, such as blood pressure or heart rate [7],[8]. Biomarkers are molecules that can be found in body fluid or constituents of tissues, that offer a sign of risk factors or a disease, and can extend the information about the underlying pathogenesis of diseases; inflammation [97]. Biomarkers can be inflammatory mediators or blood cells such as leukocytes that involve in inflammation.

Here in, we review the techniques aimed at developing non-invasive electronic/ electrochemical sensors and biosensors to detect those signs for continuous monitoring and discuss their prospects and limitations toward advanced detection.

II. SWELLING DETECTION

A. Bio impedance Analysis

Swelling in one of the inflammatory response which decrease in impedance in tissues[10]. This phenomenon in tissue impedance occurs due to changes in external environment in inflammation and cell properties [8]. Moreover, Bio-Impedance Analysis (BIA) is associated with inflammatory Biomarkers, therefore, BIA can be used as an indicator for inflammation [9],[11]. Furthermore, the extracellular liquid provides a significantly considerable parameter in traumatic injuries, and to measure inflammations pathologies which are obstructive [13]. In practice, tissue parameters response to impedance varies with the frequencies of the applied signal, hence, a broad band of frequency is used to perform impedance analysis to have a better understanding on physiology, anatomy and pathology of biological tissues [12]. In a research by Neves EB, it is found that sensitivity in raw bioimpedance parameters is associated with physiological changes of knee arthritis which is an inflammatory disease non-invasively [8]. To distinguish patients with inflammatory diseases and to monitor the response to treatment BIA provides a rapid bloodless tool in the clinical setting [9].

Figure no 1 : Illustration of electrodes placement in the protocol of BIS data acquisition.(Source: adapted from [8])

B. Outer-Circumference Measuring

Peripheral edema is swelling of the hands, legs or feet due to accumulation of excess fluid in tissues [75]. Leg swelling, nerve damage, and circulatory problems are common symptoms of diabetes and other chronic conditions. Before occurring of a permanent nerve damage, these symptoms must be addressed early in the propagation of the disease. Developing and testing an edema monitoring system which is wearable is important to provide a good understanding of related symptoms and to avoid nerve damage [16].

Pitting and tape measure is a method that is commonly used to detect peripheral edema in clinical practice [75]. For non-invasive detection and tracking, digital systems can be developed using Dielectric Electro-Active Polymer (DEAP) stretches sensors [14], combining a resistive polymer cord and capacitive sensors [83], using inductive coil [16] or flex sensors [75] attached to a textile support, to detect relative changes in outer circumference and changes in joint curvature such as ankle.

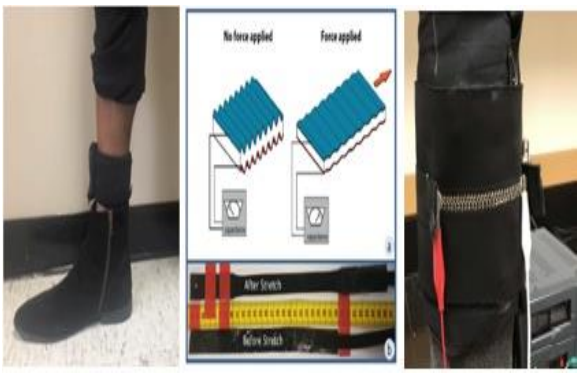

Figure no 2 : Setup for detect circumference changes (Source: adapted from [75],[16],[83])

C. Resonance Frequency based Detection for Fluid Accumulation

A decrease in total capacity can be caused due to damaged cell membranes associated with acute injury [17]. The ability of the RF sensor to detect fluid shifts and its high penetrating ability makes the sensor a feasible method to detect the early stages of edema inside complex environment of human body [15], [16]. Therefore, a possibility exists for characterization of deeper tissue layers using a dielectric patch and radio frequency signals [15], [16]. Moreover, for monitoring of pulmonary edema RF based dielectric patches are commonly in use[84],[85],[15]. Open circuit electromagnetic resonant skin patch sensors are also capable of detecting fluid volume shifts due to the relationship of the fluid volume pressure and resonance frequency relationship. Jacob Griffith has developed such a sensing system to non-invasively measure cranial fluid volume shifts.[31].

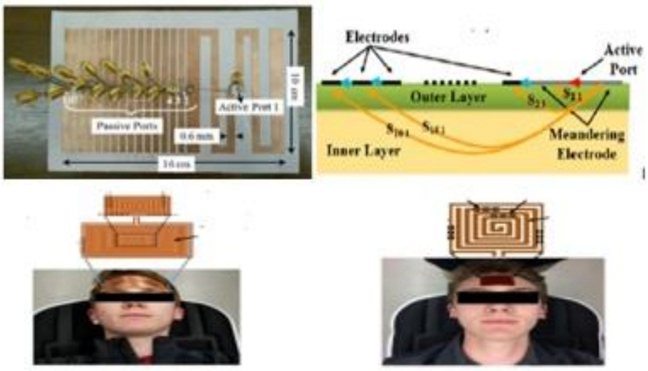

Figure no 3 : Dielectric skin patches to detect fluid accumulation (Source: adapted from reference [15],[31])

D. Ultrasound Detection for Vascularity and Muscle Thickness and Joint Gap Measuring

To measure the deformation and thickness of different layers in an indentation area of body ultrasound can be used as its utilization of time-of-flight (ToF) and sound velocity information [24]. The sound speed in the soft tissues of the human body is considered to be 1540 m/s in average [23]. Ultrasonic waves cannot penetrate through hard tissues such as bones although it passes through soft tissues depending on the sound wave frequency [23].

Vasodilation is a common condition and cause of edema. Ultrasound devices are designed to be skin conformal and capable of recording blood pressure waveforms at deep arterial and venous sites [22]. In addition, vessel cross-sectional area can be accurately quantified to calculate the BP waveform by using ultrasound imaging of the human body, which is especially valuable for measuring the central venous pressure (CVP) of jugular veins that irregularly shaped since vascularization is sensitive to ultrasound studies [22]. Additionally, muscle contractile properties of skeletal muscles [23],[18],[19] joint gap(i.e: knee, wrist) by detecting cartilage region [25], tissue thickness and elasticity measurement can be monitored [24].Ultrasound is sensitive for effusion and synovial thickening in inflammatory arthropathy and erosion of articular surface in degenerative arthritis which is an inflammatory disease [20],[21].

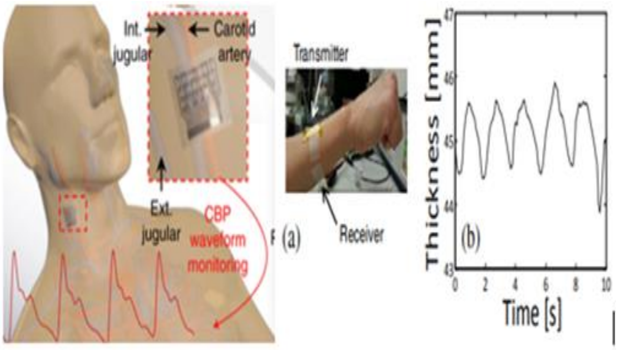

Figure no 4 : Wearable ultrasonic bio sensors/devices (Source: adapted from [22,18])

E. Sound Sensors for Analyze Edema in Knee Joint Gap Measuring

Inflammation leads to changes of the inflammatory cells and the extracellular matrix. In addition, Edema makes fluid accumulation in knee joint [41][42]. Crepitus is a prominent feature during knee motion that can be detected to generate vibroarthrographic (VAG) signals [82],[26]. VAG signals are generated by the properties of the structures within the joint.

A study using a knee sound signal obtained with an innovative stethoscope with goniometer showed that the accuracy rate of the median ratio algorithm (93%) was better than that of the mean coefficient algorithm (88%) for clinician cross-validation [44]. Another study using the same procedure showed an overall accuracy of up to 82.69%, showing good sensitivity and specificity [41].

In another study, a non-invasive knee osteoarthritis(OA) diagnosis system was conducted via VAG signal analysis. The classification result illustrated a sensitivity of 89.52% and a specificity of 67.50%, with a total accuracy rate of 81.52%. The AUC values obtained were 0.68 (95% CI 0.61-0.74). The rates of correctly predicting the lack of OA were approximately 78.6% and the proportions of patients with OA who are correctly diagnosed were approximately 82.8% [82].

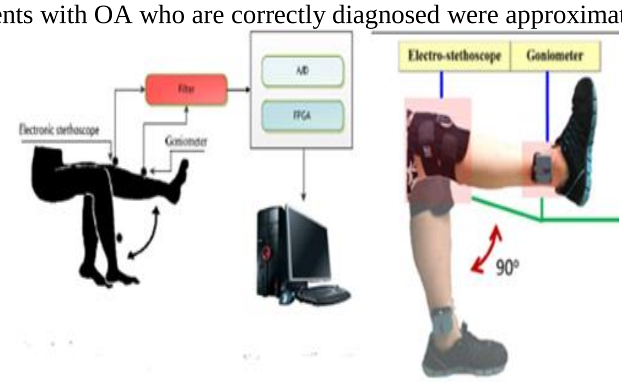

Figure no 5 : Knee flexed (90°) and full extension with goniometer (Source: adapted from [41], [43])

III.PAIN DETECTION

A. Pain Signal Detection

Pain can be classified by its duration and occurring mechanism. The acute pain is a term often refers to the tissue damage occurrence. This is a short-term pain that acts as a body's warning sign. Nociceptive pain caused by injury to body tissues.[86]. Electroencephalogram (EEG) is used for record brain activity for brain-related studies (e.g., stress-related studies, changes in emotions or anesthesia-based consciousness studies, etc.) [86].

EEG data can be obtained by keeping the reference electrode was chosen on the vertex, and the ground electrode is placed on the forehead [87]. Human olfactory bulb(EBG) potentially can be implemented as a clinical tool for everyday clinical tool to detect pathology-related changes in human central olfactory processing in neurodegenerative diseases [51].

Inflammatory pain can be caused by sensory nerve signals or by direct exposure of the brain to mediators. Thus, inflammatory pain can be detected by peripheral sensory nerves [50]. Some groups are working on the creation of neuro processing to restore sensorimotor functions lost in patients with spinal cord injury or stroke [45],[46],[47]. However, many applications require contact with the target peripheral nerve for high resolution and stability, therefore, non-invasive detection is challenging [88].

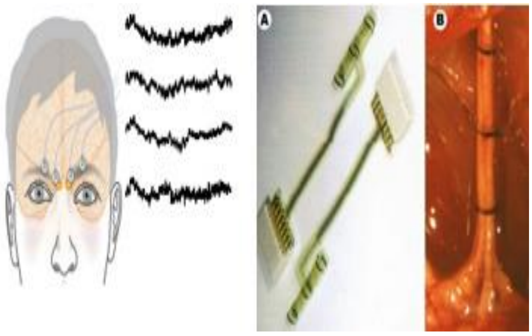

Figure no 6: Electrode placement in olfactory processing, Cuff electrode wrap around nerve (Source: adapted from [51,50])

IV.HEAT DETECTION

A. IR Thermal Images Analysis

The phenomenon of detection and prediction of temperature change is the main purpose of using Medical Infrared Thermography (MIT) as a tool for diagnose diseases with inflammatory pain. infrared radiation emitted from the skin is taken to record and monitor the flow of body temperature in skin surface as a non-invasive, non-contact and rapid imaging technique by MIT. It is possible to detect even a slight difference in skin surface temperatures in high-resolution infrared images with use of advanced infrared cameras and following standardized methods for obtaining and processing thermograms.[91]

Body temperature measurement is one of the fundamental of clinical evaluation in medicine. Skin is the largest organ in the body of human and is can be considered as a temperature mosaic which helps to determine the blood flow rate through capillaries and arterioles adjacent to the skin.[93] However, infrared (IR) thermal imaging may become a reliable method for mapping surface temperature in disease states where the "normal" distribution of blood flow to the skin is disrupted by pathology [93]

Emerging medical applications are reviewed for thermal imaging, including inflammatory diseases, including inflammatory arthritis and osteoarthritis [90]. In a research, temperature profiles of fingers is taken using an infrared camera monitor RA inflammatory patients [89]. In contrast to previous work, optical images were obtained from the dorsal side with illumination on the palmar side, and the features of the spatial distribution of transmitted light along the joint were assessed [92].

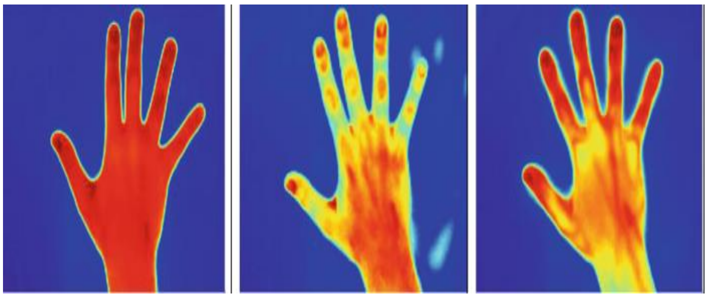

Figure no 7: Thermograms images (Source: adapted from [89])

B. Microwave Radiometry to Determine Internal Tissue Temperature

The phenomenon Microwave radiometry is a non-invasive method that determines the temperature of internal tissues in vivo within seconds [55],[52]. It is shown that temperature of internal tissues at a depth of 3–7 cm with an accuracy of $+/-0.2°C$ can be detected in vivo [52]. One-way analysis of variance statistics showed a significantly (P< 0.005) higher radiometric temperature in affected areas compared to healthy areas. [52]. Increased joint temperature of knee in depth is measured using microwave radiometry (MWR), and proven that it may reflect inflammation even in the absence of clinical signs [55]. The ability to detect inflammation in the knee joints was evaluated using a substrate-integrated waveguide antenna connected to the radiometer [54].

Articular blood flow is the most sensitive to inflammatory arthritis and indicates statistically significant difference of (P< 0.05, $power$ = 0.8) between inflamed and healthy joints [53],[53]. The core temperature of the joint is related to the its blood flow. While the temperature of a normal healthy knee remains at 28° , the temperature of joints with inflammation remains above 33°C [54]. It is hypothesized and shown that MWR is useful for evaluating patients with RA and spondylarthritis [55].

Figure no 8: Microwave radiometry system-Antenna placement (Source: adapted from [54],[52])

V.REDNESS DETECTION

A. Changes in Blood Flow Detection

To evaluate changes in humans blood flow, Diffuse Correlation Spectroscopy (DCS) is highly being used in optical imaging field due to its real-time and non-invasive performance and its ability of label-free bedside monitoring [56], [57]. The inflammatory disease, arthritis seems to be most sensitively linked to Joint blood flow and could detect statistically significant difference ($P<0.05$, power = 0.8) between healthy and inflamed joints [53]. Diffusion Correlation Spectroscopy and Near Infrared Frequency Spectroscopy can measure microvascular blood flow in dynamically exercising muscles of human. Diffusion correlation spectroscopy (DCS) is considered to be an emerging visual method for measuring cortical cerebral blood flow [58]. Moreover, DCS can play a key role in personalized patient management and expanding the understanding of neurovascular connectivity and activation [58]

First, it is challenging to detect relative changes non-invasively in blood volume and blood flow. fiber laser spectroscopy can get blood flow measurements in deep tissues in real time [60],[62],[61]. In addition, it can determine the oxygen concentration (HbO2, (Near Infrared Spectroscopy) NIRS-DOS system) [66]. Site specific skin blood flow is measured at the forehead, earlobe and fingertip using a micro integrated laser Doppler blood flow meter [96].

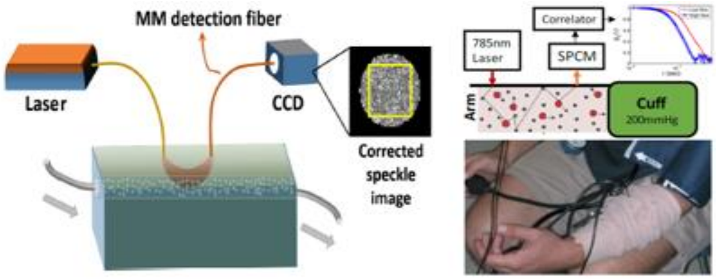

Figure no 9: Schematic of a DCS system, NIR laser is directed onto the forearm via a fiber. (Source: adapted from [56],[57]).

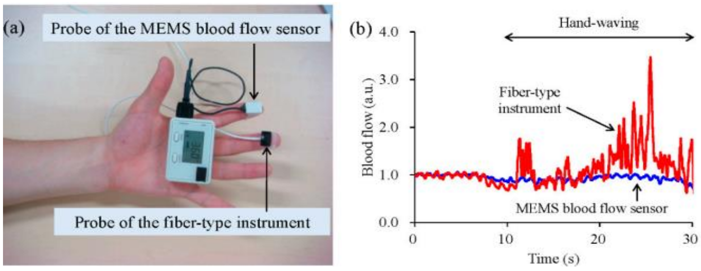

Figure no 10: Schematic of a DCS system, NIR laser is directed onto the forearm via a fiber. (Source: adapted from [56],[57]).

VI.LOSS OF FUNCTION DETECTION

A. Gait Analysis for Joint Functionality Detection

Inflammation can create contractile parametric changes, joint orientation changes, loss of functionality and pain in knee joint. Currently, special gait laboratories are often used to objectively diagnose functional movement deficits or treatment outcomes [80]. Measurement of the three-dimensional (3D) angle of the knee joint outside the laboratory is useful in clinical examinations and therapeutic treatments [64].

The proposed system for measuring knee peak sagittal angles consists of a flexible conductive polymer block connected to a wireless data acquisition unit. Comparison of knee peak flexion angles calculated with the sensor and the gold standard yielded an absolute error of 0.35 (± 2.9°) and an RMSE of 1.2 (± 0.4)°. These results show the ability of the sensor to monitor the sagittal angles of the knee peak with a small error and in accordance with the gold standard system [81].

Similarly, a study conducted to test a wireless wearable sensor system consisting of inertial sensors evaluated by measuring hip, knee, and ankle joint angles found that the mean RMSE values were less than 4 degrees for all joint angles, and the mean correlation coefficient was greater than 0.985 for hip and knee joint angles and about 0.90 for ankle joint angle compared to the motion measurement system [68].

Research conducted by M. Schulze et al evaluates a wearable kinematics measurement system to assess maximum knee joint angles during long periods of normal walking. The calculated maximum knee joint angles were compared with reference measurements. The results show an excellent correlation of 0.96 between clinical reference measurements and calculated angles. While the accuracy is good for slow walking at 0.28 m/s (lkm/h, average error: 2.6°±1.5) and 0.56 m/s (2 km/h, average error: 2.0°±1.6), the algorithm outperforms angles by 6.3 ± 3.6 degrees at a speed of 0.83 m/s (3 km/h), which is likely caused by soft tissue movement during heel strike [80].

The aim of this study was to propose a new calibration procedure adapted to the joint coordinate system (JCS) that only required IMU data. Compared to the reference system, this functional procedure showed high accuracy (SDo21 and CC40.75) and moderate accuracy (between 4.01 and 8.11) for the three elbow angle. In addition, this method can be adapted to measure other complex joints such as the ankle or elbow [64].

Figure no 11: Sensor positioning on the lower extremity (Source: adapted from [67],[64],[81])

VII.OTHER DETECTION TECHNIQUES

A. Photometric Detection of Inflammatory Mediators

Near infrared spectroscopy (NIRS) makes a continuous grow as an important and useful analytical technique for analysis of pharmaceuticals. [73]. It provides a unique prospective as a fast, non-destructive way for quantitative and qualitative assessment [73]. PA spectroscopy, NIR spectroscopy, Raman spectroscopy, fluorescence, and microwave sensing have higher possibility to be developed into products that affordable and usable for daily healthcare by continuous monitoring. [70], [72]. Its exceptional molecular specificity and minimal interference of water in the spectral profiles obtained from the matrix of blood tissue [70]. For measure the sensitivity to oxygenated and deoxygenated hemoglobin, and scattering and absorption of water at different wave lengths, optical behavior of Near infrared (NIR) over biological media has shown potential in its spectrum [74].

Currently, a reliable non-invasive method for the non-invasive detection of inflammatory mediators particularly in vivo is not shown though it's been conducted to detect blood glucose etc. Still, there is a possibility to get the real-time concentration of inflammatory mediators like cytokines using spectroscopy as such proteins can be found in interstitial fluid [35], [95].

A new blood glucose sensor that is cost-effective and wearable, with a short acquisition time interval that enables the use of a non-invasive long-term continuous blood glucose monitoring (CGM) system. The reflected optical signal was measured in combined visible and near infrared (Vis-NIR) spectroscopy. By collecting reflected light at different optical wavelengths at different levels of BG concentration, we will obtain several spectral data that can be used for multivariate analysis [71]. Spectroscopy is used for non-invasive monitoring of blood glucose levels [70],[71],[72]. Moreover, blood types can be instantaneously detected using optical sensing in vivo procedure [74].

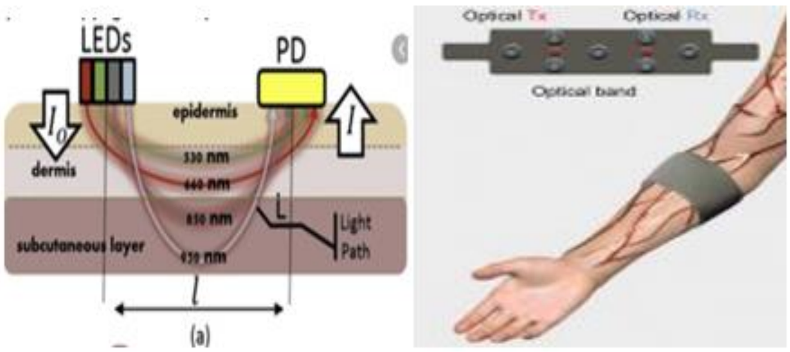

Figure no 12: Reflection mode optical measurements (Source: adapted from [74])

B. Oxygen Sensing

Local inflammation is also often linked with hypoxia of tissue due to a combination of increased oxygen demand and reduced oxygen supply of infiltrating and resident cells as a result of the inflammatory response [94]. Moreover, hypoxia can cause inflammation itself [78]. Patients with inflammatory diseases are shown to have less level of oxygen in many different tissues that are inflamed [78].

Conducted research shows that skin inflammation can measure using paint-on oxygen sensing bandage by mapping skin inflammation noninvasively in a model of porcine inflammation. [94]. A study has shown that macromolecular optical probe with bandage could effectively distinguish image of inflammation of healthy and inflammatory areas in a mouse model of induced inflammation- lipopolysaccharide (LPS) with low background interference [79]

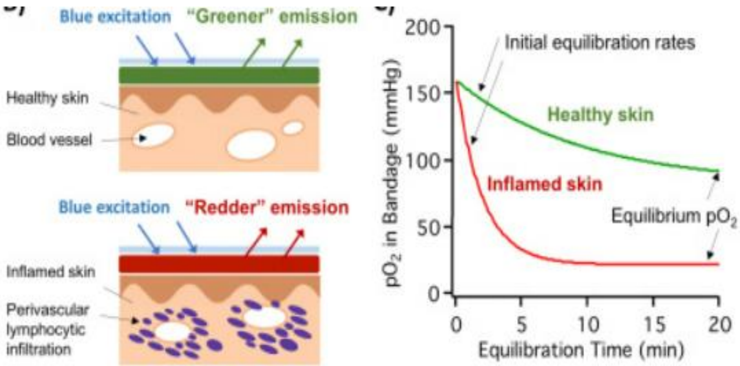

Figure no 13: pO_2 equilibrium rate on bandage applied healthy and inflamed skin (Source: adapted from [95])

C. Leukocytes Detection

In the inflammatory tissues, migration of leukocytes is an important occurrence. Techniques for recognition of non-adherent and adherent leukocytes are developed [98],[99]. It is challenging to effective imaging and identifying leucocytes in vivo within the blood stream. Still, at different imaging depths within small vessels, blood cells are imaged noninvasively using an optical probe by a method called Spectrally Encoded Flow Cytometry (SEFC) [99].

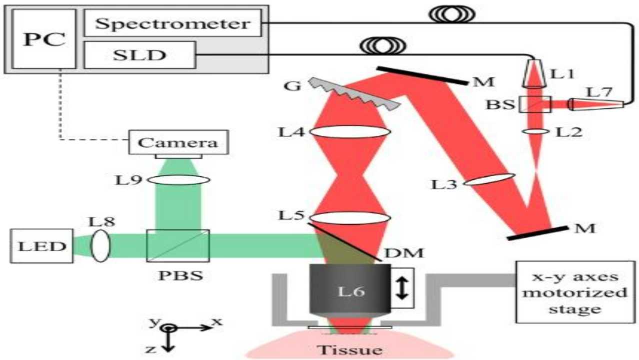

Figure no 14: Schematic illustration of the in vivo SEFC system (Source: adapted from [99])

VIII.CONCLUSION

This review investigates the potential techniques to noninvasively detect inflammation and track the progression for daily health care. Detecting analytes in human cardinal signs relevant to the inflammatory disease is important to monitoring of health condition and progression.

Many diseases are linked with inflammation. Therefore, the ability to monitor inflammatory level continuously will allow patients to actively treat inflammation and reduce harmful consequences.

In recent years, many research has been conducted on providing non-invasive, real-time analysis of analytes of inflammation integrated with signal processing. Still. further development in the field is required, Nevertheless, from recent rapid development, it can be concluded that non-invasive inflammation analysis for health monitoring has potential to make further significant advancement in the medical field.

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