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Monitoring tissue perfusion during extracorporeal circulation with laser speckle contrast imaging

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ABSTRACT

Objective: The laser speckle contrast imaging (LSCI) system is a method to evaluate microcirculation. The primary aim of our study is to evaluate the relationship between LSCI and perfusion markers in coronary artery bypass grafting (CABG). Our second aim is to investigate the relationship between LSCI and extubation time in the intensive care unit.

Patients and Methods: Fifteen patients aged 43-80 years who will undergo on-pump CABG were included in the prospective study. Mean arterial pressure (mmHg), heart rate (min-1), PO2 (mmHg), PCO2 (mmHg) and lactate (mmol/L) levels were measured pre-induction, post-induction, 10th minute of the extracorporeal circulation, post-crossclamp, and post-operatively. At the same time points, LSCI values from the skin were measured and recorded. The intubation times of the patients were also recorded.

Results: There was no significant change in systemic tissue perfusion markers (P>0.05). LSCI perfusion values decreased significantly from induction and remained low until the end of surgery (P<0.05). The perfusion value (98±11 PU) of the patients who were intubated for less than 8 hours was better than the perfusion value (52±4.8 PU) of the patients who were intubated for more than 8 hours (P<0.05).

Conclusion: In our study, a significant change occurred in skin tissue perfusion before systemic perfusion parameters in CABG, and low perfusion was associated with prolonged intubation time.

Keywords: Skin perfusion, Laser speckle contrast imaging, Extracorporeal circulation, Coronary artery bypass grafting, Extubation time

1. INTRODUCTION

Detection of predictive factors for perioperative complications is important in terms of protecting organs and stopping possible organ damage in the intraoperative and postoperative period [1]. Organ damage begins with disruption of tissue microcirculation [2]. Invasive methods have been defined to obtain direct or indirect information about tissue microcirculation. These include assessment of blood gases, mixed-venous oxygen saturation (SvO_2 > 70%) [3], lactate level (<2 mmol/L) [4], veno-arterial carbon dioxide difference (<6 mmHg) [5], gastric tonometry (pH>7.35) method [6]. However, these approaches have some limitations such as being invasive and providing site-specific information. Therefore, non-invasive monitoring is needed.

The laser speckle contrast imaging (LSCI) is a system that does not require special expertise and is used to evaluate the perfusion of tissues such as the retina and skin without using any dyes [7]. The technique is based on the principle of processing backscattered light from a tissue surface illuminated by laser light. It can give real-time images without touching the tissue. The light reflected from the erythrocytes moving in the tissue creates ripples on the detector. These fluctuations appear as color spectrum and give numerical values as LSCI perfusion unit [8]. In recent studies on tissue perfusion, it has been shown that skin perfusion is closely related to the microcirculation of internal organs [9-11]. By evaluating the skin microcirculation, the vascular mechanisms of systemic diseases such as hypertension, diabetes and chronic renal failure are investigated [12]. Ijzerman et al., found impaired skin vasodilation in people with high coronary heart disease scores [13]. In this way, it has been shown that a non-invasive evaluation of peripheral tissue can be used in the diagnosis of a systemic vascular disease.

The primary aim of our study is to measure the skin tissue perfusion with LSCI during the surgery in patients who will undergo coronary artery bypass grafting (CABG) and to investigate its relationship with systemic tissue perfusion markers. The secondary aim of our study is to investigate the

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relationship between skin tissue perfusion and intubation times in the intensive care unit.

2. PATIENTS and METHODS

Patients

Fifteen American Society of Anesthesiologists patients aged between 43 and 80 who were going to undergo on-pump CABG operation were included in this prospective study. The Ethics Commitee of the University approved the study (ATADEK: 2015-15/17) and written informed consent was obtained from the patients. Exclusion criteria: Active congestive heart failure, emergency cardiac surgery, need for inotropic support before surgery, elevation of any systemic hypoperfusion parameter before surgery, coagulopathy, renal failure, liver dysfunction, local or systemic infection and inflammation.

Anesthesia and Surgery

Anesthesia and surgical management of the patients were performed by the same anesthesiologist and surgical team. Standard anesthesia and surgical techniques were used. The night before surgery, patients were given Alprazolam (0.5mg [p.o]) (Xanax®). Midazolam (Dormicum®) (125 µg/kg i.m.) was administered 30 minutes before the operation. A standard monitoring regimen including invasive arterial pressure, central venous pressure, peripheral oxygen saturation, 5-lead electrocardiogram and end-tidal CO_2 monitoring was applied.

Anesthesia induction was performed with fentanyl (20-30 µg/kg, i.v.) and propofol (2-3 mg/kg, i.v.), and tracheal intubation was with rocuronium (0.6-1.0 mg/kg, i.v.). Anesthesia was maintained with the minimum alveolar concentration (MAC) :1 sevoflurane in air/oxygen, and rocuronium and fentanyl in maintenance doses. The ventilation of the patients was adjusted to maintain normoxia and normocapnia.

Standard extracorporeal circulation (ECC) techniques were used with pump flow 2.0–2.4 L/min/m^2 body surface area and moderate systemic hypothermia (32°C). Cardiac arrest was achieved with intermittent antegrade cold-blood cardioplegia. Homogeneous cooling and reheating were done.

The erythrocyte suspension was transfused so that hemoglobin levels were ≥ 7 g/dL at the pump and ≥ 8 g/dL after reperfusion. To monitor tissue perfusion during surgery, blood gas analysis was performed during ECC, as well as monitoring of systemic blood pressure, venous-arterial carbon dioxide difference, lactate levels and urine flow rate. Freshly frozen plasma and platelet transfusions were used according to laboratory and clinical findings. An isotonic (0.09% NaCl) solution was used to supplement the volume lost through evaporation and urine. After the operation, the patients were transferred to the cardiac surgery intensive care unit.

Sampling and Laser Speckle Contrast Imaging System

Patients' hemodynamics (mean arterial pressure [MAP], heart rate) and blood gas measurements (PO_2 (mmHg), PCO_2 (mmHg) and lactate (mmol/L)) were measured and recorded at 5 time points: T1-Before induction of anesthesia, T2-After induction of anesthesia, T3-10th minute of extracorporeal circulation (ECC), T4-After cross-clamp (CC) and T5-End of surgery. The skin area on the palmar surface of the left 2nd, 3rd and 4th fingers of the patients was used to monitor perfusion changes with LSCI during surgery. A commercially available system (Moor Instruments, Devon, UK) using a class 1 laser diode was used for LSCI measurements. Laser speckle images were acquired using a charged-coupled device (CCD) camera and converted to speckle contrast images by pseudocoloring where perfusion scaled from blue (low perfusion) to red (high perfusion). Finally, the extubation times of the patients in the intensive care unit were recorded.

Statistical Analysis

The normal distribution of all datasets was presented as mean ± SD after evaluation with the Kolmogorov–Smirnov test. Statistical analysis was performed using GraphPad Prism v5.0 (GraphPad Software, La Jolla, CA, USA). A one-way ANOVA-Bonferroni post hoc test was used for comparisons. $P<0.05$ was considered statistically significant. In the experimental setup where the tissue perfusion change was accepted as 60%, the power analysis with 80% power and 0.5 alpha error resulted in n=15 sample numbers.

3. RESULTS

The hemodynamic and blood gas data sets of the patients are shown in Table I. There was no significant difference in heart rate, MAP, or serum lactate levels during the surgery when compared with pre-induction ($P>0.05$). A significant increase was found in blood pO_2 (mmHg) values after induction, the 10th minute of ECC and after CC when compared with pre-induction ($P<0.05$). The blood pCO_2 (mmHg) value was found to be significantly lower than the post-operative value after CC ($P<0.05$).

Table I. *Hemodynamic and blood gas parameters*

	Before Induction	After Induction	ECC 10. min	After CC	End of Surgery
Heart rate (min^{-1})	71 ± 2	68 ± 5	-	72± 5	84± 5
MAP (mmHg)	80 ± 2	67 ± 4	55± 4	70 ± 3	76± 4
pH	7.41 ± 0.01	7.40 ± 0.02	7.42 ± 0.01	7.45 ± 0.01	7.40 ± 0.02
PO_2 (mmHg)	104 ± 19	178 ± 21*	197 ± 9*	193 ± 13*	145 ± 13
PCO_2 (mmHg)	36 ± 1	37± 1	37± 1	32 ± 1+	37 ± 1
Lactate (mmol/L)	1.2 ± 0.1	1.4 ± 0.1	1.2 ± 0.1	1.4 ± 0.2	1.5 ± 0.1

**P<0.05; Before induction, +p<0.05; According to the end of surgery time point. MAP: Mean arterial pressure, ECC: Extracorporeal circulation, CC: Cross-clamping, PO2:Partial oxygen pressure, PCO2: Partial carbon dioxide pressure*

Findings obtained from the LSCI are presented in Figure 1, and the related images are presented in Figure 2. The perfusion values (Perfusion Unit,_PU) of the patients were measured as 301±23 PU before anesthesia induction, 207±19 PU after anesthesia

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induction, 102±10 PU at the 10th minute of ECC, 107±11 PU after CC and 103±9.8 PU after surgery. The skin perfusion levels on the palmar surface of the fingers decreased significantly from the pre-induction measurement and remained low until the end of the operation (P<0.05).

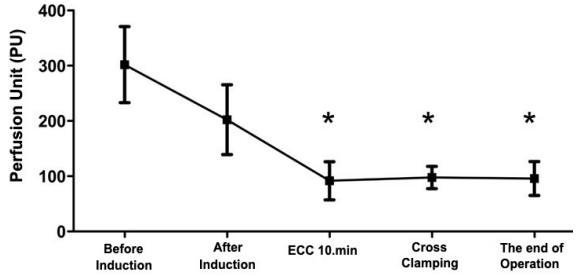

Figure 1. *Change in LSCI perfusion level throughout the surgery*

**P<0,05; Compared to before induction. ECC: Extracorporeal circulation*

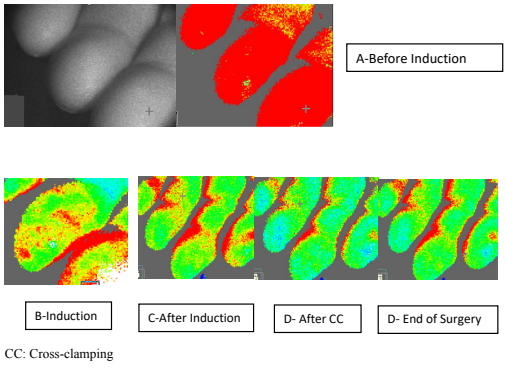

Figure 2. *Laser Speckle images of the change of skin perfusion in the fingers during the surgery*

The relationship between intubation times in the intensive care unit and skin perfusion is shown in Figure 3. It was found that the median perfusion values (98±11 PU) of the patients who were intubated for less than eight hours (388±36 minutes) were higher than the perfusion values (52±4.8 PU) of the patients who were intubated for more than eight hours (634±45 minutes) (P<0.05).

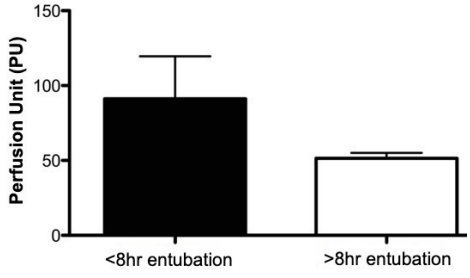

Figure 3. *Postoperative LSCI perfusion levels according to postoperative intubation times*

4. DISCUSSION

The main finding of our study is that hypoperfusion, which cannot be detected by standard hemodynamic monitoring techniques in CABG surgery, can be detected by LSCI. In addition, in our study, it was found that the level of skin perfusion was directly related to the duration of intensive care intubation.

In surgeries where macrocirculation is monitored with standard monitoring techniques, unexpected organ dysfunction may occur in the postoperative period [14]. In adition, improving macrocirculation data does not always improve microcirculation [15]. In cases such as sepsis, it is known that microcirculation is impaired while macrohemodynamic values are not impaired yet. Yin Wu et al., observed liver functions, MAP, heart rate, and liver microcirculation with LSCI in rats with cecal sepsis. They found that perfusion values decreased in LSCI while MAP and heart rate were not impaired in the early (12th hour) period of sepsis [16]. In the same period, they found that the subjects' plasma bilirubin, aspartate transaminase (AST) and alanine transaminase (ALT) levels also increased. However, they also observed signs of sepsis in the histopathological examination of the liver of rats. As a result of the study, they stated that the evaluation of septic hepatic microcirculation with LSCI would provide invaluable information for the early diagnosis and treatment of sepsis.

Depending on the damaged organ, findings such as cognitive dysfunction, urea, creatinine, AST, ALT, troponin-I and pro-brain natriuretic peptide (BNP) elevations, ischemic ECG (electrocardiogram) changes, and hypoxemia due to respiratory failure may occur in the postoperative period. These signs and symptoms may be temporary or have long-term effects. The main cause of organ damage during surgery is the deterioration of the oxygen supply-consumption balance by worsening the microcirculation in the organ. MAP, heart rate, and peripheral tissue oxygen saturation provide limited information on organ microcirculation. De Backer et al. investigated the relationship between macrohemodynamic parameters (MAP, cardiac output) and microcirculatory markers in sepsis. Microcirculation measurements were made in the sublingual region with sidestream darkfield (SDF) technology. As a result of their research, they found a weak correlation between global hemodynamic values and sepsis survival parameters, while they found a high correlation with SDF microcirculation values [17].

Macrohemodynamic monitoring is insufficient for the evaluation of organ perfusion. Therefore, a more reliable method is needed. SvO_2, lactate level monitoring, veno-arterial carbon dioxide differences can be mentioned among the methods showing tissue microcirculation. However, the need for invasive catheterization is its most important limitation [18]. Therefore, there is a need for non-invasive monitoring. It is important in anesthesia management to have information about the microcirculation of organs with noninvasive methods, especially in long-term surgeries. Various techniques have been developed, including fluorescent intravital microscopy,

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Marmara Med J 2023;36(3): 339-343

SDF imaging, orthogonal polarization spectral imaging (OPS), and laser doppler flowmeter (LDF) [7].

As a new technique, LSCI can monitor continuous and real-time tissue perfusion over a larger area. LSCI has been used successfully to assess microcirculation in the skin, gastrointestinal mucosa, and cerebral cortex [19]. Ambrus et al. investigated the relationship between the blood flow in the intra-abdominal organs and the microcirculation in the same organ with LSCI in their study in pigs. They performed a central block with an epidural catheter on the experimental animals. There were similar changes in both the blood flow of the intra-abdominal organs and perfusion values with LSCI [20]. Eriksson et al. measured the microcirculation of the liver with LSCI intraoperatively in liver surgery. They observed that the perfusion unit was zero on the LSCI when the patients' hepatic artery and hepatic vein were fully occluded [21].

In addition to demonstrating macrohemodynamic changes in organs with laser speckle imaging, studies showing similar vascular changes in the skin are available in the literature [22]. The earliest finding in the pathogenesis of cardiovascular diseases is vascular endothelial disruption. Systemic endothelial disruption causes similar changes in the microvascular structure of cutaneous tissue [23]. Therefore, monitoring the microcirculation of the cutaneous tissue can provide information about systemic events. Galliard et al., compared patients with systemic sclerosis with healthy volunteers. They measured postocclusive hyperemia after 5 minutes of ischemia with LSCI. They found that distal digital perfusion was decreased in patients with systemic sclerosis. In this way, they showed that the diagnosis and treatment follow-up of a systemic vascular disease can be made from skin tissue [24]. Kiss et al., performed fulminant sepsis in pigs with E.coli and followed the microvascular changes in the skin with LSCI. While no change was found in the control group, they detected early microvascular deterioration in the skin in pigs with sepsis. Thus, they showed that early detection of systemic vascular changes is possible with non-invasive evaluation [25]. Barcelos et al. measured skin microcirculation with LSCI in patients with subacute and acute endocarditis. It was stated that noninvasive skin circulation monitoring in patients with endocarditis would be beneficial in the follow-up of the disease and in the early diagnosis of complications [22].

In our study, systemic macrohemodynamic parameters were monitored at the beginning of the operation, at the end of the operation and during the ECC in CABG. At the same time, the cutaneous microcirculation was monitored by LSCI. While no significant changes were observed in MAP, heart rate, or blood lactate levels throughout the operation, LSCI perfusion values started to decrease after induction and remained low until the end of the operation (Figure 1). In addition, we evaluated intubation times as a secondary output in our study. Extubations made in the first 8 hours in the intensive care unit after CABG are considered early extubations (fast track). It is known that these patients have a better outcome. It was found that patients who were intubated for more than 8 hours in the ICU had lower perfusion values (Figure 3).

The pressure-volume relationship is lost in long-lasting major surgeries. Therefore, standard monitoring techniques cannot provide information about organ microcirculation. Advanced hemodynamic monitoring is both an invasive method and has certain limitations [26] In addition, when choosing advanced hemodynamic monitoring methods, their advantages and limitations should be well known. It is best to choose the methods that will give us the most accurate information according to the patient and the surgery [27]. LSCI can monitor the cutaneous microcirculation without contacting the patient and can provide valuable information about the systemic microcirculation.

Among the limitations of our study, we can mention that the microvascular reactivity of the measured skin tissue is affected by the ambient temperature [13]. If the operating room temperature is low, microvascular reactivity is reduced [28]. This should be taken into account during measurements.

Conclusion

A sudden decrease in the perfusion of skin tissue in the extracorporeal circulation and a prolonged intubation time associated with this decrease were detected. In addition, despite the decrease in tissue perfusion, no change was observed in other measured macrohemodynamic parameters. This suggests that clinically, skin perfusion measurement may be a potential microcirculation monitoring parameter. However, further studies are needed to evaluate the relationship between skin perfusion, environmental conditions and internal organs.

Compliance with Ethical Standards

Ethical approval: This study was approved by the Acibadem University Ethics Committee (approval number: ATADEK: 2015-15/17) and conducted following the guidelines of the 1964 Helsinki Declaration. Written informed consent was obtained from the patients.

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REFERENCES

[1] Zarbock A, Hollmann MW. Perioperative organ failure: A preventable complication? Anesth Analg 2020;131:1663-5. doi:10.1213/ANE.000.000.0000005244

[2] De Backer D, Orbegozo Cortes D, Donadello K, Vincent JL. Pathophysiology of microcirculatory dysfunction and the pathogenesis of septic shock. Virulence 2014;5:73-9. doi:10.4161/viru.26482

[3] Van Beest P, Wietasch G, Scheeren T, Spronk P, Kuiper M. Clinical review: use of venous oxygen saturations as a goal – a yet unfinished puzzle. Crit Care 2011;15:232. doi:10.1186/cc10351

[4] Vellinga NAR, Boerma EC, Koopmans M, Donati A, Dubin A, Shapiro NI. Mildly elevated lactate levels are associated with microcirculatory flow abnormalities and increased mortality: a microSOAP post hoc analysis. Crit Care 2017;21:255. doi:10.1186/s13054.017.1842-7

[5] Huette P, Beyls C, Mallat J, et al. Central venous-to-arterial CO(2) difference is a poor tool to predict adverse outcomes after cardiac surgery: a retrospective study. Can J Anaesth 2021;68:467-76. doi:10.1007/s12630.020.01881-4

[6] Zhang X, Xuan W, Yin P, Wang L, Wu X, Wu Q. Gastric tonometry guided therapy in critical care patients: a systematic review and meta-analysis. Crit Care 2015;19:22. doi:10.1186/s13054.015.0739-6

[7] Senarathna J, Rege A, Li N, Thakor NV. Laser Speckle Contrast Imaging: theory, instrumentation and applications. IEEE Rev Biomed Eng 2013;6:99-110. doi:10.1109/RBME.2013.224.3140

[8] Zheng C, Lau LW, Cha J. Dual-display laparoscopic laser speckle contrast imaging for real-time surgical assistance. Biomed Opt Express 2018;9:5962-81. doi:10.1364/BOE.9.005962

[9] Dubin A, Henriquez E, Hernandez G. Monitoring peripheral perfusion and microcirculation. Curr Opin Crit Care 2018;24:173-80. doi:10.1097/MCC.000.000.0000000495

[10] Neubauer-Geryk J, Hoffmann M, Wielicka M, et al. Current methods for the assessment of skin microcirculation: Part 1. Postepy Dermatol Alergol 2019;36:247-54. doi:10.5114/ada.2019.83656

[11] Neubauer-Geryk J, Hoffmann M, Wielicka M, Piec K, Kozera G, Bieniaszewski L. Current methods for the assessment of skin microcirculation: Part 2. Postepy Dermatol Alergol 2019;36:377-81. doi:10.5114/ada.2019.83657

[12] Holowatz LA, Thompson-Torgerson CS, Kenney WL. The human cutaneous circulation as a model of generalized microvascular function. J Appl Physiol (1985) 2008;105:370-2. doi:10.1152/japplphysiol.00858.2007

[13] RG IJ, de Jongh RT, Beijk MA, et al. Individuals at increased coronary heart disease risk are characterized by an impaired microvascular function in skin. Eur J Clin Invest 2003;33:536-42. doi:10.1046/j.1365-2362.2003.01179.x

[14] Vincent JL, Rhodes A, Perel A, et al. Clinical review: Update on hemodynamic monitoring—a consensus of 16. Crit Care 2011;15:229. doi:10.1186/cc10291

[15] Dyson A, Cone S, Singer M, Ackland GL. Microvascular and macrovascular flow are uncoupled in early polymicrobial sepsis. Br J Anaesth 2012;108:973-8. doi:10.1093/bja/aes093

[16] Wu Y, Ren J, Zhou B, et al. Laser speckle contrast imaging for measurement of hepatic microcirculation during the sepsis: a novel tool for early detection of microcirculation dysfunction. Microvasc Res 2015;97:137-46. doi:10.1016/j.mvr.2014.10.006

[17] De Backer D, Donadello K, Sakr Y, et al. Microcirculatory alterations in patients with severe sepsis: impact of time of assessment and relationship with outcome. Crit Care Med 2013;41:791-9. doi:10.1097/CCM.0b013e3182742e8b

[18] Huber W, Zanner R, Schneider G, Schmid R, Lahmer T. Assessment of regional perfusion and organ function: Less and non-invasive techniques. Front Med (Lausanne) 2019;6:50. doi:10.3389/fmed.2019.00050

[19] Briers D, Duncan DD, Hirst E, et al. Laser speckle contrast imaging: theoretical and practical limitations. J Biomed Opt 2013;18:066018. doi:10.1117/1.JBO.18.6.066018

[20] Ambrus R, Strandby RB, Svendsen LB, Achiam MP, Steffensen JF, Sondergaard Svendsen MB. Laser speckle contrast imaging for monitoring changes in microvascular blood flow. Eur Surg Res 2016;56:87-96. doi:10.1159/000442790

[21] Eriksson S, Nilsson J, Lindell G, Sturesson C. Laser speckle contrast imaging for intraoperative assessment of liver microcirculation: a clinical pilot study. Med Devices (Auckl) 2014;7:257-61. doi:10.2147/MDER.S63393

[22] Barcelos A, Lamas C, Tibirica E. Evaluation of microvascular endothelial function in patients with infective endocarditis using laser speckle contrast imaging and skin video-capillaroscopy: research proposal of a case control prospective study. BMC Res Notes 2017;10:342. doi:10.1186/s13104.017.2660-3

[23] Feuer DS, Handberg EM, Mehrad B, et al. Microvascular Dysfunction as a Systemic Disease: A Review of the Evidence. Am J Med 2022;135:1059-68. doi:10.1016/j.amjmed.2022.04.006

[24] Gaillard-Bigot F, Roustit M, Blaise S, et al. Abnormal amplitude and kinetics of digital postocclusive reactive hyperemia in systemic sclerosis. Microvasc Res 2014;94:90-5. doi:10.1016/j.mvr.2014.05.007

[25] Kiss F, Molnar L, Hajdu E, et al. Skin microcirculatory changes reflect early the circulatory deterioration in a fulminant sepsis model in the pig. Acta Cir Bras 2015;30:470-7. doi:10.1590/S0102.865.0201500.700.00004

[26] Marik PE, Baram M, Vahid B. Does central venous pressure predict fluid responsiveness? A systematic review of the literature and the tale of seven mares. Chest 2008;134:172-8. doi:10.1378/chest.07-2331

[27] Vincent JL, Pelosi P, Pearse R, et al. Perioperative cardiovascular monitoring of high risk patients: a consensus of 12. Crit Care 2015; 19:224. doi: 10.1186/s13054.015.0932-7

[28] Margouta A, Anyfanti P, Lazaridis A, et al. Blunted microvascular reactivity in psoriasis patients in the absence of cardiovascular disease, as assessed by laser speckle contrast imaging. Life (Basel) 2022;12:1796. doi:10.3390/life12111796