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From bench to bedside: A review of the application and potential of microcirculatory assessment by hand-held videomicroscopy

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ABSTRACT

In clinical practice, there is vast knowledge regarding the evaluation of macrocirculatory parameters, such as systemic blood pressure and cardiac output, for the hemodynamic monitoring of patients. However, assessment of the microcirculation has not yet been incorporated into the bedside armamentarium. Hand-held intravital video microscopy enables the direct, noninvasive, evaluation of the sublingual microcirculation at the bedside, offering insights into the status of the systemic microcirculation. It is easily performed and may be employed in several clinical settings, providing immediate results that may help guide patient management. Therefore, the incorporation of hand-held intravital video microscopy into clinical practice may lead to tremendous improvements in the quality of care of critical, unstable patients or offer new data in the evaluation of patients with chronic diseases, especially those with microcirculatory involvement, such as occurs in diabetes.

1. Introduction

The microcirculation comprises the network of small blood vessels, including arterioles, capillaries, and venules, that are responsible for the exchange of nutrients and waste products between the blood and the surrounding tissues and play a crucial role in maintaining tissue health and organ function [1]. Consequently, the microcirculatory system is an essential component of the circulatory system. Arterioles are small arteries that branch out into numerous capillaries, which are tiny, thin-walled vessels where the actual exchange of substances occurs (Fig. 1).

Disruptions in microcirculatory function can contribute to various health conditions, mostly in the early phase of critical illness, including sepsis, ischemic diseases and heart failure. Moreover, microcirculatory dysfunction is an independent risk factor for a higher mortality rate [2–5]. Thus, studying the microcirculation is of paramount importance for understanding the mechanisms underlying these conditions and developing appropriate therapeutic interventions.

Relatively recent microcirculatory imaging techniques, such as orthogonal polarization spectral imaging and sidestream dark-field (SDF) imaging, have allowed direct observation of the microcirculation at the bedside [6,7]. Additionally, hand-held vital microscopes (HVMs) allow clinicians to directly assess the behavior of the microcirculation in the face of different physiologic or pathologic stimuli or under various pathologic conditions [8,9]. Recently, a third generation of HVMs based on incident dark field illumination (IDF) has been developed [10] and introduced for clinical use [11]. Some reports have demonstrated that, compared to the SDF video microscope, the IDF video microscope, using technical and ergonomic improvements, provides better-quality image acquisition of the human sublingual microcirculation [12,13].

HVMs have several advantages, such as direct noninvasive real-time point-of-care visualization of the microcirculatory network, with the sublingual microcirculation being the most frequently studied microcirculation at the bedside [8]. The CytoCam-IDF, for instance, consists of a portable device, described as a pen-shaped probe, that incorporates a dark-field incident light illumination system with a series of high-resolution lenses that project images to a dedicated computer system (Fig. 2). The probe is covered by sterilized plastic tips [11].

Here, we describe some clinical and surgical applications and potential benefits of hand-held intravital microscopy for microcirculatory assessment.

2. Clinical applications

2.1. Intensive care monitoring

Hemodynamic monitoring, which frequently guides treatment in the intensive care setting, has traditionally focused on blood pressure and

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cardiac output; however, these measurements imperfectly reflect tissue perfusion. Transforming microcirculation monitoring from an important research tool into an essential bedside monitoring technique used by clinicians to individualize hemodynamic resuscitation based on microvascular parameters is an important goal in this scenario.

In patients with shock of various origins, several studies have consistently demonstrated that persistent microcirculatory changes are associated with organ dysfunction and mortality [2,8,14]. In this context, the goal of hemodynamic resuscitation is to meet the oxygen demands and metabolic needs of the various organs, which can only occur through optimization of the microcirculation. Even though optimization of macrohemodynamic variables such as blood pressure and stroke volume may occur, it may remain unclear whether the microcirculatory environment is also optimized [15]. Ideally, there should be "hemodynamic coherence" between the macrocirculation and the microcirculation; however, corrections of macrocirculatory parameters may fail to improve tissue perfusion in the presence of microcirculatory derangements, such as changes in blood viscosity. The loss of coherence between the macrocirculation and the microcirculation is predictive of organ failure and unfavorable outcomes in a more sensitive and specific manner than systemic hemodynamic and biological parameters [16–18]. Heterogeneity of microcirculatory flow, with the presence of occluded capillaries next to perfused capillaries, inducing microcirculatory shunting responsible for the decreased oxygen extraction capacity, has been demonstrated in COVID-19, for instance [19].

Another risk is to "overcorrect" the macrocirculation in relation to the needs of the microcirculation and to end up with fluid overload or overuse of vasopressors, which may be harmful for tissue oxygenation. Microcirculatory evaluation may help to assess the response to fluid administration and guide fluid titration. In the study by Ospina et al. [20], fluid administration increased microvascular perfusion through a combined increase in the proportion of perfused small vessels and in small-vessel density in the early but not in the late phase of severe sepsis (i.e., within 24 h after the diagnosis vs. $>$ 48 h after the diagnosis). Of note, these microvascular effects of the fluids were not related to changes in the cardiac index or mean arterial pressure [20]. Pranskunas et al. [21] found that, in response to IV fluid administration, a significant increase in microvascular blood flow and a reduction in the clinical signs of impaired organ perfusion occurred only in patients with a microvascular flow index (MFI) $<$ 2.6 at baseline (which represented 2/3 of the hemodynamically unstable, intensive care unit patients who comprised their study population). This response was also independent of a change in stroke volume. These results indicate that the noninvasive assessment of microvascular perfusion may help to identify patients with a potential need for fluid therapy, as well as to evaluate its effect.

In summary, with the current methods clinicians are unaware of what is happening in the microcirculation, which prevents individualized resuscitation with a microcirculatory target.

3. Anesthesia and surgery monitoring

3.1. Cardiac surgery

Another field for application of the technique is anesthesia and surgical monitoring. In cardiac surgery, for instance, systemic microcirculatory changes are frequently associated with reduced organ perfusion and vital organ dysfunction due to the combination of different factors, such as the surgery itself, the anesthesia protocol, hypothermia, and cardiopulmonary bypass (CPB) [22]. De Backer et al., using an orthogonal polarization spectral imaging technique to evaluate the sublingual microcirculation, reported that systemic microcirculatory alterations are observed in patients undergoing cardiac surgery whether CPB is used or not [22]. The degree of organ dysfunction is associated with the length of intensive care unit stay and mortality [23]. CPB induces an inflammatory reaction, and the release of inflammatory mediators may exert deleterious effects on the microcirculation, similar to severe sepsis [22,24], resulting in the uncoupling of macrocirculatory and microcirculatory hemodynamics [5]. According to a recent systematic review, CPB-induced microcirculatory perfusion disturbances are represented by a decrease in functional capillary density, perfused vessel density, or the proportion of perfused vessels [24]. In view of this evidence, the potential and challenges that face the implementation of hand-held microscopy in everyday clinical practice have been noted [25].

CytoCam-IDF monitoring of the sublingual microcirculation during coronary artery bypass grafting surgery demonstrated that the use of blood cardioplegia ameliorates CPB-induced microcirculatory alterations better than crystalloid cardioplegia, which may reflect attenuation of the systemic inflammatory response [26]. Another study using CytoCam-IDF in the sublingual microcirculation showed that early decreases in perfused vessel density associated with increases in microcirculatory heterogeneity are associated with an increased intensity and duration of lactic acidosis after cardiac surgery [27].

Interestingly, a study revealed that changes in the CPB pump flow rate within 20 % (80 %-100 %) of its theoretical value do not alter the sublingual microcirculation using SDF imaging [28]. The authors concluded that during perioperative adjustments of the CPB pump rate, blood flow autoregulation mechanisms are activated so that limited changes in the pump flow can be considered safe not only at the sublingual site but also for the entire microcirculation [28]. Similar results were obtained by Elbers et al. [29] using SDF imaging of the sublingual microcirculation, which showed that pulsatile perfusion during CPB does not alter human microvascular perfusion using standard equipment in routine cardiac surgery.

Regarding blood cell transfusions in patients undergoing cardiac surgery, the increase in systemic hemoglobin concentration and hematocrit is accompanied by increased microcirculatory density, as shown using sublingual SDF imaging [30]. Along with the microcirculatory measurements, spectrophotometry showed that the microcirculatory hemoglobin content and oxygen saturation increased significantly, suggesting that blood transfusion improves the systemic microcirculation and oxygen-carrying capacity [30].

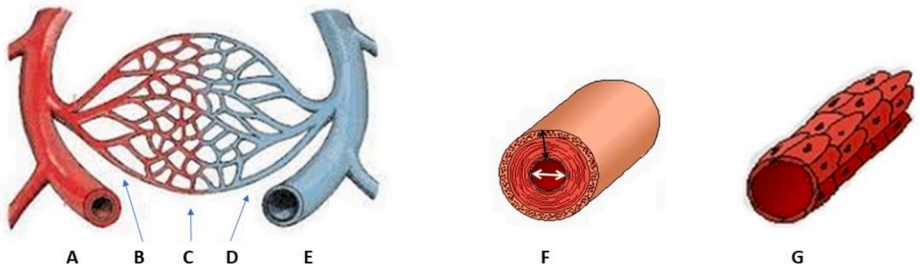

Fig. 1. Elements of the microcirculation. A: artery; B: arteriole; C: capillary network; D: venule; E: vein; F: schematic representation of a muscular artery, with its layers (adventitia, media, intima); G: schematic representation of a capillary vessel, with its monolayer of endothelial cells.

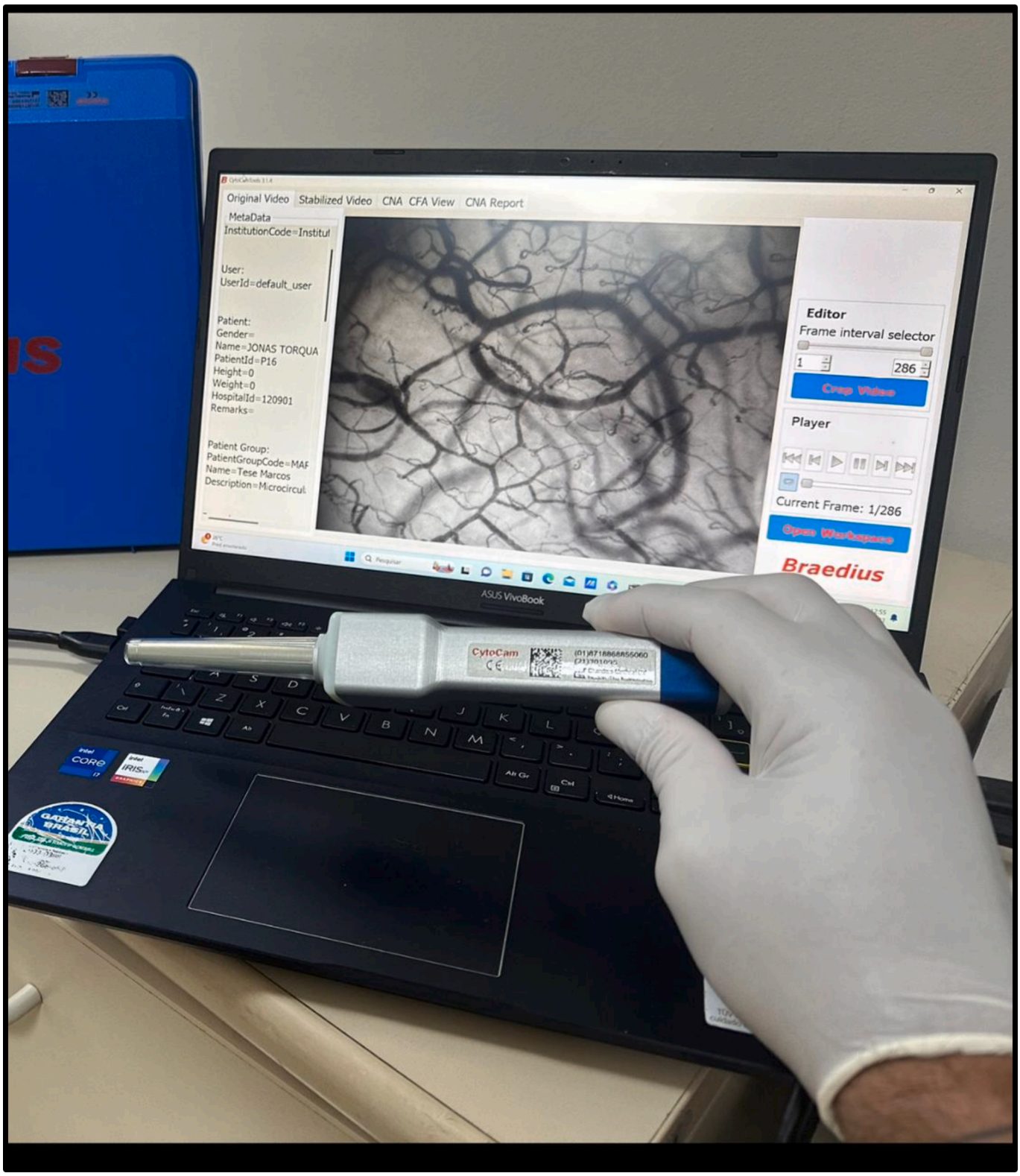

Fig. 2. The CytoCam-IDF handheld video microscope used for the visualization of microcirculatory parameters in our department, based on incident dark field technology (IDF). The CytoCam is a pen-like device and is held as such. The low weight of the device (120 g) minimizes pressure artifact problems that were present in the earlier heavy devices. The camera is connected to a device controller based on a medical grade computer or a suitable portable device such as laptop or tablet, which is used for image storage (from https://braedius-medical.com/products/).

Considering the effects of vasopressors on the microcirculation, a subject that arises from considerable academic debate, it was shown that during CPB with constant flow, increasing the systemic perfusion pressure using the selective α_1-adrenoreceptor agonist phenylephrine resulted in a decrease in sublingual small-vessel microcirculatory blood flow (observed by SDF imaging) [31]. This phenomenon could be explained by the occurrence of arteriovenous blood "short-circuiting" during phenylephrine infusion [31].

We have evaluated endothelium-dependent microvascular reactivity during CPB in surgery for the correction of cyanotic and acyanotic congenital heart disease (CHD) in children and infants using laser Doppler perfusion monitoring [32]. The microvascular reactivity was significantly blunted during CPB when compared with the values obtained after the induction of anesthesia, both in acyanotic and cyanotic patients. Nonetheless, the microvascular reactivity virtually normalized after the discontinuation of CPB [32]. This impairment of microvascular function appeared to be related to a reduced systemic bioavailability of nitric oxide, resulting from the inflammatory and pro-oxidative response typical of this surgical procedure [33]. Similar results were reported by Cortés et al. [34], who showed that children with congenital heart disease displayed decreased vascular density and microvascular blood flow and increased microvascular heterogeneity during CPB. All these parameters returned to baseline values after surgery [34]. Using hand-held intravital videomicroscopy, Erdem et al [35] observed that children with CHD undergoing cardiac surgery with CPB, compared to children undergoing elective, non-cardiac surgery, had less perfused vessels, lower perfusion quality, and higher small vessel densities preoperatively, while after cardiac surgery, perfused vessel densities and perfusion quality of small vessels declined, while red blood cell velocity increased. The study therefore demonstrated that the sublingual microcirculation of children with CHD was substantially different from that of children without CHD, and that CPB promoted new and additional microcirculatory disturbances.

Mohamed et al. [36] reported a randomized controlled clinical trial designed to test the hypothesis that dexmedetomidine, a selective α2-adrenoreceptor agonist that causes a central reduction in sympathetic nervous system activity and attenuation of the systemic inflammatory response [37–39], could reduce sublingual microcirculatory alterations generated by CPB in patients undergoing on-pump coronary artery bypass graft surgery (CABG). They used side-stream dark field imaging, during which the camera placed on organ surfaces provides sharp images of the red blood cells and leukocytes flowing through the microcirculation [40]. This study demonstrated that, compared to placebo treatment, dexmedetomidine infusion improved the sublingual microcirculation indices in patients undergoing on-pump CABG surgery [36].

Another study compared the effects of different inhalation anesthetic agents, including sevoflurane, isoflurane and desflurane, on sublingual microcirculatory density during coronary artery bypass grafting surgery using orthogonal polarization spectral imaging [41]. The study showed that these three inhalation agents affected the microcirculation to different degrees: sevoflurane had a negative effect on the microcirculation, isoflurane decreased the vascular density but increased flow, whereas desflurane had stable effects on the microcirculation [41].

In conclusion, given the critical role of the microcirculation in tissue perfusion, the early detection and prompt reversion of tissue hypoperfusion during CPB resulting from microvascular alterations appear to be crucial factors in reducing organ dysfunction after cardiac surgery. Moreover, real-time point-of-care imaging might be a valuable tool to monitor alterations in microcirculatory perfusion in patients undergoing cardiac surgery with CPB and guide interventions in the perioperative period [24].

3.2. Miscellaneous surgery types

Regarding other types of surgery, monitoring of the sublingual microcirculation using IDF imaging in patients submitted to major liver resection showed that the rolling behavior of the microcirculatory leukocytes allows for early identification of patients at risk of increased inflammatory response following liver surgery [42].

Interestingly, in women with epithelial ovarian cancer, a study using visualization of the microcirculation using IDF imaging during surgery showed that there is a reduction in the perfusion of the microvasculature in peritoneal metastases, which may limit the efficacy of chemotherapy and affect the behavior of metastases on the peritoneum [43].

3.3. Extracorporeal membrane oxygenation

Extracorporeal membrane oxygenation (ECMO) is another condition in which real-time evaluation of the microcirculation may be useful. The primary purpose of ECMO, or mechanical circulatory support, is performed by replacing the function of the heart and lungs, which gives these organs considerable time to recover and provides clinicians time to treat underlying pathophysiological conditions [25,44]. However, the machine-blood interaction that occurs during the use of these techniques activates proinflammatory and procoagulant pathways, which can further impair the microcirculation in patients previously hemodynamically unstable [45–47].

Nevertheless, some studies assessing different sublingual microcirculatory parameters during veno-arterial ECMO (VA-ECMO) showed that the evaluation of microcirculation at initiation of VA-ECMO can be used to predict intensive care unit mortality in patients with cardiogenic shock [46,48,49]. In fact, altered baseline perfused sublingual microcirculatory vessel density was found to be related to intensive care unit survival in cardiogenic shock patients treated with VA-ECMO [48)]. In another study, sublingual microcirculatory parameters, including small vessel density and the proportion of perfused vessels, appeared to be lower in the 28-day nonsurvivors than in the survivors, even if macrovascular parameters such as the mean arterial pressure, inotropic score, and lactate level did not differ significantly between the 28-day nonsurvivors and survivors [49]. This was confirmed in the study of Chommelou et al. [46], which showed that the microcirculatory parameters of perfused small-vessel density, small-vessel density, and percent perfused vessels were consistently higher for patients successfully weaned off extracorporeal membrane oxygenation. Interestingly, failure to rapidly restore the microcirculation, despite normal macrocirculatory hemodynamics, was associated with death on ECMO [46].

3.4. Cardiovascular disorders and chronic conditions

Wadowski et al [50] evaluated patients with acute cerebrovascular events (acute stroke, either ischemic, ischemic with hemorrhagic transformation or hemorrhagic, and transitory ischemic attacks) within 24 h after hospital admission and compared them to an age- and sex-matched control group. The investigators observed that functional and perfused total capillary density were reduced and in patients with ischemic strokes when compared to healthy controls, suggesting that cerebrovascular events are associated with altered systemic microvascular perfusion.

Regarding chronic diseases, Li et al. [51] used SDF for the evaluation of sublingual microcirculation as an early noninvasive screening technique for diabetic nephropathy. In their study, diabetic patients had impaired microcirculatory parameters when compared to controls, and the reductions in total vessel density (TVD) and perfused vessel density (PVD) were more severe in patients with diabetes presenting with microvascular complications. Sublingual microcirculatory impairment was accompanied by a higher urinary albumin/creatinine ratio, and the authors suggested that TVD and PVD might be used as indicators for screening for diabetic nephropathy [51]. In a large study of individuals with obesity, the Netherlands Epidemiology of Obesity study, van der Velden et al [52] employed hand-held videmicroscopy to assess the sublingual microcirculation, and the Framingham Risk Score was used to calculate 10-year cardiovascular risk, divided into low-, intermediate-

, and high-risk groups. The latter had a reduction of the smallest perfused capillaries and also increased red blood cell velocity.

In patients with congestive heart failure assessed with hand-held videmicroscopy, median functional and total perfused capillary densities were 30 % and 45 % lower than in healthy controls, indicating a systemic microcirculatory reduction in this condition [53]. Patients with pulmonary artery hypertension have also shown a lower sublingual microvasculature flow index than healthy control individuals [54].

Currently, there are less studies on the use of hand-held videmicroscopy outside the scenarios of surgery, anesthesia or intensive care. Further investigations are necessary to define whether sublingual microcirculatory evaluation can provide information on disease prognosis and/or response to therapy in chronic conditions. Nonetheless, as described for acute diseases and in the intensive care or surgical settings, there is also tremendous potential for this technique to be used as an alternative assessment in chronic diseases to understand the status of the microcirculation after long-term pathophysiologic insults.

3.5. Miscellaneous conditions

Finally, there are other scenarios in which the use of HVMs has been assessed. In early-onset preeclampsia, glycocalyx degradation and reduced microvascular perfusion evaluated with SDF microscopy were found to be associated with endothelial dysfunction and vascular injury [55]. Schmitz et al. [56] employed SDF to investigate whether high-intensity interval training had microcirculatory effects. Increased high-intensity sprinting speed was associated with an increased number of perfused vessels, possibly representing vasculoprotective effects of exercise.

4. Conclusions

The bedside analysis of the microcirculation may provide a unique understanding of microvascular damage in several conditions, superior to laboratory or macrovascular monitoring. Nevertheless, to be accepted as routine care, such evaluations must demonstrate an impact on the prevention and treatment of organ dysfunction. There is a growing number of studies in this field, mostly in acute settings, intensive care, and surgery/anesthesia, which have provided insights into its usefulness. Further investigations in other scenarios, especially in chronic diseases with microcirculatory involvement, are urgently needed to expand the possible indications for the use of bedside microcirculatory evaluation. This type of monitoring may provide clinicians with a clearer understanding of patientś physiology and better tailoring of treatment.

Ethical approval and consent to participate.

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Consent for publication

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CRediT authorship contribution statement

Andrea De Lorenzo: Writing – review & editing, Writing – original draft, Funding acquisition, Conceptualization. **Marcos Fernandes:** Writing – original draft, Visualization, Investigation. **Eduardo Tibirica:** Writing – review & editing, Writing – original draft, Supervision, Investigation, Funding acquisition.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: [Andrea De Lorenzo reports financial support was provided by Carlos Chagas Filho Foundation for Research Support of Rio de Janeiro State. Andrea De Lorenzo reports a relationship with Carlos Chagas Filho Foundation for Research Support of Rio de Janeiro State that includes: funding grants. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper].

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