Developing a hands-free video microscope concept for monitoring skin microcirculation in ICU patients

Master Graduation Report by
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Braedius Medical

Developing a hands-free video microscope concept for monitoring skin microcirculation in ICU patients

Graduation report

Master thesis

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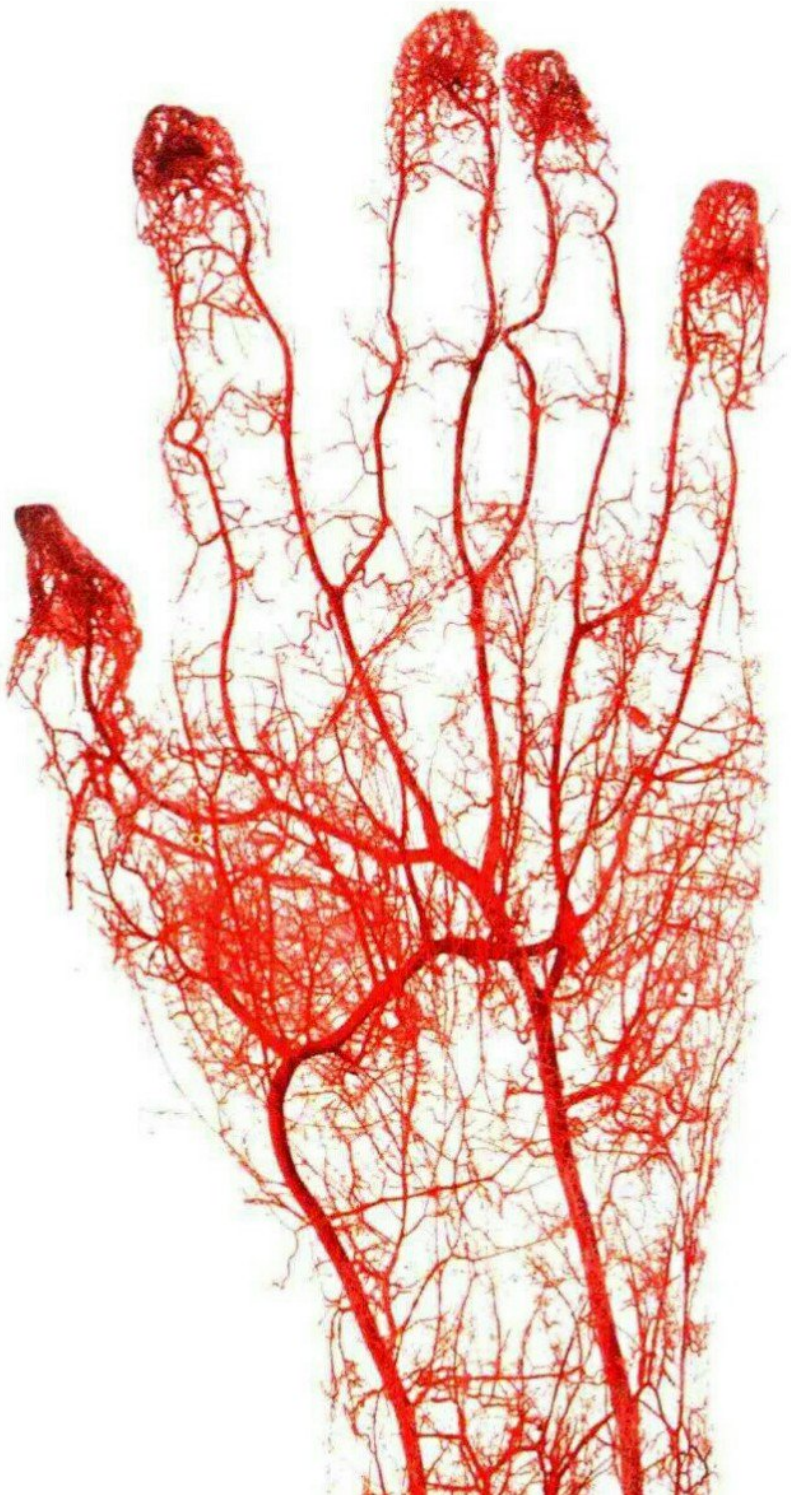

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Executive summary

This thesis describes the development of a bedside system concept for monitoring the microcirculation of intensive care patients.

Microcirculation refers to the smallest blood vessels in the body, including capillaries, arterioles, and venules. These tiny blood vessels facilitate the exchange of oxygen, nutrients, and waste products between the blood and the surrounding tissues. Microcirculation is critical for maintaining the health of tissues and organs, and any disruption in this process can lead to a variety of health problems.

In the past decades, new techniques have been developed to visualise and study the microcirculation. One of these techniques is the hand-held vital microscope. It is a portable video microscope that can visualise superficial microcirculation, such as in the mouth. These hand-held vital microscopes have been used for research purposes, but due to limitations, these devices are not suitable yet for routine clinical applications.

Braedius Medical, a manufacturer of hand-held vital microscopes has commissioned this project to use their technology to develop a new device implementation. The goal is to solve the limitations of these hand-held microscopes with the intent of creating a sustainable competitive edge and long-term profitability.

The research consisted of a discovery phase to get a better understanding of the project context such as the physiology of microcirculation and the technology landscape.

This was followed by an analysis phase to get in-depth insights such as user pains and needs and the strengths and weaknesses of the company.

These insights were used to develop the concept vision: a hands-free automated monitoring system for the ICU that uses camera probes placed on the patient's skin for video acquisition. Finally, a roadmap was made to visualise the strategic planning of all the key steps that need to be made in order to achieve this concept vision.

Content

1 Introduction

1.1 Background

This graduation project was executed in collaboration with Braedius Medical BV, a small company that develops video microscope systems to observe and analyse the microcirculation of humans.

This system consists of three main components: 1) a compact hand-held video microscope called the CytoCam, 2) software to operate the CytoCam and to analyse the videos, 3) a (Windows) computer that runs the software and powers the CytoCam. In Figure 1 this system can be seen in use. Due to technical limitations, only superficial microcirculatory beds can be visualised such as in mucosal tissue. Sublingual (under the tongue) observation is the most common way to access the mucosal microcirculation as it can be done non-invasively.

The CytoCam system is developed for clinical context but is currently only used for research purposes. Although interest has been shown to use the CytoCam system for other applications, barriers have prevented it from a wider reach.

Figure 1: A researcher using the CytoCam Model 1 on a patient. From: Fiona Pring[1].

1.2 Problem statement

The mission of Braedius Medical is to develop solutions for the visualization and assessment of microcirculation to support physicians in their decision processes and to provide new tools to guide therapy. As the company sees the importance and potential of microcirculation, it has ambitions to grow and to make microcirculatory data more accessible for clinical practice. Braedius continuously puts efforts into improving its camera and software solutions, but it is not where it wants to be yet. As a small company, it is facing several challenges which are stated below:

- For several years the sales numbers have been stagnant.
- To stay competitive and to improve its products, Braedius spends most of its resources on research and development. This means there is little money left to invest in the company's growth.
- The CytoCam system has technical limitations, which prevent it from being used for direct clinical applications. Although research on microcirculation is important, it is a very niche market and the targeted users don't always have the funds to purchase the CytoCam system.

1.3 Assignment

The goal of this project is to develop a new product strategy and concept for a suitable need in the medical industry. The outcome should make sense in regard to clinical impact and business.

Research questions have been defined to help guide the process of what to find out.

Main research question:

How can Braedius Medical improve its business by developing a new product system?

The following subquestions help answer the main question:

- What are the current limitations of the CytoCam as a product and in terms of market potential?
- Which unmet needs can Braedius' technology help solve?
- What is Braedius good at and what can they do better?
- What is the most attractive market for Braedius to operate in? Three potential markets have already been defined by the company:
  - The intensive care unit
  - Hyperbaric oxygen therapy clinics
  - Varicose veins treatment centres
- What are the business, user and product requirements?

1.4 Project scope

This project will cover the initial phases of the medical device development trajectory. The main activity is to research market needs and find a problem-solution fit that is the most strategic for the company. Low-level product design practices such as detailing and design for manufacture are not part of the scope. Since the medical device industry is regulated, it also requires a lot of documentation and risk analysis. These will be kept in mind or partially covered, but are also not part of the scope. The outcome of this project will be a concept design that forms the basis of the following phases of the product development process. Figure 2 gives an overview of the project scope.

Deliverables

This project commits to deliver the following items:

- Product system concept
  To embody the new product strategy and vision.
- Strategic Roadmap
  To determine how to realise the strategy and future vision.
- Visual prototype
  To use as a communication tool with lead users.
- Short slide deck
  For onboarding new stakeholders by explaining the values of the new concept.

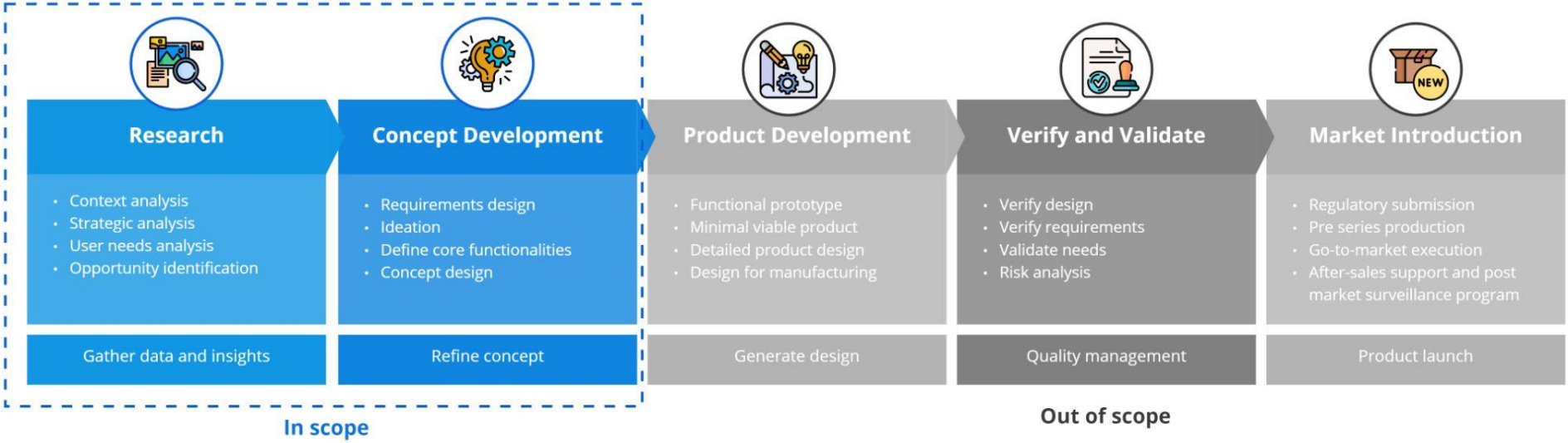


Figure 2: *Project scope*

1.5 Project approach

The project was structured in three phases:

1. **The Discovery phase:** To carry out the project effectively, a deep understanding of the contextual subjects was made. The knowledge gained from this phase acted as the fundaments to understand the problem space and also allowed for more effective communication with the users and experts in later phases.

2. **The analysis phase:** In this phase, user needs and pains, business inefficiencies, product limitations and market attractiveness were analysed in detail to find new opportunities. The most attractive market was chosen and the new user context of this market was also analysed.

3. **The conceptualisation phase:** All the data and insights from the previous phases were synthesised in this phase. A requirement design file was made which acted as the backbone for the concept design. Finally, a strategic roadmap was developed to visualise the time pacing of the various steps and milestones.

A visual representation of the project structure can be seen in Figure 3.

The three lenses of innovation by design agency IDEO was used to guide decision-making throughout the project. This project aims to develop successful innovation by questioning whether the design choices were desired, feasible and viable.

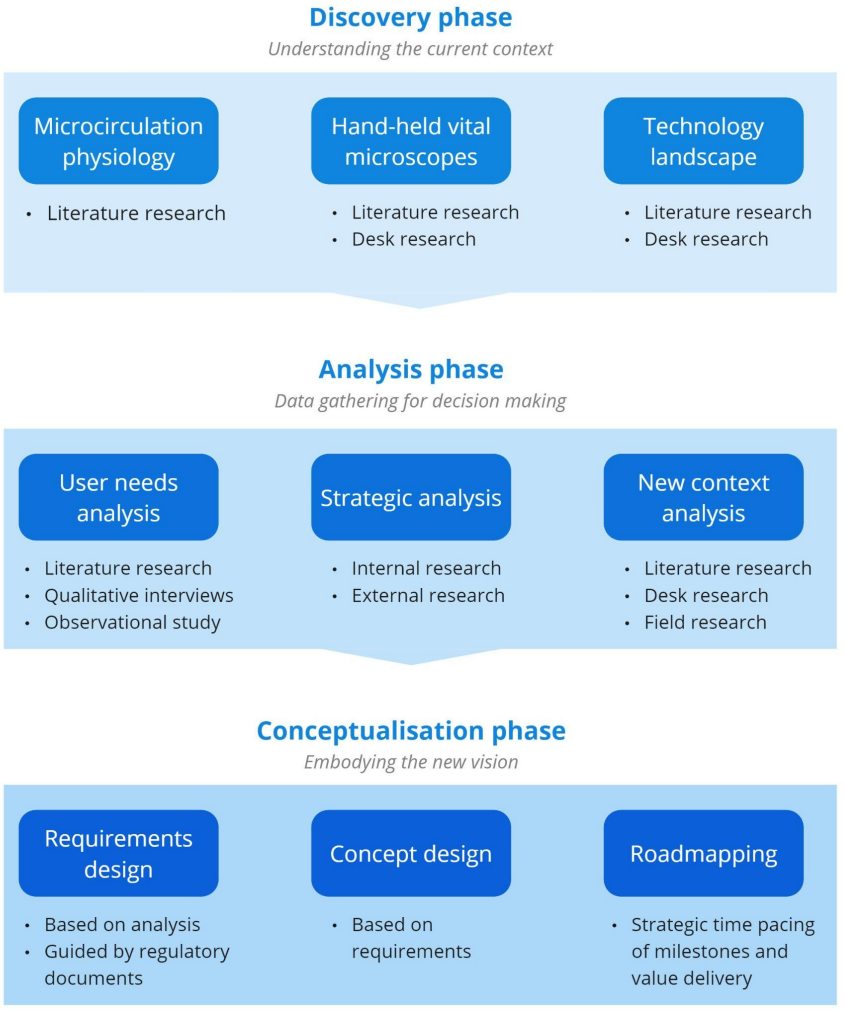


Figure 3: *Project structure.*

1.6 Reading guide

Figure sources

The figures in this report are marked into three types of images:

- Directly taken from a source. This is signified by "*Figure:*".
- Adapted from a source, but redrawn. This is signified by "***Figure**:*".
- Novel insights or a collection of various data that was not presented together in that way. This is signified by "***Figure**:*"

Examples:

Figure X: This image was taken from another source. From: [source].

***Figure X:** This image was redrawn or modified to better fit the content. Adapted from: [source].*

***Figure X:** This image contains novel and original content.*

Conclusion Boxes

After each section a blue box will signify a short summary of the main insights. The content of this blue box will be used for the final results.

Conclusion: ...

2 Discovery phase

2.1 Microcirculation physiology

Google Scholar, PubMed and ScienceDirect were used as search engines to find articles between 2000 and 2022 with keywords such as “microcirculation physiology”, “microcirculation functionalities”, “microcirculation clinical practice” and “microcirculatory alterations”.

As the main objective of the CytoCam camera is to observe and analyse the microcirculation in humans, it is important to understand what microcirculation is and how it is relevant in the medical context. A literature study was done to acquire a deeper understanding of this subject.

The circulatory system consists of the heart, the macrovasculature and the microvasculature[4]. Its purpose is to transport oxygen, nutrients, and hormones to cells and to remove waste products like carbon dioxide[5]. Blood flows away from the heart through arteries and returns to the heart through veins[5]. The arteries and veins are larger vessels and are considered to be part of the macrocirculatory system. It is characterized by relatively high pressures and a fast blood flow[6]. Typical cardiovascular screening methods such as measuring blood pressure and cardiac output involve the macrocirculation[7]. Its purpose is to supply and withdraw blood and molecules from the microvasculature[6]. Figure 4 gives a systemic overview of the circulatory system containing the macrocirculation and microcirculation.

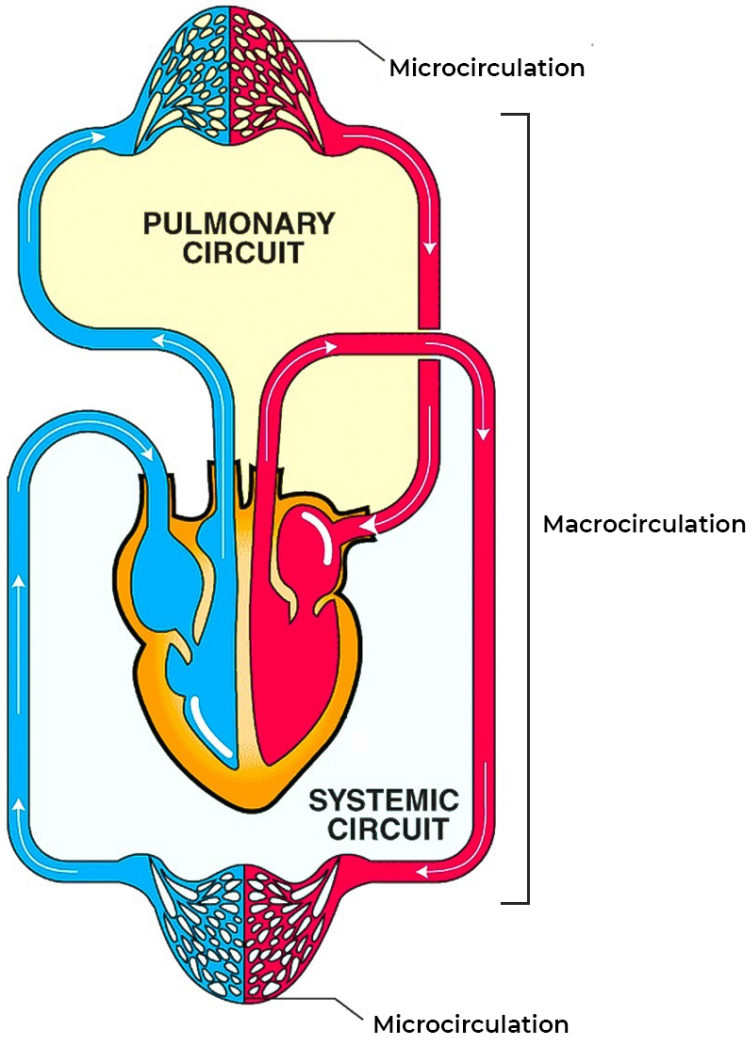


Figure 4: *A simplified overview of the human circulatory system. The bigger vessels represent macrocirculation and the smallest vessels microcirculation. Adapted from BYJU’s[2].*

The microcirculation

The microcirculation concerns the smallest blood vessels in the circulatory system[7, 8] and is responsible for tissue wellness[9]. It connects the arterial system (arteries) with the venous system (veins) and unlike the macrovasculature, it is present within organ tissue[7, 10]. Its primary function is to transport oxygen and nutrients to the surrounding cells and to maintain the function of the organs. Additionally, carbon dioxide and proton removal, transport of hormones, nutrients, drugs and immune response, among other functions, occurs at a microcirculatory level[7].

The vessels on the arterial side of the microcirculation are called the arterioles (<100 µm diameter). To match local metabolic needs, sphincters of the arterioles modulate local arteriolar tone in response to extrinsic and intrinsic stimuli[11]. The oxygenated blood flows from arterioles into the capillaries (<10 µm diameter). An overview of the different vessel types is shown in Figure 5.

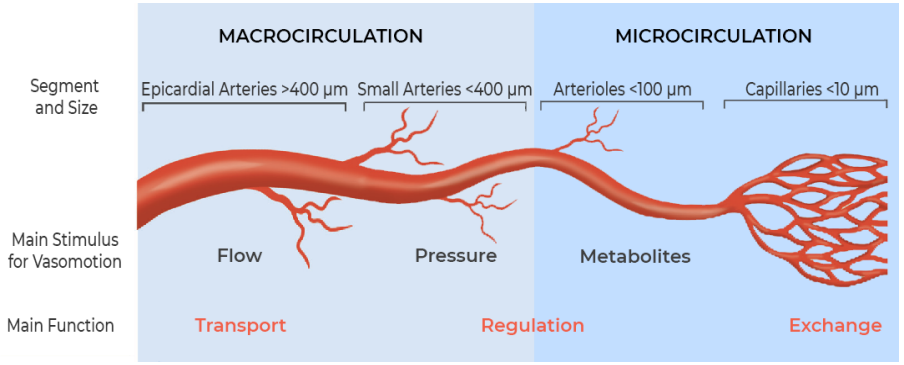


Figure 5: *(Arterial) vessels belonging to the macrocirculation and microcirculation. Adapted from De Bruyne[12].*

The term capillary exchange refers to all exchanges occurring at the microcirculatory level, mostly in capillaries. Blood and tissues exchange materials through capillaries, which branch out to maximize surface area and exchange time as well as minimize diffusion distances[13]. From the capillaries, blood flows into the venules (<100 µm diameter). Venules then feed the blood flow into the veins[8]. These microvessels are not visible to the human eye, but they have a big impact on blood pressure and flow[10]. A depiction of the microcirculatory system can be seen in Figure 6.

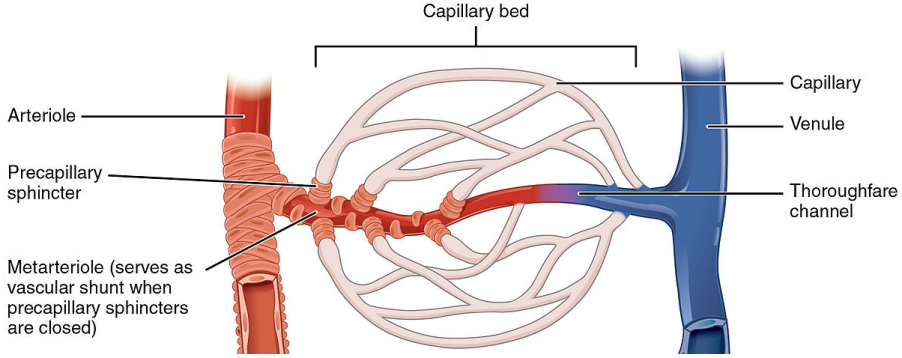


Figure 6: The microcirculatory system containing arterioles, capillaries and venules[14].

Flow regulation in capillaries

It is key for the microvasculature to work properly as abnormalities in the microcirculation can result in critical illness or even death. High blood pressure has a possibility of end-organ damage, such as kidney, heart, and brain damage[15]. On the other hand, organ failure can also occur when the blood flow is not adequate to supply oxygen or nutrients to the tissue[16]. The medical term for this sudden drop in blood flow is called shock[17]. This can be caused by sepsis, which is blood poisoning by a viral, bacterial or fungal infection[18].

Hemodynamic coherence

Macro-hemodynamic parameters (heart rate, mean arterial pressure, central venous pressure) are usually the hemodynamic targets for patients with compromised circulatory function. However, although macro-hemodynamic parameters may be restored, organ failure can still occur due to persistent alterations of microcirculatory blood flow.

The concept of hemodynamic coherence suggests that the correction of systemic cardiovascular variables results in a parallel improvement in tissue perfusion. Conversely, hemodynamic incoherence means that the normalisation of systemic hemodynamics does not improve tissue perfusion, as the microcirculation is still in shock[7]. For example, sepsis is a condition where the loss of hemodynamic coherence can occur. Currently, the treatment goal of sepsis is the stabilization of systemic hemodynamic variables (e.g. pressure) by means of volume expansion (i.e. fluid resuscitation) and pharmacological cardiovascular support (e.g. inotropes and vasopressors) which can improve systemic hemodynamic variables. However, these treatments may not simultaneously improve oxygenation and perfusion in the microcirculation[19]. Incorrect administration of fluids and cardiovascular drugs can even cause further harm due to high venous pressures or vasoconstriction of the arterioles.

Microcirculatory alterations

Four types of hemodynamic coherence losses are recognised[7, 8]:

1. **Heterogeneity** (caused by e.g. sepsis)
2. **Hemodilution** (caused by e.g. excessive fluid administration)
3. **Vasoconstriction** (caused by e.g. vasopressors or blockage of the microcirculation due to targeting high venous pressures)
4. **Tissue edema** (i.e. swelling caused by too much fluid trapped in the body's tissues)

Illustrative representations of these four microcirculatory alterations can be seen in Figures 7-9.

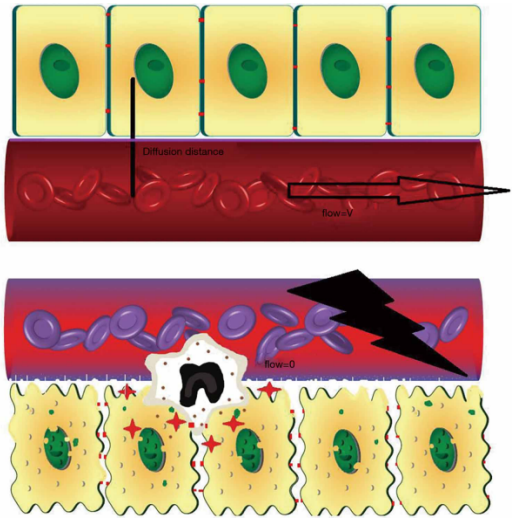


Figure 7: Heterogeneous perfusion as encountered in septic patients. From: Olcay Dilken et. al[8].

Type 1 loss of hemodynamic coherence: flow heterogeneity. Obstructed capillaries can be observed next to the flowing ones. Heterogeneous perfusion causes an oxygen deficit in the tissue causing the cells to die.

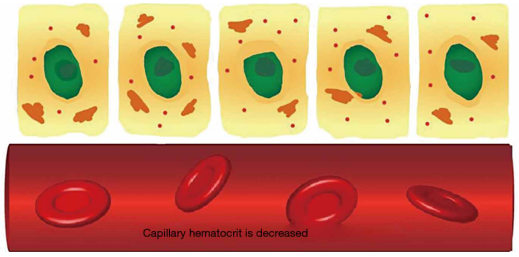


Figure 8: Hemodilution is characterised by an increased distance between red blood cells in the capillary. From: Olcay Dilken et. al[8].

Type 2 loss of hemodynamic: hemodilution. The number of oxygen-carrying red blood cells is reduced. A decreased concentration of red blood cells flowing through the capillaries causes increased diffusion distance of oxygen to the tissue.

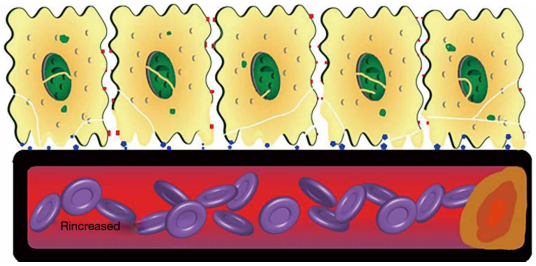


Figure 9: Stasis. The blood flow in the capillaries is impeded or completely blocked. From: Olcay Dilken et. al[8].

Type 3 loss of hemodynamic: stasis of microcirculation. Microcirculation may deteriorate when vasopressors are used excessively or when venous pressure is improperly raised.

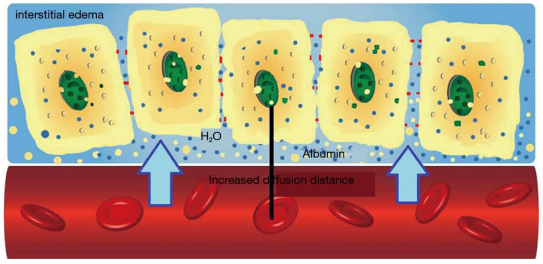


Figure 10: Edema. Fluid trapped between the cells causes the tissue to swell. From: Olcay Dilken et. al[8].

Type 4 loss of hemodynamic coherence: tissue edema. Tissue edema is caused by capillary leaks. This causes the tissue to swell, resulting in increased oxygen diffusion distance and reduced oxygen transport. As oxygen diffusion distance increases, tissue oxygen extraction is impaired.

The current state of hemodynamic monitoring

Medical specialists are expressing their opinion about the shortcomings of conventional hemodynamic resuscitation procedures and the importance of monitoring the microcirculation in such conditions[20].

Conventional hemodynamic techniques are typically applied to the macrocirculation, i.e., the heart and large blood vessels, and do not provide information on oxygen delivery at the cellular level. It remains unclear whether the microcirculation provides adequate oxygen delivery at the cellular level, even if the macrocirculation performs well[21]. Numerous studies have highlighted the significance of microcirculatory alterations and their functions as aids for assessing the severity of the clinical conditions, treatment response, and prognosis, which are superior to conventional systemic indicators[22].

It is possible to evaluate and understand what happens at a microcirculatory level using a variety of techniques. The microvascular perfusion can be measured with a variety of tools at the bedside. The most promising techniques, such as video microscopy, will be discussed in the next chapters. Currently, a lack of effective interventions and clear resuscitation endpoints prevent microcirculation monitoring from becoming part of routine clinical practice[23].

Conclusion: Microcirculation plays a vital role in maintaining good health. Even though experts have voiced the need for microcirculation monitoring it is currently not commonly adopted in clinical practice.

2.2 Hand-held vital microscopes

Information was obtained from literature and websites of the companies mentioned in this section.

The Braedius CytoCam belongs to a group of devices called hand-held vital microscopes (HVM). Hand-held microscopes are portable microscopes designed for in vivo imaging of microcirculation. They are typically used by medical professionals such as vascular surgeons, cardiologists and intensivists who need to visualise blood flow in real-time. The images obtained using hand-held vital microscopes can also be quantified and interpreted using software that allows automatic image analysis.

The evolution of hand-held vital microscopes

In the last decades, microcirculation measurement methods have improved dramatically. They have evolved from methods with limited scope, such as velocity-based laser Doppler or near-infrared spectroscopy, to hand-held vital microscopy (HVM)[24].

In clinical states of cardiovascular compromise, shock and resuscitation, hand-held microscopy is primarily used sublingually (under the tongue) to investigate the nature of microcirculatory changes and has provided insight into the clinical relevance of these microcirculatory alterations[22]. Other than sublingual applications HVMs are used to appraise the microcirculatory characteristics of different human organ surfaces such as the brain, skin, gut, intestines, conjunctiva, vagina, and liver. This wealth of information highlights the value of organ microcirculation and demonstrates the wide range of applications and prospective benefits of these imaging techniques[25].

Although the technology implemented in these hand-held video microscopes has changed and evolved throughout the years, they work with the same principle: light waves in the same frequency as the absorption peak of haemoglobin are used to create a high-contrast image. The haemoglobin containing red blood cells will appear black, while the background will be white.

Orthogonal polarization spectral imaging

The first iteration of hand-held vital microscopes utilized orthogonal polarization spectral (OPS) imaging. OPS was introduced by Groner et al.[26] in 1999 and the first commercially available device implementing this technique was the Cytoscan®, developed by Cytometrics in Philadelphia, USA[27]. This was the first meaningful step for bedside microcirculation evaluation[7].

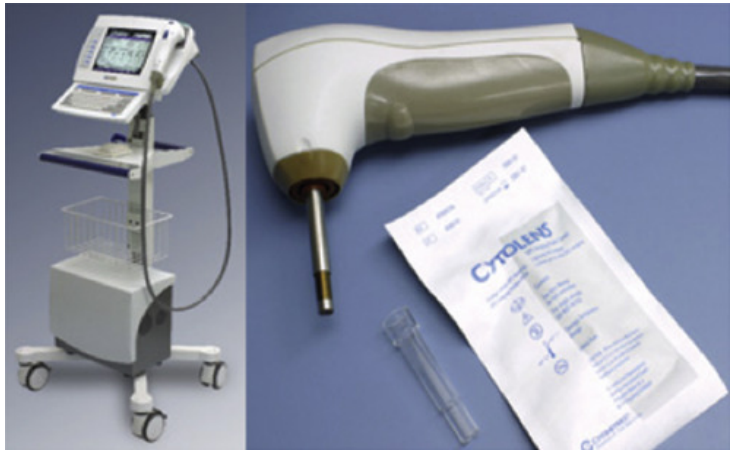


Figure 11: Cytoscan system by Cytometrics (left) and the hand-held unit (right)[28].

OPS imaging generates polarised green light which has a specific wavelength where haemoglobin absorbs this light (Figure 12).
A disposable sterile lens is put on the light guide, which can be placed on tissues, such as under the tongue (sublingual) or on the intestinal mucosa. Without the use of transillumination or fluorescent dyes, flowing red blood cells can be visualised as black particles moving through the microcirculation[27] (Figure 12).

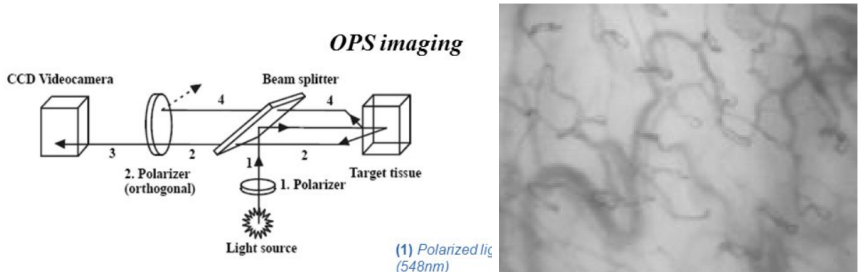


Figure 12: Schematic representation of OPS technique (left) and example of image quality (right). From: *Černý*[29].

It had a few disadvantages, however, such as suboptimal capillary visualisation and image blurring caused by the moving red blood cells[30]. Since reflected as well as emitted light passes down the same light guide, OPS imaging is highly sensitive to internal scattering, resulting in limited visualisation of the capillaries due to blurring[31].

Sidestream dark field imaging

Based on sidestream dark field (SDF) imaging, the second generation of hand-held microscopes was developed. Instead of polarised light, the illumination is provided by light-emitting diodes (LEDs)[27]. These LEDs emit green light (wavelength λ = 530 nm) and are concentrically placed surrounding the central light guide[32]. The idea behind the SDF technique is to optically isolate the LEDS from the sensing central pathway of the probe, to prevent direct surface reflections to interfere with the image of the microcirculation[32]. A comparison of the OPS and SDF imaging techniques is shown in Figure 13.

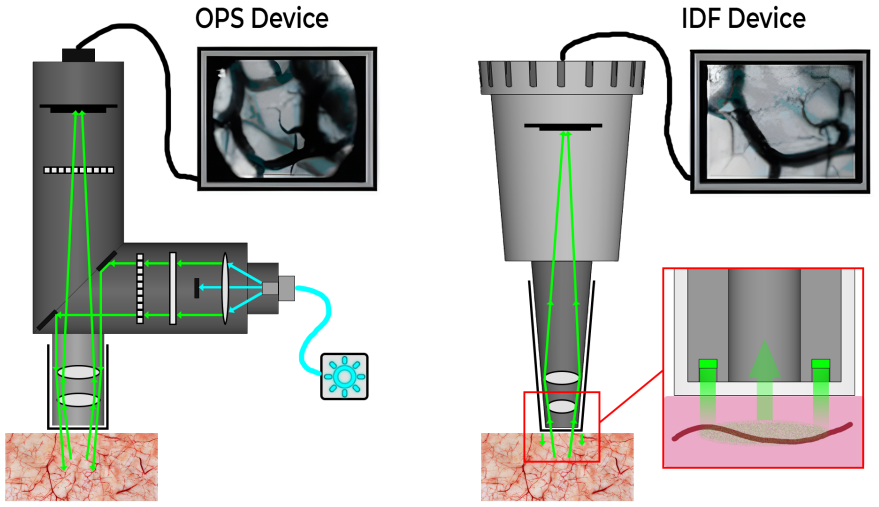


Figure 13: *OPS imaging technique compared to SDF imaging. Redrawn, adapted from Bezemer*[33].

In 2007 Microvision Medical (Amsterdam, The Netherlands) introduced the MicroScan® using the SDF technique (Figure 14). This first iteration of the device gives an analogue output which requires an external device to handle the analogue to digital conversion for the software analysis tool[27]. The SDF technique showed better capillary contrast and quality of visualisation compared to OPS. SDF devices such as the MicroScan have been widely used in experimental and clinical scenarios[7].

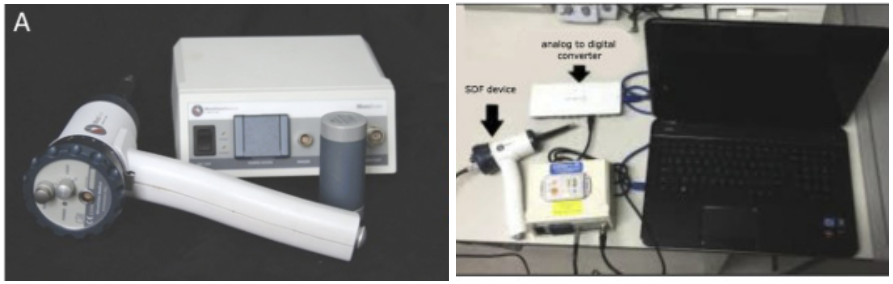


Figure 14: Original battery-operated Microscan by Microvision[7, 34].

Incidental Dark Field imaging

The third-generation hand-held microscope was introduced in 2012 by Braedius Medical (Huizen, Netherlands). The device is called the CytoCam® and uses a refined version of incidental dark field (IDF) imaging. Technical improvements have been implemented to overcome some of the limitations of earlier devices, such as having a digital output, decreasing the device weight, and increasing the optical resolution[27].

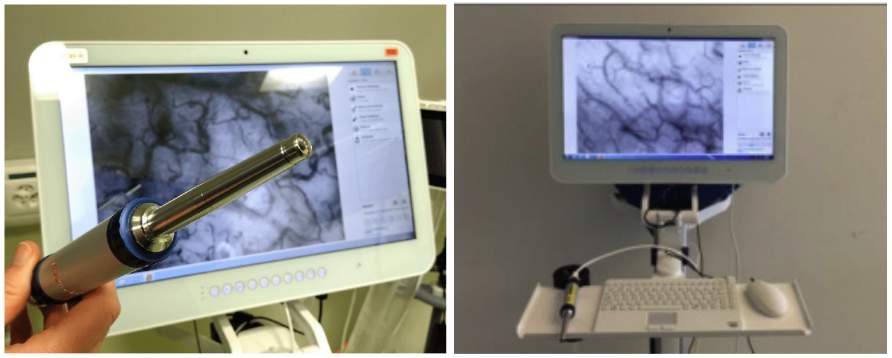


Figure 15: The CytoCam system in a trolley format. The CytoCam Model 1 with the cylindrical body is showcased here[35].

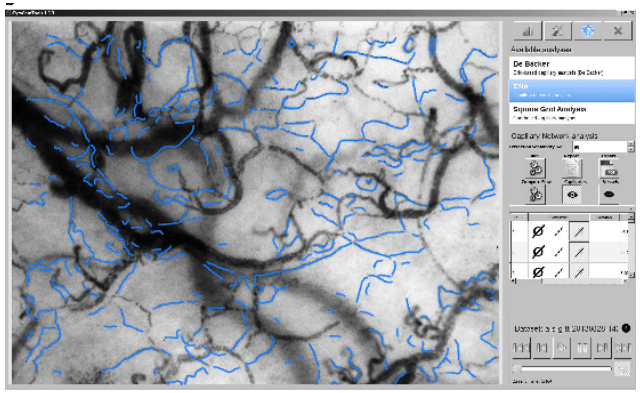


Figure 16: The original Braedius CytoTools software (interface)[36].

Multiple clinical tests have shown that IDF results in better contrast, sharpness, image quality and a three times larger field of view compared to previous-generation HVM devices[27,37,38]. Breadius Medical also used a short light pulse of 2 ms at a very high intensity, increasing the contrast. Consequently, a study found that IDF can identify 30% more sublingual capillaries than SDF[7]. Figure 16 shows the different implementations of the SDF and IDF techniques.

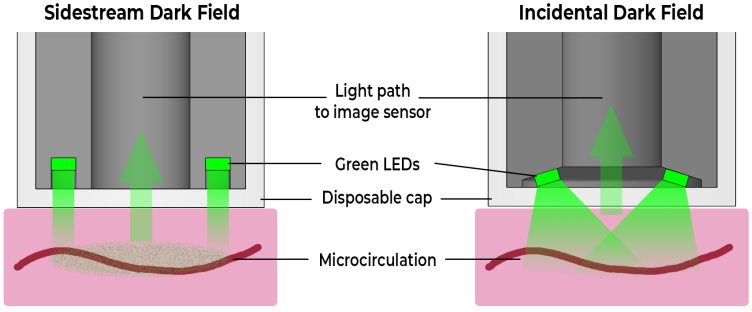


Figure 17: *Sidestream Dark Field compared to Incident Dark Field. Adapted from Van Elteren[27] and redrawn.*

State of the art

To keep up with the competition, MicroVision Medical revealed a new updated version of their camera in 2018 called the Microscan USB3 (Figure 18). The new device has several objective improvements compared to its previous iteration, such as a higher resolution, increased frame rate and digital image capture. The Microscan USB3 is also considerably lighter than their first camera, mostly due to its custom build, whereas its predecessor used a bulkier battery-operated third-party camera[34].

MicroVision still uses the SDF technique, but claims they have improved the illumination management and implemented resolution enhancement. They call this new iteration of the technique "SDF+"[39]. Microvision's Microscan USB3 with SDF+ has demonstrated better image acquisition than its predecessor[34].

Figure 18: MicroVision Microscan USB3 system[39].

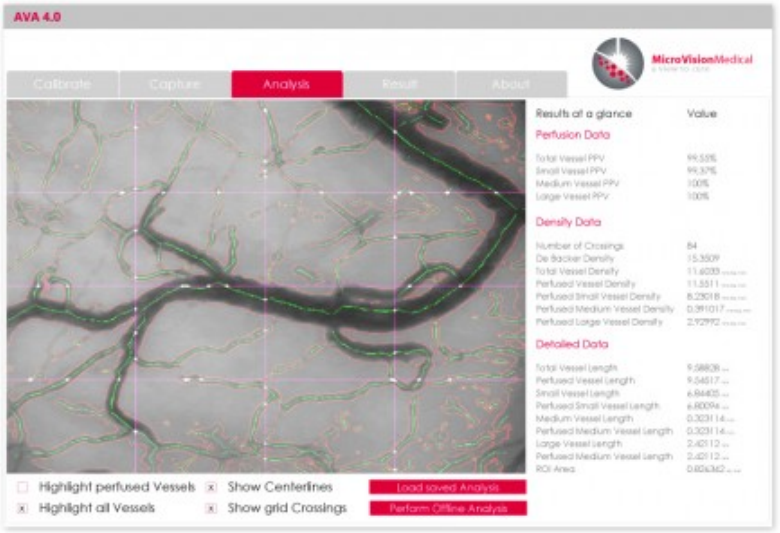


Figure 19: Microvision's AVA 5 software[39].

At the point of writing Braedius Medical has released two new cameras since Microvision's Microscan USB3's launch, the CytoCam Model 3 (2019) and Cytocam Model 4 (2023). An interesting insight would be to see how modern IDF and the new SDF+ system compare, but no research comparing IDF with the new SDF+ technique has been performed yet.

Next to hardware improvements, Braedius and MicroVision have also put efforts into improving their software solutions. Advancements were made in functionalities, workflow and user interface. Braedius' latest software suite is called CytoCamTools V4 (Figure 20) and MicroVision has AVA 5 (Figure 19).

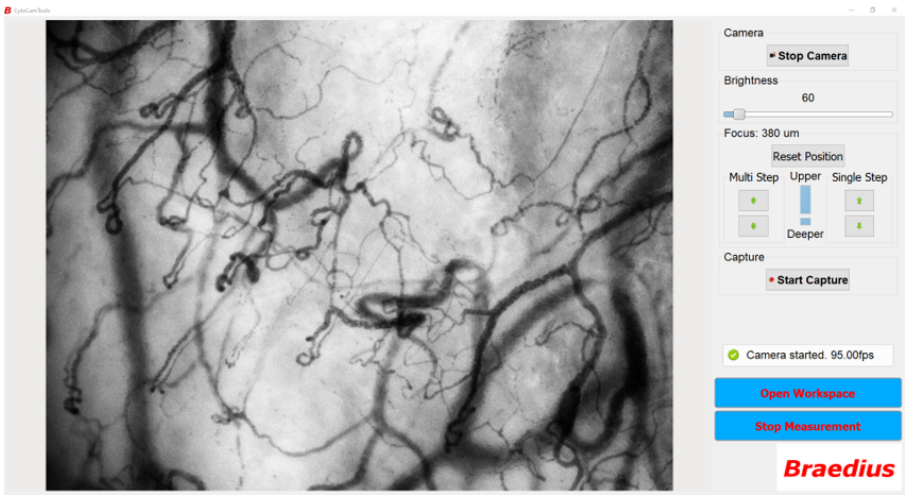


Figure 20: A screenshot of CytoCam tools V4. From: Braedius Manual.

A more in-depth comparison between the hardware of Braedius Medical and MicroVision is covered in Appendix A.

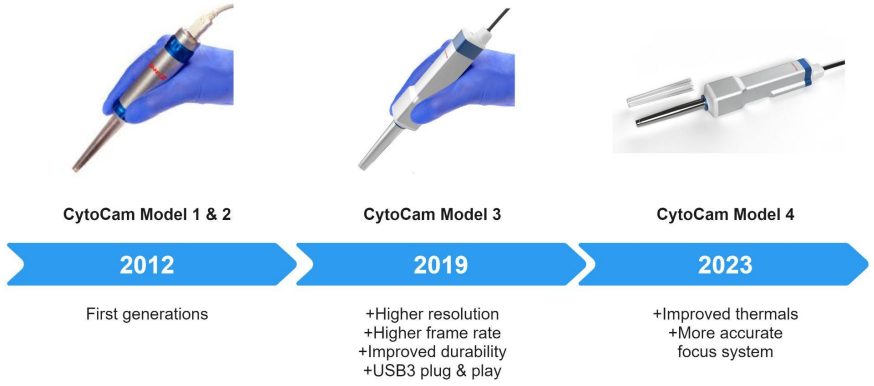


Figure 21: *The hardware evolution of the Braedius CytoCam cameras.*

Hand-held videomicroscopy has primarily been used in the intensive care setting on the adult population, although research with these cameras has also been performed on neonates and children[21, 27]. Throughout the years, HVM has become an important tool for research on microcirculation in humans and animals. In HVM, microvascular beds can be visualized non-invasively at the patient's bedside, up to a depth of around 1 mm, directly in the mucosa and on solid organ surfaces. Neonatal and pediatric microcirculatory imaging can be acquired through buccal and sublingual mucosa. Neonatal measurements can also be done transcutaneously (skin), for example, in the inner arm, axilla, ear conch, and fossa triangularis[21].

Figure 22: Internist-intensivist using the CytoCam on a patient. A trolley with the panel PC for the camera can be seen on the right of the picture. From Manu Malbrain[40].

Timeline

Figure 23 shows an overview of the most relevant developments of hand-held video microscopes throughout the years.

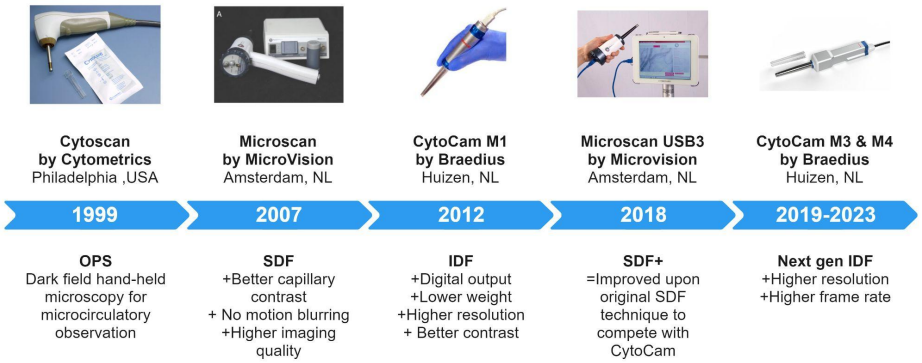


Figure 23: *Hardware advancements in hand-held video microscopes*

Limitations

Although HVM is seen as a technique that has potential for clinical applications, there are technical limitations that make it difficult to adopt for monitoring or therapy guidance.

The following implications have been mentioned:

- Compromised video recordings caused by movement or applying too much pressure on the area of measurement, affecting the flow of the capillaries (pressure artefacts)[23, 41].
- Because of the shallow depth of measurement, noninvasive in vivo measurements from adult patients can only be taken from very few locations[23]. Clinically, monitoring microcirculatory parameters is challenging. Microcirculation is usually accessed non-invasively through mucosal surfaces (containing superficial vessels) that are exposed to the environment, such as the oral cavity[42].
- Although visualisation can be done in real-time, the analysis of these video images, either manually or by means of software, takes time and can be tedious. This means the data can not be obtained immediately at the bedside at the time of recording the video samples[41].

Conclusion: As a prognostic tool and a goal for resuscitation, monitoring sublingual microcirculation appears an attractive option for monitoring critically ill patients, but significant barriers remain. Currently, the majority of these concerns video acquisition and analysis. These limitations will hopefully be overcome by improvements in automatic analysis. As of now, sublingual microcirculation monitoring mainly remains a tool for research purposes[7].

2.3 Technology landscape

Information was obtained from literature and desk research. Google, Google Scholar, PubMed and ScienceDirect were used as search engines to find articles between 2010 and 2022 with keywords such as “microcirculation imaging techniques”, “microcirculatory clinical assessments” and “microcirculatory monitoring devices”.

In this section, an overview of the technology landscape regarding microcirculatory data acquisition techniques is covered. The objective was to see how the technology of the Braedius CytoCam compares to other existing techniques and devices. The goal was to identify competing technologies or potential solutions that can improve the current implementation.

The near-infrared window

Hand-held vital microscopes such as the Braedius Cytocam emit light in the visible spectrum with a wavelength of around 510-580 nanometres. We see this as a green light and it is absorbed well by the haemoglobin-containing red blood cells. This results in high contrast black and white imaging obtained by the hand-held vital microscopes. However, this type of light can not penetrate deep into the tissue, due to light scattering and other molecules in the skin absorbing the light (Figure 25).

When the light has to travel further into the skin, devices have adopted the use of near-infrared (NIR) light. The near-infrared window is also known as the optical window or therapeutic window. Within this region, the light can penetrate organic tissue up to several centimetres[43].

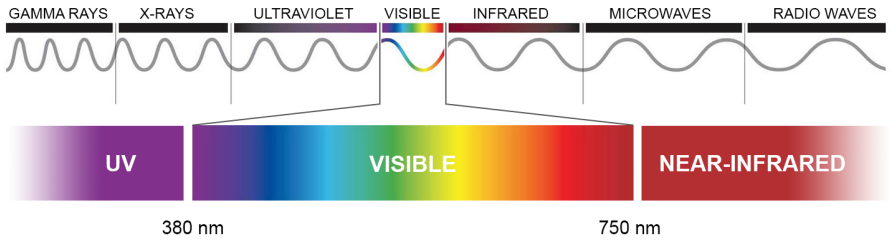


Figure 24: *The electromagnetic wave spectrum. Adapted from Azom[44].*

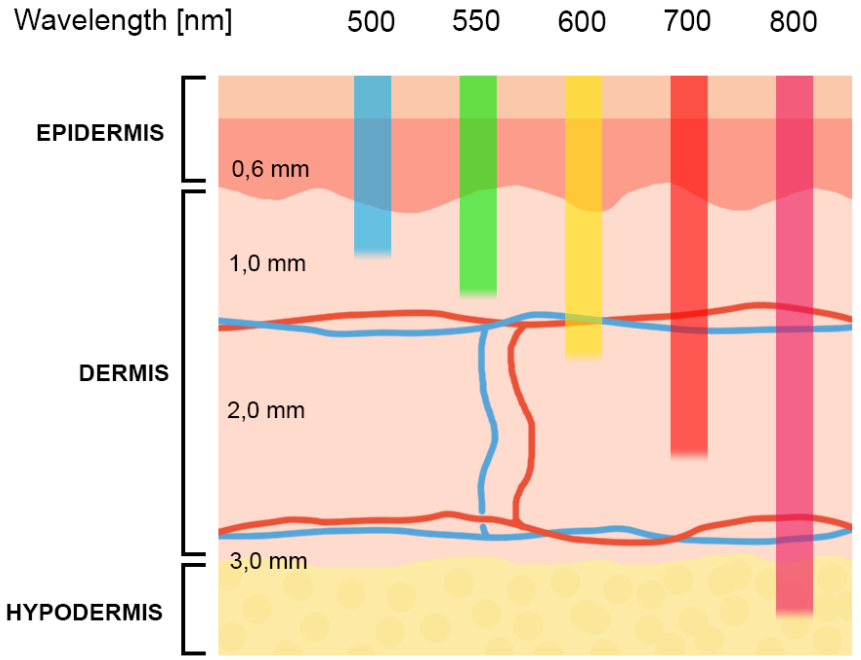


Figure 25: *Schematic representation of different lightwaves and their respective penetration depth into the skin tissue. Adapted from: Nutte[45].*

Within the NIR window haemoglobin (Hb) has distinctive absorbance peaks (Figure 27B). This chromophore is an oxygen carrier in the blood.

Furthermore, the oxygenated or deoxygenated states of these macromolecules have different absorbance characteristics[46, 47].

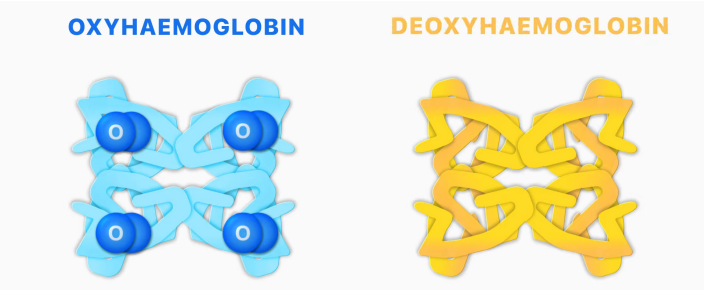


Figure 26: Oxyhaemoglobin and deoxyhaemoglobin.

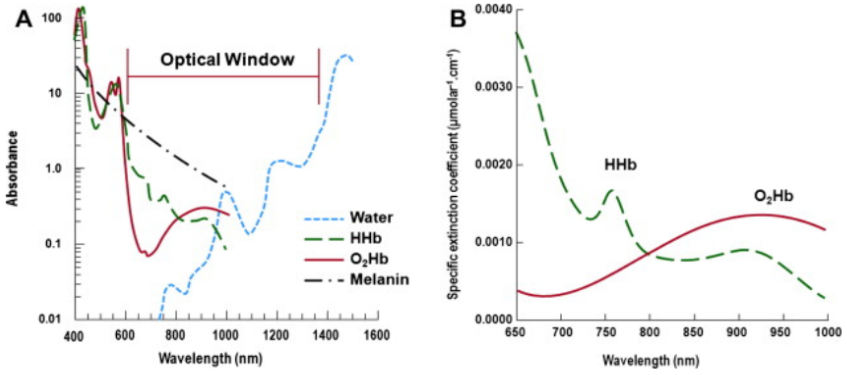


Figure 27: (A) Different molecules found in skin tissue and their light absorption spectra. (B) Absorption peaks of oxyhaemoglobin and deoxyhaemoglobin in the NIR window. From: Murkin[43].

Commercial devices using near-infrared are typically designed to use wavelengths of NIR light that are sensitive to these biologically important chromophores. These wavelengths are usually selected between 700 and 850 nm, where the absorption spectra of deoxyhaemoglobin and oxyhaemoglobin are maximally separated and overlap with H2O is minimal[43] (Figure 27).

Near-infrared spectroscopy

One of the techniques utilising the optical window is called near-infrared spectroscopy (NIRS). Light spectroscopy studies how the absorption and emission of materials are affected by different wavelengths.
NIRS is used as a noninvasive method to make real-time quantitative measurements of tissue oxygenation[19]. Similar to the HVMs NIRS technology utilises carefully chosen wavelengths to target specific molecules. An important difference is that NIRS measures regional tissue oxygenation, whereas IDF visualizes and measures red blood cell (RBC) activity and occurrence in the microcirculation.

Figure 28: Near-infrared spectroscopy device containing the main monitor unit and four probes[48].

The device utilises probes that can be stuck on the patient's body to measure oxygen saturation of the skin, muscles or brain. The probes

contain light emitters and optodes (light detectors) to measure how much the tissue absorbs the light. This value is then used to calculate the oxygenation of that tissue area.

Pulse oximetry

Another technique that utilizes the NIR window is pulse oximetry. Even though it is currently not applied to observe microcirculatory perfusion, it is worth mentioning for this study. Even though the technique has similarities with NIRS, Pulse oximetry has been used as a common tool in the ICU to non-invasively measure blood oxygen levels to guide therapeutic interventions[49].

This relatively simple device clips on the end of the patient's finger and uses LEDs to emit two different light wavelengths (660nm and 940nm) to emit through the tissue (Figure 29). On the other end sits a photodetector to collect the light that has not been absorbed. These lights are also chosen to be optimized for deoxy- and oxyhaemoglobin[50].

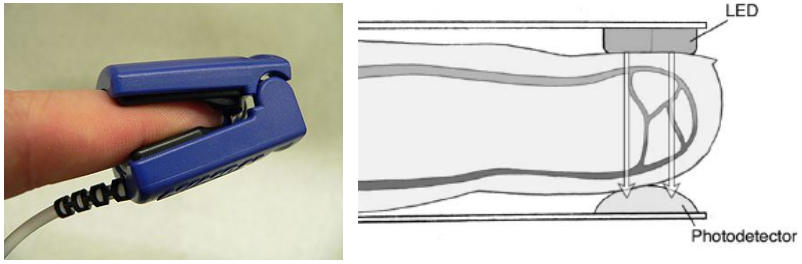


Figure 29: (Left) Pulse oximetry clipped onto the finger[51]. (Right) LED illuminates through the finger to measure how much light is absorbed.

Multi-spectral imaging (MSI) and hyperspectral imaging (HSI)

One of the newest non-invasive techniques that have been used to measure tissue oxygenation and microcirculatory perfusion is multi- or hyperspectral imaging (HSI/MSI)[52].

Spectral imaging combines conventional imaging with spectroscopy to provide both spatial and spectral information about an object. Originally developed for remote sensing, this technology has been extended to the biomedical engineering field as a powerful analytical tool for biological and biomedical research. This technique also utilizes the principle of spectrometry and the NIR window, like NIRS and oximetry. However, it does not require light sources that emit specific wavelengths. Instead, the optics and digital camera sensor can filter different wavelength bands. This method is similar to how a modern colour camera works. By filtering specific lightwaves it can visualise the oxygenation of tissue areas, which can indicate whether that area has adequate or inadequate microcirculatory perfusion (Figures 30 and 31).

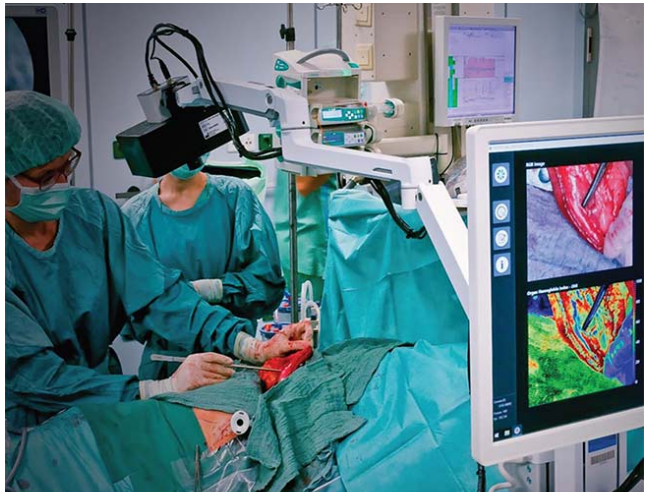


Figure 30: Hyperspectral imaging used during surgery[54].

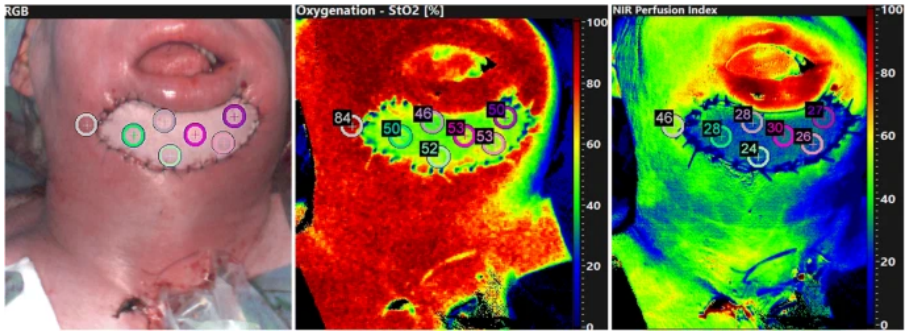


Figure 31: Intraoperative monitoring of the oxygenation and perfusion of a skin flap. From: Thiem[55]

Photoacoustic imaging

Another emerging technique based on the principle of spectroscopy is photoacoustic imaging (PAI). Like the other technology in this section, it utilizes specific wavelengths of light to target (macro)molecules like oxy- and deoxyhaemoglobin, melanin, lipids, water, collagen and fluorescent agents. A laser emits light in short pulses which get absorbed by the specific molecules that correspond with the wavelength of the light. This generates heat, causing these molecules to expand and contract. The acoustic waves from these vibrations are picked up by an ultrasound transducer. Using algorithms, these ultrasound signals are reconstructed into an image[56, 57].

The result is highly detailed (3D) spatial images with high contrast. Different variations of PAI have been developed where there is a trade-off between tissue depth and resolution. Maximum depth and lower resolution are more suited for visualizing macrocirculation, whereas the highest resolution is advised for microcirculatory microscopy. However, the maximum penetration depth of the tissue is limited to 3 mm with the latter[57].

Oxyhaemoglobin and deoxyhaemoglobin are the most common chromophores used in PAI applications. As cancer cells have increased metabolic activity, these are particularly useful for tumour screening. The Imagio breast imaging system from Seno Medical (San Antonio, TX) was specifically designed for this purpose. After the United States Food and Drug Administration (FDA) granted premarket approval, it became the first PAI system to cross the "valley of death"[58].
In addition to cancer screenings, PAI's affinity for haemoglobin detection also makes it attractive for vascular imaging[58].

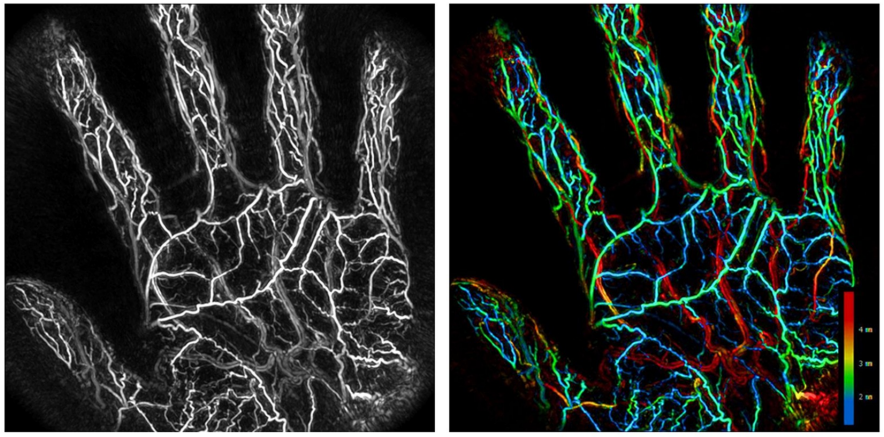


Figure 32: Kyoto University (Japan) researchers used PAI to create three-dimensional maps of blood vessels inside human palms. It contains a hemispherical ultrasound detector array and dual 755 nm and 795 nm lasers. The research team was only interested in measuring total blood concentration and thus chose to exclusively use the 795 nm signal. This is where the absorption coefficients of HHb and HbO_2 are equivalent. From: Matsumoto[59].

Other techniques

In addition to techniques that are based on spectrometry, there are other technologies that can study the microcirculation. They will be briefly mentioned here, but there will be no in-depth analysis or explanation of how they work. However, the advantages and limitations were looked into and identified. At the end of this chapter, an overview of all the advantages and limitations of the mentioned techniques can be found.

Laser Doppler Flowmetry

Laser Doppler Flowmetry (LDF) is a technique that can measure tissue blood flow (Figure 31). It uses laser lights to illuminate the vessels. The light bounces off the red blood cells and scatters back to the surface into a photodetector. The velocity of the red blood cells is calculated based on the Doppler-shift principle, also known as the Doppler effect[60]. Among its uses are skin flap assessment and liver transplantations[61]. It is an established technique for real-time measurement of microvascular red blood cell perfusion but it has many drawbacks. The first one is that it can not measure the flow of individual microcirculatory vessels. As a result, it can not detect microvascular heterogeneity.
This technique is useful when a hemorrhagic shock is present (for example, during surgery or after trauma), but it cannot be used to detect sepsis[23]. Another drawback is that it is very prone to movement artefacts, both by the patient as well as probe displacement[61].

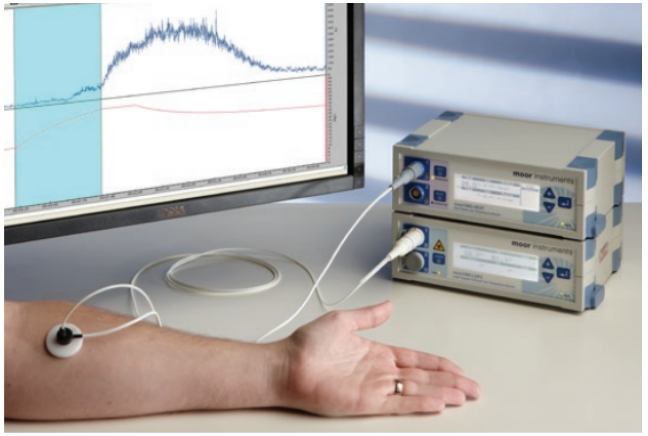


Figure 33: A Laser Doppler FLowmetry probe is placed on the forearm to measure the tissue blood flow[62].

Reflectance-mode confocal-laser-scanning microscopy

The last technique that will be covered is Reflectance-mode confocal-laser-scanning microscopy (RCLM). RCLM or RCM for short is a three-dimensional computed tomography, which allows for the observation of the structure of the epidermis and superficial dermis on a cellular level[63]. It is mostly used as a real-time non-invasive skin disease examination method. Since microcirculatory beds are situated in the skin, it can also observe the flow of red blood cells in capillaries. The main drawbacks of this technique are the very high costs ($50.000) and the bulky size of the camera[30] (Figures 34 and 35). Furthermore, it has a limited depth of imaging (250-300µm), and time is required for imaging larger surfaces[64].

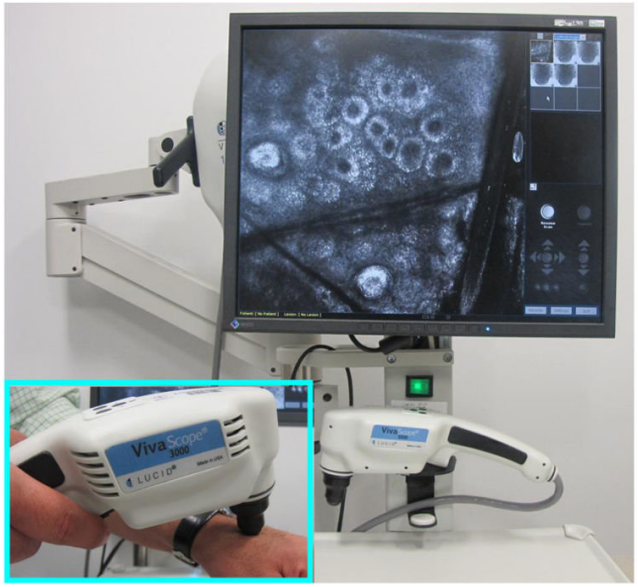


Figure 34: RCLM imaging system in a hand-held operation setup[64].

Figure 35: RCLM imaging system in a hands-free operation setup[65].

Although not mentioned in literature, it can be seen in the picture that the camera puts significant pressure on the tissue.

Comparison of covered techniques

Based on the results of the analysis of the covered techniques an overview of the relative advantages and limitations is made (Figure 36). The data is based on 11 articles, collected from 1988 until 2023, in journals such as the Journal of Clinical Monitoring and Computing, Nature Medicine and Journal of Biomedical Optics. The paper from 1988 is an outlier as it covers pulse oximetry, which is a relatively old technology.

Figure 36: Advantages and limitations of microcirculation analysis techniques.

Technique	Advantages	Limitations
Hand-held Video Microscopy (HVM)	+ Evaluation of perfusion heterogeneity + High refresh/sample rate (60+Hz) + Can observe on a cellular level and distinguish individual vessels + Ability to derive a complete set of microcirculatory data needed for clinical application	- Requires cooperation or sedation of the patient - Shallow depth of measurement (1 mm) - Movement and pressure artefacts - No immediate availability of microcirculatory video analysis - Requires practice
Near-infrared Spectroscopy (NIRS)	+ Real-time quantitative values + Measurements at deep levels of the tissue can be made + No operator required to hold the probes in place	- Unable to detect perfusion heterogeneity - Influenced by many different variables - Can not be used for absolute value measurements, only for trend monitoring - No standard established between manufacturers causing significant differences in measurements
Pulse oximetry	+ Accurate real-time monitoring with quantitative outputs	- Can not measure on a microcirculatory level
Multi- or hyperspectral imaging (MSI/HSI)	+ Non-contact operation + 3D spatial images + Multiple biomarkers can be measured/visualized at the same time	- 3D images take time to scan, not suitable for high-frequency monitoring - Can result in blurry images if the patient moves during the scanning procedure - Currently still big and bulky - Powerful lamp required, which can significantly heat up the skin of the patient - Penetration depth is relatively unclear -Significant data storage capacity is necessary
Photoacoustic imaging (PAI)	+ Highly detailed 3D spatial images with high contrasts + Very well suited for vascular imaging	- Limited tissue depth (3 mm) when high resolution microscopy is required - It takes several minutes to generate an image of acceptable quality - Not established yet and expensive
Laser Doppler Flowmetry (LDF)	+ Easy to use + Small probe + Not expensive + High sample rate (4000 Hz)	- Cannot show microcirculatory vessels nor heterogeneity in perfusion - Very sensitive to movements (both in tissue and the device itself, such as the probe or the fiber optic wire) - Prone to pressure artifacts - Cannot measure/display a flowrate of zero (biological zero)
Reflectance-mode confocal laser scanning microscopy (RCLM)	+ Highly detailed 3D images of the epidermis and superficial dermis + Cellular level of detail	- Very high cost - Bulky size, prone to pressure artifacts - Limited depth of imaging (<0.3 mm) - Low sample rate (1Hz)

The covered techniques are plotted in graph x to compare spatial resolution (x-axis) and temporal resolution (y-axis). Spatial resolution refers to the amount of (smallest) details in the area of measurement the technique can observe. A numerical output that represents an average measurement of the whole region is considered as having a low spatial resolution. Whereas an output showing small details and intricacies throughout the observed region is considered a high spatial resolution. Temporal resolution can be seen as the sampling rate which refers to how many measurements or data points can be produced per time unit.

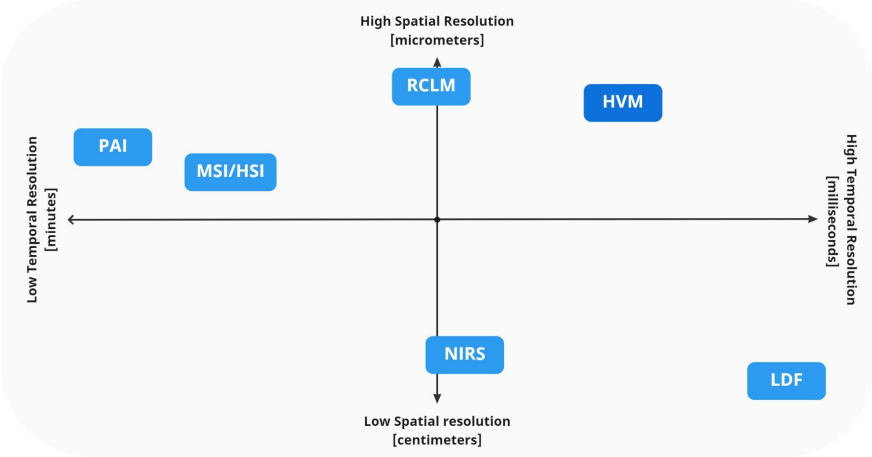


Figure 37: *Various techniques plotted against spatial resolution (X-axis) and temporal resolution (Y-axis).*

The capabilities of how fast or detailed the techniques are have a direct influence on the types of data and derived measurements that can be made. For instance, a technique that takes seconds or even minutes to render a singular image or moment, can not be used to calculate blood flow or velocity. And a technique that is not capable of distinguishing individual blood cells or capillaries can not be used to detect heterogeneity in blood flow between the different capillaries.

Blood flow	Total vascular density	Blood cell concentration	Tissue oxygenation	Heterogeneity in blood flow
- HVM - LDF	**- HVM** - MSI/HSI - PAI	**- HVM** - RCLM	**- HVM** - NIRS - MSI/HSI - PAI	**- HVM**

Figure 38: Microcirculatory parameters and the techniques that can measure them.

Figure 38 indicates that the technique used for HVMs, such as Incidental Dark-Field imaging with a high refresh rate video sensor can offer a complete set of parameters for the microcirculation. Its disadvantages like shallow measurement depth, difficult video acquisition and long processing time are currently preventing it from clinical usage.

Conclusions

- *One of the critical benefits of the hand-held video microscopy technique is its ability to visualise microcirculatory alterations such as heterogeneity of perfusion.*
- *Unlike other techniques, hand-held video microscopy can visualise the capillaries and the red blood cell flow in high detail, at a high refresh/sample rate.*
- *Current hand-held videomicroscope solutions have difficulties achieving clear image capture and the software solutions cannot assess the video fast enough to output real-time continuous quantitative data.*
- *The light wave (~540nm) used by current hand-held videomicroscopes can not penetrate deep into the skin tissue. Because of the limited image capture depth of max. 1 mm, the only feasible location for adult patient measurements is on mucosal tissue e.g. in the mouth) or nail cuticles. These locations have much more superficial microcirculation whereas the microcirculation in the skin is 1.9 mm deep.*
- *Other techniques such as near-infrared spectroscopy and multispectral imaging have advantages over HVM such as measuring more deeply into the tissue. But they also have critical limitations compared to HVM such as not being able to observe the characteristics of individual capillaries.*
- *The solution might be to improve the technical ability of HVM by incorporating elements of other techniques, while still keeping its core capabilities and advantages.*

3 Analysis phase

3.1 User needs analysis

Knowing who your customers are, what they want to achieve and which demands are currently unmet gives key insights into innovation opportunities. The goal of this analysis was to gather user data for finding an opportunity space and to help formulate the requirements for the new concept.

Customer insights

An internal document of Braedius Medical containing 101 customers was used to identify who the current users are of the company. The main insights will be summed up in this report.

Main insights:

- **Currently, all cameras are primarily used in a research context.**
- **The customers are mostly university hospitals also known as academic medical centres (Figure 35).**
- **The main fields of application are cardiology and perioperative care (Figure 34).**
- **Of all the known instances (61%), the camera is used in an ICU setting. Application context setting is not mentioned in all entries.**
- **The camera is mostly used in human-only studies (71%).**
- **Most customers are from Europe (62%) (UK, Netherlands, Germany, Italy, Belgium) and North America (21%) (specifically, USA)**

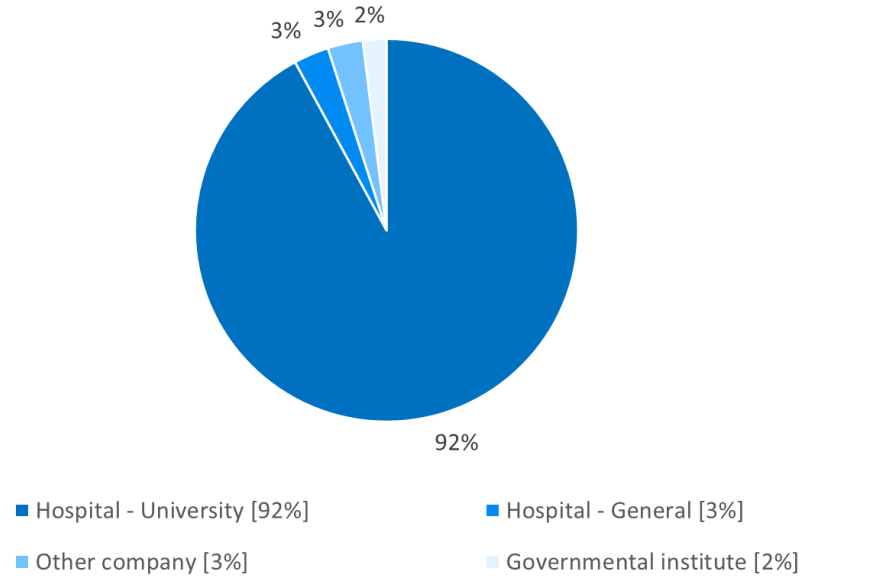


Figure 39: *Institution types and the percentage they represent of the total customer database.*

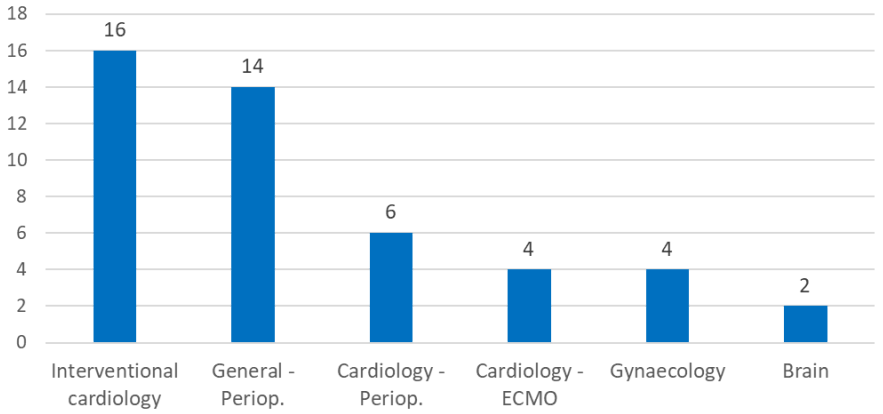


Figure 40: *Amount of customers per application type. Note: This figure only contains data from 46 entries. For 55 organisations the application type was not mentioned.*

Customer pains and needs

The data from this section was taken from both literature findings and primary research in the form of qualitative interviews and an observational study.

Data from literature

The literature about hand-held vital cameras that was found during the Discovery phase also mentioned limitations and wishes for future developments. The more recent papers (2018 and newer) were analysed again to find insights that are still relevant. An overview of the main points is shown here.

Current limitations of hand-held vital cameras

- The camera can only visualise the microcirculation if the tissue layer is very thin. The skin of newborn babies is thin enough, but for adults, the mucosal tissue, such as in the mouth is the only easily accessible area for measurements[21].
- Capturing video samples of the microcirculation is difficult. Putting too much pressure on the tissue with the camera influences the flow of the capillaries. The recording is invalid due to these pressure artefacts[7, 21, 41].
- Moving the camera will cause movement artefacts. A blurry image is not usable for video analysis[7, 21, 41].
- Validated fully automated video analysis is currently not available. This makes bedside monitoring more difficult[7, 21].

Data from the qualitative interviews

To gain more detailed and in-depth knowledge about areas of improvement a qualitative interview was conducted to acquire the opinions of customers who have used the CytoCam camera first-hand. Six medical professionals from different institutes and countries participated. For detailed information on the interviews such as research design and participant details, please see Appendix B.

Workflow

To help put the pains and needs into context, the participants were asked to describe the steps they took when using the camera. Figure 41 shows these steps. Although not part of the interview, other stakeholders such as technical support staff (n=1) were also asked about their involvement surrounding the CytoCam system. An overview of the stakeholders directly involved with handling the camera and their respective activities is portrayed in a product journey (Figure 42).

Figure 43 shows the flow of data involved with the video acquisition and analysis. The camera operator is tasked to record high-quality video samples. The video is then analysed by a computer to create (semi-)quantitative microcirculatory data. See Appendix C for a detailed explanation of the output parameters. This data is then used for research purposes, clinical assessment or patient data logging. In most cases, the camera operator and researcher/clinical practitioner are the same people. Video analysis can be done in the same facility or even on the same computer used for the hand-held camera or outsourced to a third party.

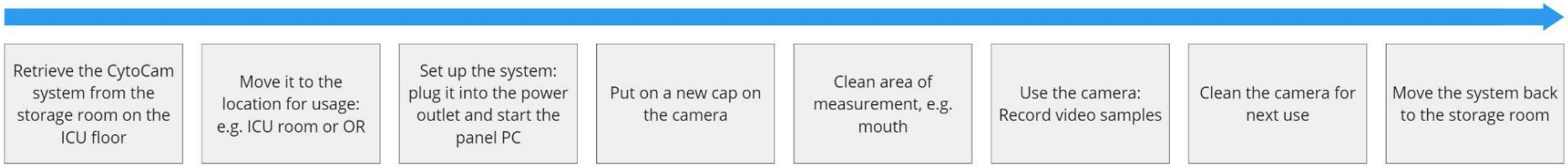


Figure 41: *Workflow of the user when using the camera.*

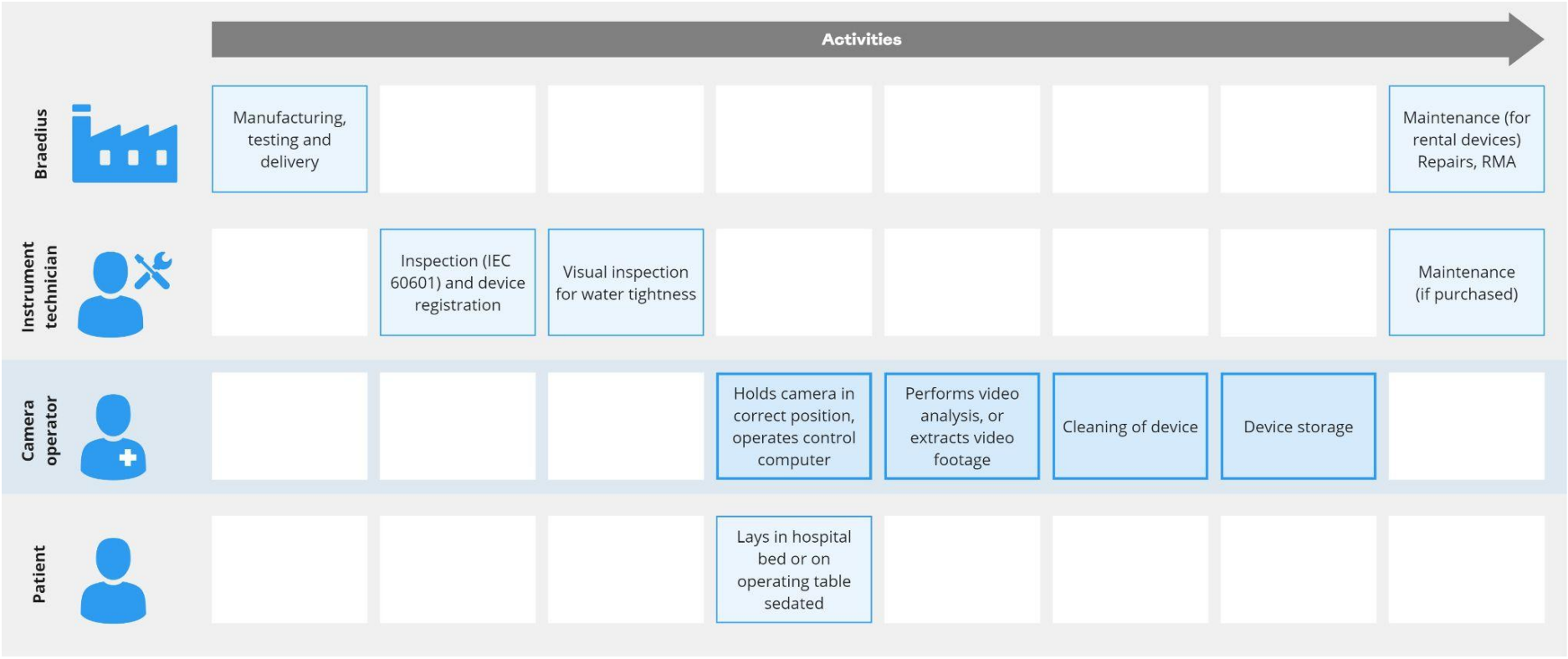


Figure 42: *Stakeholders directly involved with the camera and their activities.*

	Camera Operator	Video assessment software	Researcher/Clinical practictioner
Activities	- Acquire video images - Assess video content - Save/export videos (to usb stick)	- Process and analyse video - Convert into quantitative data - Export datasets (e.g. Excel)	- Analyse datasets - Synthesize conclusions based on data
Data types	- Video files - Text based notes, patient info	- Total Vessel Density (TVD) - Perfused Vessel Density (PVD) - Flow velocity by use of Space-Time Diagrams - Microcirculatory Flow Index (MFI) - Heterogeneity index	- Findings will be used for publications or internal research - Written information - Graphs - Tables
Data purpose	The real-time video feed can be assessed by a clinical practitioner during the procedure as means of monitoring. If quantitative data needs to be extracted from the video, it is exported.	Video analysis can be done by Braedius software or by an external party. The quantitative data is analysed by a researcher clinical or clinical practitioner	Research findings help to fill in gray areas regarding the workings of the microcirculation. The data can also be used for clinical assessment and decision making

Figure 43: *Data flow of video acquisition and analysis.*

User pains

The interviews with the participants confirmed the statements found in the literature. However, the data from the qualitative research was much more detailed and rich. Furthermore, other insights were also discovered. The main pain points can be summarised as follows:

The participants mentioned the following experiences:

1. The acquisition of video samples of acceptable quality is challenging. This is caused by:
    a. Pressure and motion artefacts - It takes some skill and practice to hold the camera correctly and with minimal movement.
    b. Contamination of the tissue - The users must frequently clean the area under the tongue. During prolonged measurements, this area can also become dry and clotted.
    c. Physiology - Not every spot under the tongue will give suitable video images. These need to be found by the operator. During the training given by Braedius, they will be given theory on the anatomy of the sublingual tissue and the suitable spots.

2. The ergonomics when using the camera are usually not optimal. Examples are:
    a. Obstruction in the mouth caused by other devices - The measurements were primarily taken from ICU and OR patients that were anaesthetised. Tubes from life support devices also run through their mouths, which makes manoeuvring the camera even more challenging.
    b. Obstructions for the operator caused by other devices or people - Due to the cramped space the camera operator has to stand in a very awkward position in order to position the camera at the right angle. In such cases, it is very difficult to hold the camera with one hand and operate the computer with the other hand. The view can sometimes also be obstructed. Critical moments can get very hectic in the intensive care room or operating room (Figure 44). During operation, it is also not uncommon

that the head of the patient is obstructed by work surfaces (Figure 45).

3. It is impossible to do measurements at the exact same location over a prolonged time, or multiple times. The video image represents an area of about 1,5mm by 1,1 mm. The slightest movement or shift translates into a different image. Finding this same location at a later time is also near impossible.

4. Video analysis is very cumbersome and takes time - After the clips are recorded they need to be analysed one by one for a (semi-)quantitative output. The users have to transfer the videos from the panel pc of the CytoCam system via a USB stick to a more powerful computer. If the video analysis is done in another facility, the videos need to be sent to a different city where the computer runs the analysis software. At LUMC (Leiden) they send the videos to Rotterdam for analysis, for example.

5. For adult humans, the locations for in vivo non-invasive measurements are very limited. That's why it is almost always done under the tongue

The causes of the user pains have been coded and put into a table which can be seen in Appendix D.

Figure 44: A user using the CytoCam during a critical moment[41].

Figure 45: Operation work surface obstructs access to the patient[66].

User wishes

The participants saw value in the following features:

1. Feedback on applied pressure - To see whether the measurement is compromised by pressure artefacts
2. Real-time quantitative analysis - A participant mentioned that in the ICU, they always work with quantitative data
3. Buttons on the camera, instead of (only) via the software
4. Possibility to measure the same spot, at a prolonged timeframe
5. Possibility to measure the same spot, at different times
6. Measure deeper in the skin
7. Being able to measure at other locations than sublingual
8. Usage of (fluorescent) nanoparticles to help visualise the flow
9. Combining the (quantitative) output of the camera together with other biomarkers, depending on the intended therapy

Possible new applications

The participants were asked which new applications based on microcirculatory data could be implemented, including potential therapies if the technical limitations are solved in the future.

1. Fluid resuscitation - Administration of fluids and electrolytes to the body to restore lost blood volume to optimize tissue perfusion and ultimately the tissue oxygen delivery.
2. Further research on microcirculation - There are still many grey areas regarding the knowledge of microcirculation. Cause and effect relationships between the microcirculation and its affecting factors (i.e. illness, therapies) need to be established and validated before clinical applications can be proposed.
3. Studying the dynamic flow or movement by tracing individual molecules in the blood flow.
4. Monitoring the microcirculation along with other biomarkers.
5. Integration into routine patient checkups.

Data from the observational study

Ideally, the interactions between the user and the camera system should also be observed directly. A training session for two new users of the CytoCam system was made available to attend and make the observations. Not only did this give a new and additional perspective, but it also showed how inexperienced users handled the camera and software system.

The pair of participants practised acquiring sublingual video samples on each other and also on themselves. The video output of the computer of the camera was displayed on a big screen. How to use the software was also shown.

The most interesting observations are as follows:

- It was shown how difficult it was for the (inexperienced) participants to hold the camera perfectly still as the video image kept moving around. Even a video sample of several seconds seems challenging.
- The software is very technical and has a lot of settings, which is good for setting up different types of research studies. However, this increases the learning curve. There are a lot of steps and actions that need to be memorised.
- Moving the image around to find a suitable measuring location showed that the microcirculation (under the tongue)

Other methods

Other ways were used to get feedback on the current CytoCam system. Although these methods were less conventional, they gave valuable insight and summed up the needs well.

Webinars

The European Society of Intensive Care Medicine, also known as ESICM, is an association of more than healthcare professionals. During this project, several live webinars were attended and archived webinars were studied with the intent to gain more insight into industry trends and relevant needs or problems of healthcare professionals.

1) "Which haemodynamic tool?" [2021][67]: Two speakers discuss which methods and tools should be used in the operating room and intensive care unit for hemodynamic monitoring and therapy guidance. At [00:37:10] in the recording, Xavier Monnet (Professor of intensive care, Paris) mentioned that the tools for the ICU need to measure in real-time, continuously and be very precise in order to show the changes over time.

2) *"What really matters in septic patients?" [2023]*[68]: Two speakers discuss antibiotic treatment and resuscitation targets for septic patients. Marc Leone (Professor of Anesthesiology and Critical Care Medicine, Marseille) highly recommends using microcirculatory data at the bedside [00:43:05] for fluid resuscitation. At [00:34:00] he mentions hand-held vital microscopes being one of the few bedside tools, but that these are not incorporated into routine practice. As this webinar was attended live, there was a chance to ask the experts questions at the end of the webinar. The opportunity was used to ask whether there is a place for sublingual microscopy in the ICU and whether this type of monitoring can be used for resuscitation targets and therapy guidance in the future [00:59:00]. Marc's first response was that the microcirculation should be targeted and that there needs to be some clue to resuscitate based on microcirculation. His second response was that it is currently not easy to translate the imaging into clinical practice immediately.

"We need something at the bedside, very simple, very direct, so we can change the management immediately" - Prof. MD Marc Leone

Social media

The picture of Figure 22 was posted on Twitter. Another intensivist mentioned the following as a response to that picture[40]:

"The challenge would be to modify it into daily day to day hand-held procedure to be able to replicate it during the rounds or see the hourly trends to predict improvement or worsening hemodynamics! Would love to see if anything concrete can be developed in that direction!"

Conclusion: There are several areas that can be improved upon the CytoCam system. The most significant user pains are caused by the hand-held operation and the mouth being a difficult location for measurements. Usability needs to be improved both on hardware design and software implementations in order for a more widespread clinical implementation.

A need for real-time automatic and continuous monitoring of the microcirculation at the bedside has been expressed by multiple experts.

3.2 Strategic analysis

A great product does not guarantee a successful business. And without a healthy business, the product won't be on the market for long. This section covers the internal company analysis and competitor analysis.

Company internal analysis

After learning about the importance and potential of microcirculation Braedius Medical was founded in 2011 by Frank Messie with the aim of developing a microscopy video camera using state-of-the-art technology.

The core of Braedius Medical BV consists of two people. Their backgrounds lay in mechanical engineering and industrial product design. Because the small company can not manufacture and develop everything in-house, the company partners with specialised organisations to deliver a high-quality product utilising high-tech manufacturing and development methods. This allows Braedius Medical to develop and produce cutting-edge products with very low volume. The company acts as a system integrator where it can leverage the specific competencies of its partners. Overall hardware and software design is done in-house, but manufacturing of the components, electronics and software development is sourced from various companies in Europe.

The current business model is summarised in the form of a business model canvas (Figure 46).

Financial insights

- Most of the revenue is made by the sales of the CytoCam camera.
- The camera costs ~€4.000 to manufacture including assembly.
- Training and auxiliary products have very narrow margins.
- Most of the costs go to salaries, both internal and outsourced.
- Due to constant R&D costs, either to improve products or to adapt to external forces (e.g. chip shortage), the company operates at the break-even point.

Points for improvement:

- The website is currently the only form of marketing and looks dated, it should be improved in terms of aesthetics, navigation, information and customer onboarding.
- The company relies mostly on one product for its revenue: the CytoCam camera. The sales of the camera also directly influence how much training and peripheral products will be sold.
- No dedicated salesperson is busy with customer acquisition or account management.
- Little to no money left for growth (e.g. adding staff).
- Increasing scales of economy: the low number of cameras produced (~20/year) means the parts are relatively expensive to produce. Doubling the order quantities should roughly save 25% in parts costs.
- Giving training to bigger groups should also yield bigger margins. The cost to rent out the location and the time to give the training to a small group should be similar to bigger groups.
- Software is included with the purchase of the camera. It is not uncommon anymore to have customers pay for software (updates).

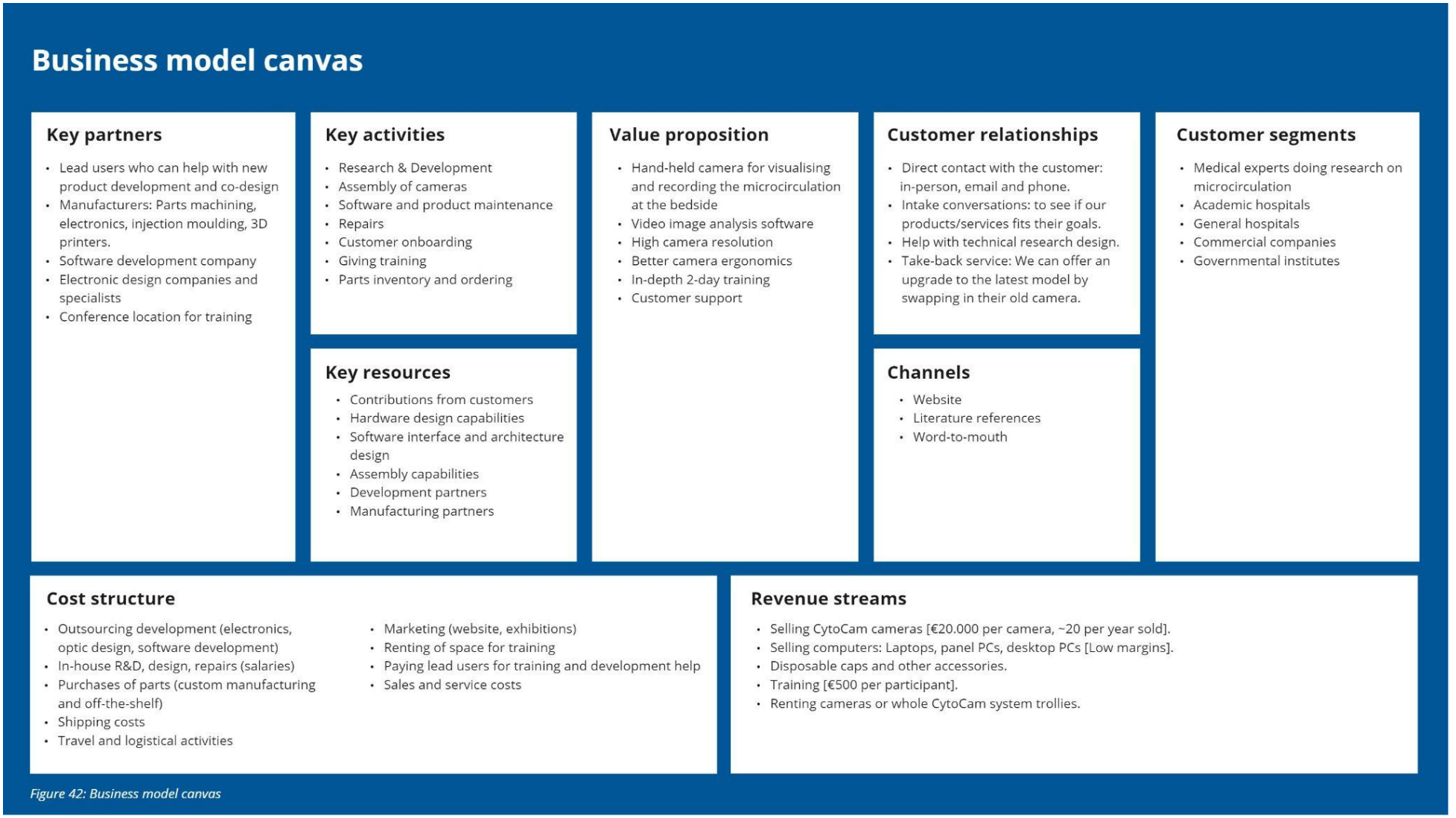


Figure 46: *Business model canvas of Braedius Medical BV.*

Competitor analysis

The goal of identifying and understanding the competition should also give insight into the relative strengths and weaknesses of your company. Combined with other factors opportunities and threats can be unveiled.

In section *3.2 Technology landscape* other techniques were explored to see if these were superior and could therefore render videomicroscopy obsolete in the future. It was concluded that the technique used for hand-held vital microscopes has added benefits compared to the other devices. However, other companies exist that develop hand-held vital microscopes.

MicroVision's Microscan was concluded to be the direct and biggest competitor. Microcirculation Academy and Active Medical are also worth mentioning as they offer video analysis and training services. The other companies are either not operational anymore, use outdated technology or do not compete in the same market.

About MicroVision

Founded in 2004, the Amsterdam-based company has a team of three people consisting of a CEO, a Chief Science Officer and a medical software engineer[39]. The CEO has a background in intellectual property rights and the CSO has a degree in medicine with a specialisation in microcirculation and medical device regulation[69].

About Microcirculation Academy and Active Medical

After doing research it has been found out that Professor Can Ince, a researcher in the field of microcirculation, is the main figure behind both these companies. Microcirculation Academy and Active Medical both use the same software for video analysis called MicroTools. Already in 2013, it claims to have real-time analysis capabilities[70], but this can not be confirmed as no evidence has been found in literature or real-world scenarios.

Comparing cameras

MicroVision's MicroScan USB3 (2018) is currently the closest competitor to Braedius' CytoCam Model 4 (2023). Their latest camera was shown to have better image quality compared to their first model in a study from 2020[34]. No study exists yet comparing the latest camera from MicroVision and Braedius Medical. However, comparing the technical specifications and overall design suggests that the CytoCam Model 4 is the superior camera (Appendix A). Price of the MicroScan USB3 is about 15% more expensive than the CytoCam, which is around 20.000 euros.

Figure 47: (Left) MicroScan USB3; (Right) CytoCam

Comparing software

A comparison of CytoCamTools (Braedius), AVA (MicroScan) and MicroTools (Microcirculation Academy and Active Medical) by directly testing the software could not be done as acquiring the competing software is not possible. There are also no studies comparing the software suites. The capabilities of the three options seem to be very similar. However, AVA5, the latest version from MicroVision has a more

updated user interface and also guides the user through the analysis procedure. On the other hand, CytoCamTools is open-source, which allows its users to know how the data is processed. Little is known about, Microtools. This software is used as part of an analysis service, meaning, users don't have access to this tool themselves. This can be seen as a positive or negative thing.

Comparing services

Braedius offers extensive two-day training for its customers, complete with catering and lodging in the same complex as the training location. The company also tries to stand out in its customer service with its technical support and option to modify the camera to the user's wishes. MicroVision allegedly doesn't put as much emphasis on their service or training. Little is known about the quality of the training and other services of Microcirculation Academy and Active Medical, so no statements can be made on that.

Strengths and weaknesses

All of the mentioned companies consist of a small team of very few people. However, the expertise and backgrounds of the people running the companies differ from each other. The strengths and weaknesses of Braedius will be covered here.

Strengths

Braedius has more in-house capabilities in terms of hardware development as the core members have a background in mechanical engineering and product design. This can be seen in the more frequent camera updates and more advanced features.

Weaknesses

- Unlike MicroVision, Braedius does not have an in-house software developer. The company has external partners, but this also results in significantly more expensive development costs.
- The sales channels can be improved. Currently, the website is the only resource for customer onboarding. Various people were asked about what they thought of the website, and they responded with it looking dated and not easy to navigate. MicroVision's website has a more modern and professional look. Furthermore, the website of the latter does a better job of trying to sell its products. Active Medical and Microcirculation Academy on the other hand can take advantage of Professor Can Ince's influence and network.

Conclusion:

- ***The main competitor is MicroVision.***
- ***Microcirculation Academy and Active Medical also compete with Braedius Medical as they offer video analysis services.***
- ***In terms of camera hardware the MicroScan USB3 from MicroVision seems to be the only device that poses a real threat to the CytoCam.***
- ***There is much more competition in regard to software as there are other solutions available that are just as, if not more capable than the CytoCamTools software suite.***
- ***Regardless of technical specifications, the CytoCam and comparable hand-held vital microscopes all suffer from the same limitations. However, this can also be seen as an opportunity. Instead of marginal improvements, a more radical solution that solves the inherent problems of these can be developed for a long-term competitive advantage.***

3.3 New context analysis

Braedius Medical and its direct competitors currently serve the microcirculation research niche market. The attractiveness of this market will be assessed and potential new markets will be explored.

Current market attractiveness

Both the customer analysis and literature indicate that the CytoCam is predominantly used for research purposes. In order to make decisions on the direction of the new product development strategy, the current market will be assessed on whether it has enough potential to sustain the growing ambitions of Braedius.

Market Size

The camera systems are usually sold if a new research initiative requires the use of it. This also means that only one or two cameras are being sold to that customer. Although 20 cameras per year is not a direct reflection of the market size, due to the current passive customer acquisition strategies, it is a good indication of the small size. Even if there are a lot of researchers or institutions who want to study microcirculation, they don't all have the funds to purchase it.

Buying power

Because of the nature of the current use of the CytoCam, most customers require a research fund to purchase the camera. Because the camera is not used for clinical therapies, it is not funded by e.g. healthcare insurance funds. This renders the number of potential customers that can actually purchase the expensive camera to a small group. However, sometimes small groups can grow into a large amount.

Market growth

It is difficult to acquire direct metrics on the market growth of this niche market. However, an indirect estimation can be made by looking at the number of publications made related to microcirculation studies. Since most cameras are used for research, the output of these studies is usually scientific papers. An increase in papers related to microcirculation can also indicate a growth in the interest in using handheld vital microscopes.

Google Scholar, app.dimensions.ai, and elsevier.com were used to acquire the data for publications. The results of this study can be found in Figure 48. "Microcirculation" was used as the keyword and the range was set between the years 2013-2022.

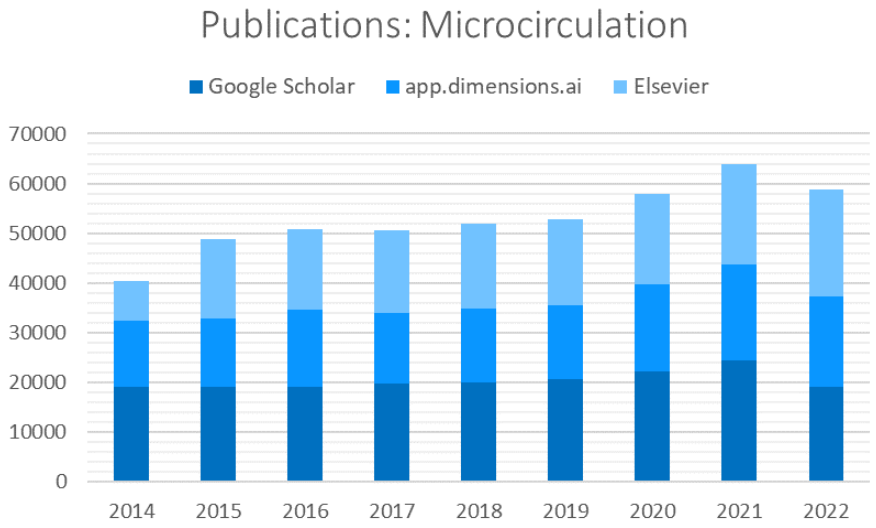


Figure 48: *Stacked bar chart representing the publications per year for the search term "microcirculation".*

The data and charts from these sources suggest that the yearly number of publications regarding microcirculation in the last decade has been fairly constant, although a bump starting from 2020 can be seen in the chart. The hypothesis for this would be that it has to do with the COVID-19 pandemic as there has been an interest in how the virus affects the microcirculation. To see if this is correct, a new search will be done with the keywords: "microcirculation + covid" (Figure 49).

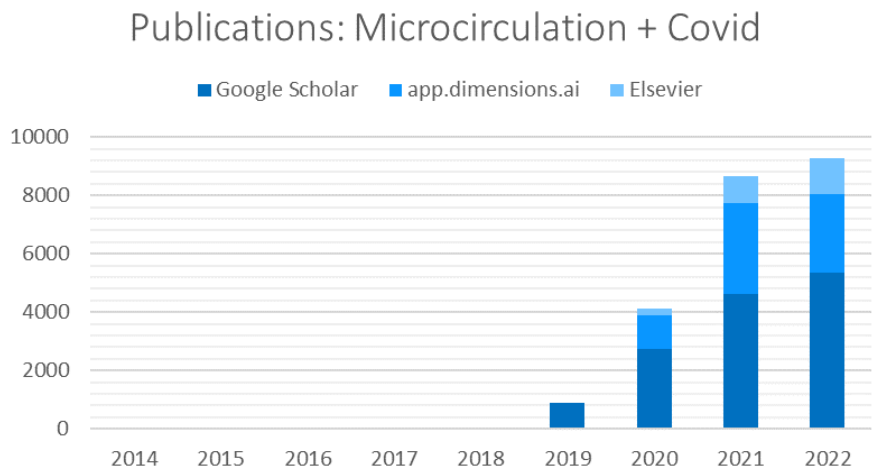


Figure 49: *Publications for Microcirculation + Covid.*

From the new search data, it can be assumed that the bump was caused by the covid related studies. By the end of 2022, this surge also is starting to decrease again. From the new search data, it can be assumed that the bump was caused by the covid related studies. By the end of 2022, this surge also is starting to decrease again.

Conclusion: The microcirculation research market is regarded to be not very attractive based on the following insights:

- ***Very small niche market***
- ***Limited customers that can afford to buy the camera system. One of the participants of the interview mentioned that there are many people that want to do research on microcirculation, but there are no funds to allow them to do their research.***
- ***No market growth prospects***

New market opportunity

If the current market can't accommodate the business growth, the logical next step would be to look at other markets. In the project brief three potential markets have already been outlined:

- Intensive care unit
- Hyperbaric oxygen therapy
- Varicose veins therapy

The potential markets are assessed by the following metrics:

1) *Relevancy:* Is there a market pull? Is there evidence for an unmet need that can be solved by the technology? Do they want to pay? Can they pay for the product/services?
2) *Market size:* Are there enough customers?
3) Market growth: Are there enough customers in the future?

The three potential markets are explained and analysed on their market attractiveness in Appendix E.

Conclusion: The Intensive Care market came out to be the most attractive market based on the following insights:

- ***With over 70.000 ICU beds in Europe and over 80.000 beds in the USA, it is the largest market out of the three. The need for intensive care is also growing.***
- ***The intensive care unit utilises cutting-edge and expensive equipment. Furthermore, a clear market pull for bedside microcirculatory monitoring has already been shown.***

The hyperbaric oxygen therapy market should not be disregarded completely as it also has shown a market pull, good market-technology fit and decent market size with steady growth over the last few years.

The varicose vein treatment market came out as less attractive due to the unlikeliness of videomicroscopy being able to bring added value to their current established routine and the small market size.

Value innovation

In order to be successful in the target market, it is imperative that 1) the technology can deliver substantial value to the market and 2) the technology is implemented in a manner that is well suited to the users and context.

Several attempts have already been made to introduce microcirculatory data to the ICU context. Examples are hand-held vital microscopes and other technologies such as NIRS. Even though efforts have been made to improve the usability and technical abilities of these devices, these are still considered compromised options. NIRS technology is becoming more accurate and is already used for several clinical applications, however, the lack of observing microcirculatory alterations such as heterogeneity is still a shortcoming to consider it a complete solution for microcirculatory monitoring. Technical improvements have also been made to hand-held video microscopes resulting in better image quality. Nonetheless, significant limitations remain with the usability, which is inherent to the hand-held operation and also the lack of real-time data output. In 2021 a solution by Veira[71] has been proposed for hands-free operation. It involves a brace-like contraption for the patient's head to which the HVM camera can be affixed (Figure 50).

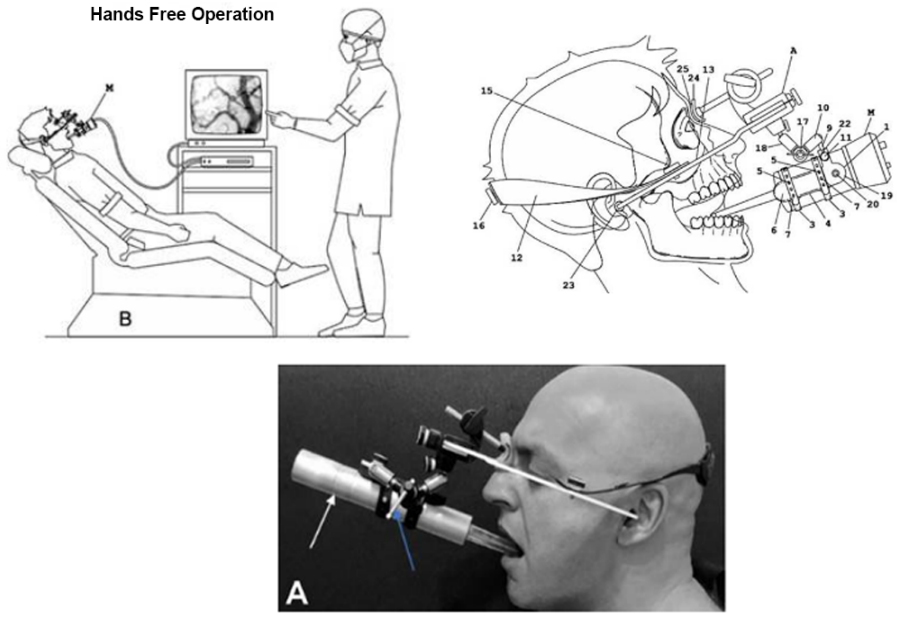


Figure 50: Hands-free operation method as proposed by Veira[71].

Even though the data Veira presented by comparing test results with and without the hands-free contraption suggests a significant improvement by using the contraption, it is not a convincing solution. Since the decision has been made to target a new market, a sustainable strategy has to be made that aligns with the company's goal, resources and capabilities. The devices used in the ICU are predominantly developed by big corporations with significantly more resources and brand awareness. For a small company like Braedius, it will be almost impossible to directly compete with the likes of Medtronics or Siemens. On the other hand, similar small companies that currently compete with Braedius in the handheld video microscopy market should not be given the chance to catch up. Therefore, a Blue Ocean strategy will be pursued. Unlike Red Oceans, where companies compete in existing (saturated) markets, Blue Oceans are new markets that have yet to be defined. This means that new demand has to be created and that there will be little to no competition.

Value innovation by Blue Ocean framework:

- ➔ ***Eliminate:*** *i) Analysis downtime for quantitative output ii) image artefacts*
- ➔ ***Reduce:*** *i) User-based errors ii) Operational waste iii) Required training/exercise to understand and successfully obtain microcirculatory images and data*
- ➔ ***Increase:*** *i) Depth of measurement ii) locations of measurement iii) Ease of use*
- ➔ ***Create:*** *A system that can easily and continuously acquire automated microcirculatory data in real-time without hand-held operation. Measurements can be done over the span of days and at the same location. The data is displayed in such a way that it can be interpreted at a glance by medical professionals.*

New context analysis: Intensive Care Unit

The information for this part is gathered from the following sources:

- Literature and desk research
- Information and training videos for ICU nurses and doctors
- Field research: Amsterdam UMC (location VUmc) and LUMC were kind enough to give a guided tour through their intensive care unit departments and show the ICU rooms. Observations and commentary by the staff were noted down.

In order to successfully develop and integrate a new technology or solution, the context needs to be thoroughly understood. This section will dive deeper into the technicalities and specifics of what is going on in the ICU departments. As mentioned before, the intensive care unit is meant for patients with serious illnesses or injuries requiring constant, specialised and intensive care. Most major hospitals have intensive care which is the highest advanced and critical care. In the following sub-sections, the various relevant components of the ICU will be explained.

Most common diseases

The hospital of Ottawa[72] states the following diseases or cases to be the most common for ICU admittance:

- Sepsis
- Traumatic Brain Injury
- Shock
- Stroke
- Ruptured Brain Aneurysm
- Trauma

- Post-operative Intensive Care
- Cancer-related Intensive Care
- Heart Failure
- Respiratory (Lung) Failure

This list was used as a search space to find the most impactful potential applications for videomicroscopy in the ICU.

ICU professionals

The intensive care units are staffed with highly specialized medical and supporting staff. The professionals that are most likely to interact with the new concept are outlined below:

Medical staff

- Intensivists: These critical care physicians oversee the majority of the patient's care and decide upon treatment, testing, procedures, consultations, etc.
- Resident doctor (senior and junior): These are doctors in training that help the intensivists with various tasks such as patient monitoring and evaluation, documentation and coordination (conversing with staff, patient and patient's family).
- Nurses: Monitoring patients, administering medications, providing basic needs assistance, charting care, and responding to emergencies are some of the responsibilities of ICU nurses.

Support

- Medical technicians: They're responsible for maintaining equipment used by other healthcare professionals.

Devices

It is important to be aware of the equipment and devices that are already being used, as these need to be taken into account to avoid incompatibility with the new device concept.

An overview of the most common devices used in the ICU is shown in Figure 51. A more extensive list of devices, their functionalities and the location of interface with the patient's body can be found in the appendix.

Figure 51: *Common devices used in the ICU. (1) Patient monitor, (2) bed, (3) ventilator, (4) infusion pumps, (5) tube feeder, (6) supply unit.*

Many of these devices are attached to the patient's body in the form of sensor probes, catheters, tubes or masks as they monitor various markers and administer or extract fluids and gasses. The real estate of the patient's body is limited and some devices require to occupy a certain body part. The various locations corresponding to ICU devices have been mapped on a body (Figure 52). Literature[73, 74, 75, 76] and images and videos of ICU patients were used as data sources.

New locations of measurements

As concluded in *section 3.1*, the mouth is a difficult location for video acquisition due to anatomy and physiology. Tubes and other devices going in or surrounding the mouth also increase the difficulty of manoeuvring the hand-held camera (Figure 52). Therefore, a new location for easier video acquisition will be explored. This was done by looking at where the other techniques such as NIRS and Laser Doppler Flowmeter measure microcirculatory data. It was concluded that these measure cutaneous (skin) microcirculation. A pros and cons comparison between cutaneous and mucosal (e.g. mouth) was then made (Appendix F). Cutaneous microcirculation was then deemed as an easier target for video acquisition. After looking at many images of probe applications, the thenar eminence (base of the thumb) and the underside of the forearm came out as the most popular locations for measurements. This was confirmed in literature, with the forearm being the superior location because of its superior vascular response[77]. Looking at Figure 46, the forearms and thumb are not yet occupied by other devices.

New measurement locations: Forearm and thenar eminence.

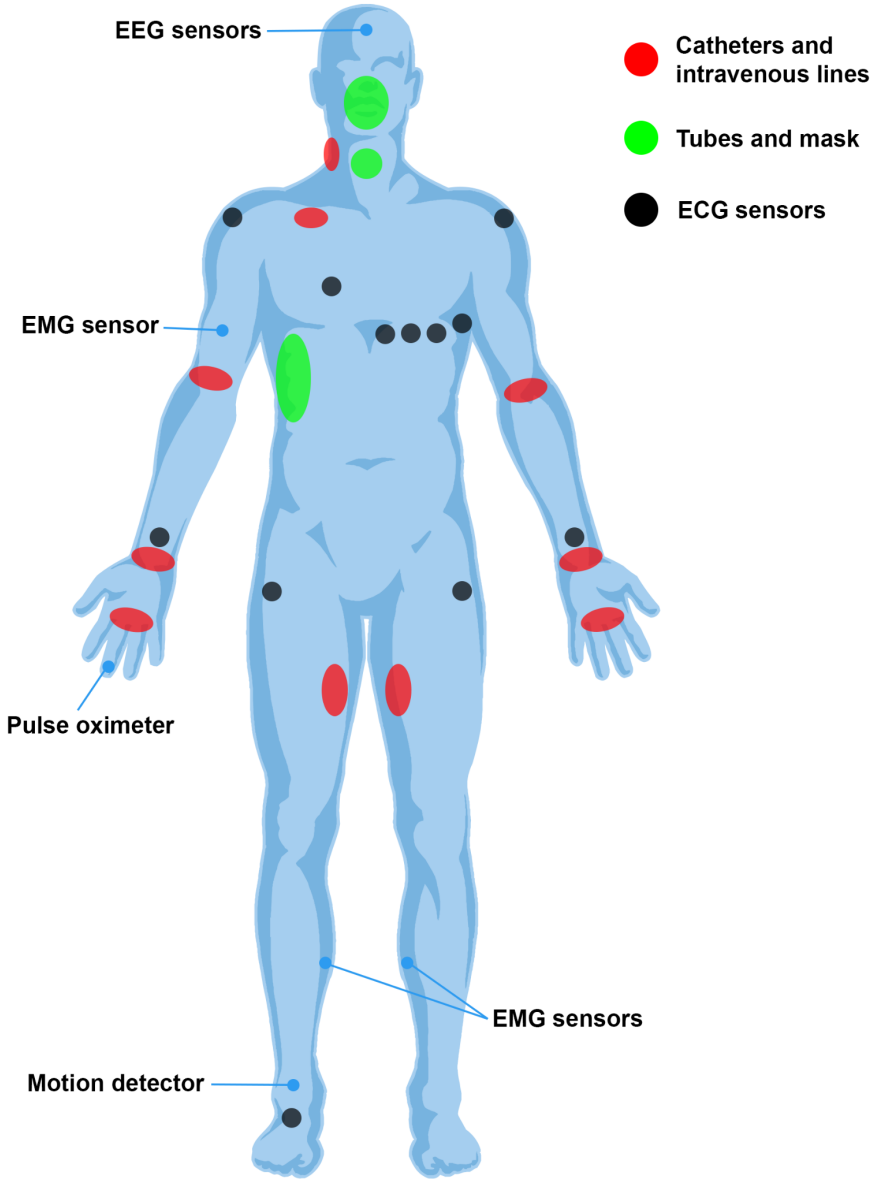


Figure 52: *Locations on the patient's body occupied by medical devices.*

Room design and dynamics

Over the years ICU rooms have evolved from large halls with many beds or cramped rooms to more spacious single- or double-bed rooms. It is important that the staff has enough space to treat the patient and is not obstructed in their workflow. Most devices sit stationary in the supply units or are integrated into trollies that can be pushed around.
Modern ICU layouts are flexible for improved accessibility to the patient. For example, the bed sits on wheels and can be reconfigured. In Figure 53 a top view is illustrated to showcase two different situations.

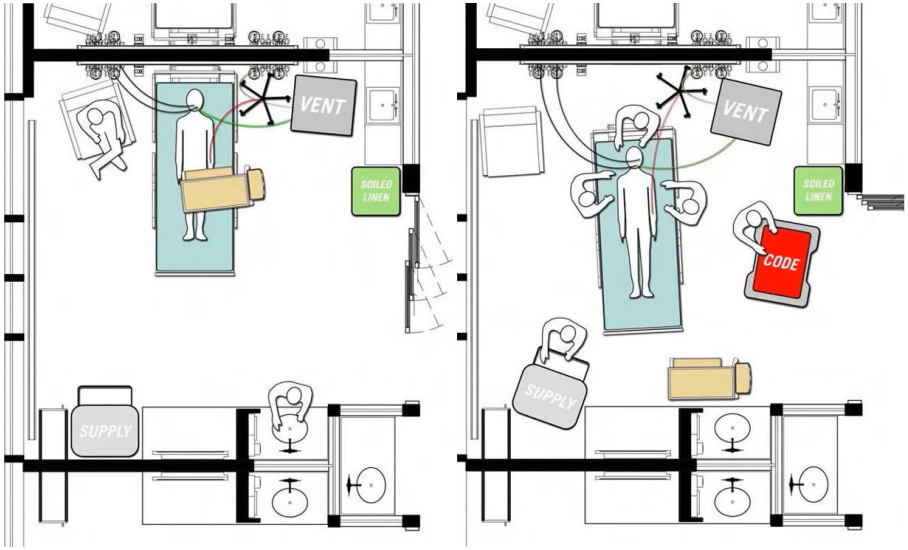


Figure 53: Top view of an ICU room depicting two situations.

It is important to note that in reality, the ICU rooms look nothing like the pictures shown in Figure 51 during use. Due to the critically ill state of the patient, rapid deterioration can occur at any time. This means that constant monitoring is required of many different biomarkers. As a result, the patient is hooked up to a large number of devices that make a lot of noise and emit bright lights. A cluster of many wires is used to transmit the data from the probes in the patient to said devices, along with tubes that administer medication, fluids or oxygen. More representative examples can be seen in Figure 54.

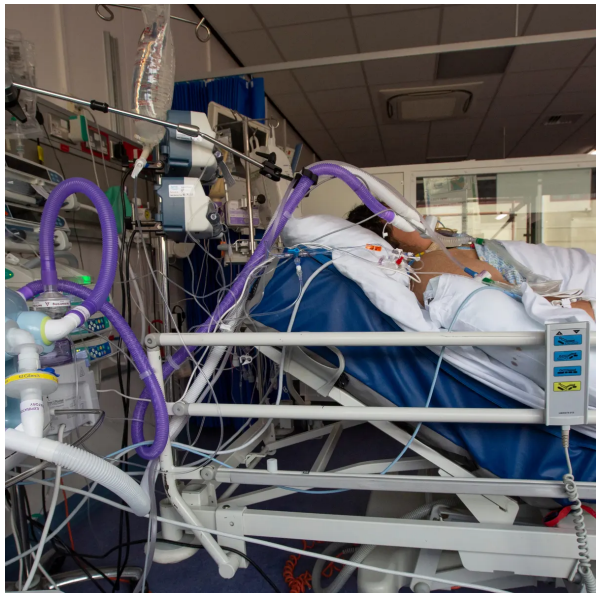


Figure 54: A large number of wires and tubes to the patient need to be managed.

As you can see, ICU caregivers already have to deal with a large number of devices. It is therefore paramount that the new device does not add complexity or workload. The healthcare professionals' aim is to treat the patient, and not to constantly manage the devices, which would be counterproductive.

Conclusion: One of the aims of the new device is its optimised usability for the medical and supporting staff. This means it should be easy and quick to:

- ***Prepare the device for use***
- ***Administer and remove the "probe/sensor" on the patient***
- ***Read and interpret the data***
- ***Clean the device***

Furthermore, the new device should not get in the way of existing devices used in the ICU or cause significantly more clutter.

Potential new applications for the Intensive Care Unit

Studies have demonstrated that microcirculatory changes are superior to conventional systemic parameters at predicting clinical severity, response to therapy, and prognosis, as they assist in recognizing the severity of clinical conditions, the response to therapy, and prognosis[22].

Based on the research of this project, three possible applications have been identified which are the most beneficial. These are chosen based on clinical evidence and impact.

- **Early sepsis detection:**
    - Sepsis is the most common cause of admission to an intensive care unit and the most expensive cause of hospitalisation[78].
    - The mortality rate for septic shock is between 30% and 40%, but mild sepsis is usually recoverable. In addition, severe sepsis increases the likelihood of recurring infection[79] and can affect the patient in the long term such as late mortality, immune dysfunction, secondary infections, impaired quality of life, and unplanned readmissions[80].
    - There is an early manifestation of microcirculatory malfunction in the pathophysiology of sepsis, with the severity and prognosis of the condition being determined by microcirculatory dysfunction. This condition is associated with increased heterogeneity of perfusion and decreased capillary density[81]. However, identifying and treating sepsis as early as possible has been a challenge for emergency care and critical care physicians.
    - Among techniques that can observe the microcirculation videomicroscopy has the unique ability to detect perfusion heterogeneity, an early indicator of sepsis.

- **Precision medicine for haemodynamic management:**
    - Fluid resuscitation and admission of medicine such as inotropes (affect heart pump rates) and vasopressors (constricts vessels) are common therapeutic procedures in the ICU.
    - These procedures can be used to increase systemic hemodynamic pressure, a common target goal to treat conditions like (septic) shock. It is used as an indirect biomarker for restoring vessel perfusion.
    - However, systemic parameters such as pressure do not always correlate with microcirculatory parameters and are therefore not adequate for therapy guidance[82].

- Administering fluids and medicine can improve systemic hemodynamic values, but can also impair the microcirculation. Incorrect dosage and overdose have led to death in the ICU[83].
- The end goal should be perfusion, not pressure. It is therefore important that the effects of the medicine are monitored on a microcirculatory level for more accurate therapy guidance by observing the direct effects.

- **Post-incident recovery monitoring**
  - Patients can be admitted to the ICU for recovery after a major procedure such as surgeries (e.g. organ transplantations) or extracorporeal membrane oxygenation (ECMO).
  - After cardiac surgery, 25–40% of patients experience circulatory shock and perioperative organ injury despite modern resuscitation practices[84].
  - Even after optimal macro-hemodynamic parameters are achieved, some patients still suffer from microcirculatory dysfunction, which increases postoperative complications[85].
  - The feasibility of monitoring tools for evaluating microcirculation in routine clinical practice is still insufficient[7, 9].
  - Studies have shown that parameters of microcirculation, measured by hand-held vital microscopes, reflect a recovery from cardiogenic shock, operations and predict successful weaning from ECMO. A lower rate of morbidity and mortality is associated with sustained microcirculatory perfusion[86].
  - Monitoring the microcirculation along with the systemic parameters can give critical insights into the recovery of the patient.

The ability of these technologies to provide uniform and reproducible measurements across different clinical settings, decrease the use of hospital resources, and improve clinical outcomes would strengthen the role of peripheral perfusion monitoring in the bedside evaluation of hemodynamic status[87].

Conclusion: Both the qualitative research and a multitude of studies have concluded that there is a need to include microcirculatory data in high-risk surgeries and critical care.

The cases where videomicroscopy has the biggest potential of making a positive impact in the ICU are:

- ➢ ***Early sepsis detection***
- ➢ ***Precision medicine for haemodynamic management***
- ➢ ***Post-incident recovery monitoring***

4 Conceptualisation phase

4.1 Requirements design

After all the data has been gathered, the decisions that have been made based on the research can be used to formulate the requirements for the to-be-developed concept. The product requirements document is meant as an alignment tool for all stakeholders in the development process of a new product. It is a living document and can therefore be changed throughout time. The version that will be shown in this project can be seen as the first iteration. The design phase will use the requirements documents as a guideline. Each project phase will undergo testing and validation. This development methodology is called the V-model and is often used for medical device development. A simplified version of the v-model has been made to fit the scope of this project and can be seen in Figure 55. The requirement documents consist of three main parts: business requirements, user requirements and product requirements (Figure 56).

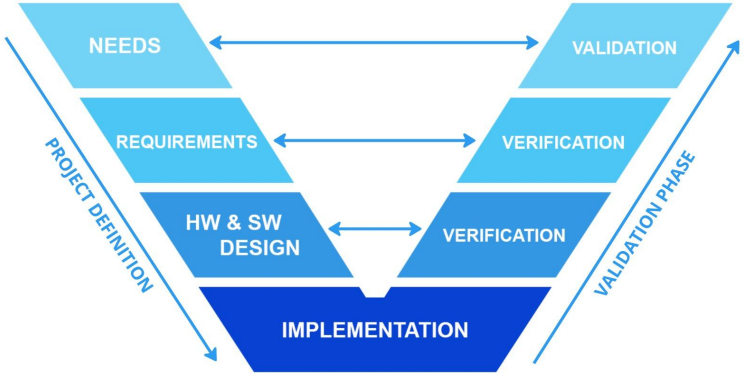


Figure 55: *V-model representing the approach of this project.*

Scope of the new product

User problem: No complete solution exists that can monitor the microcirculation in a clinical context.

Opportunity: Create a system that can continuously monitor cutaneous microcirculation on a cellular level in real-time for clinical applications.

Context: ICU setting, critically ill patients.

Users: Intensivists, critical care doctors and nurses
User role: Monitor and interpret data to make clinical decisions. Apply sensors on the patient. Clean and store the device.

Features: Hands-free operation, automated continuous video analysis, real-time data display, quick and easy video acquisition without motion or pressure artefacts.

Technology: 1) Based on incidental dark-field videomicroscopy. 2) Using existing technologies/solutions already proven to work in a clinical context.

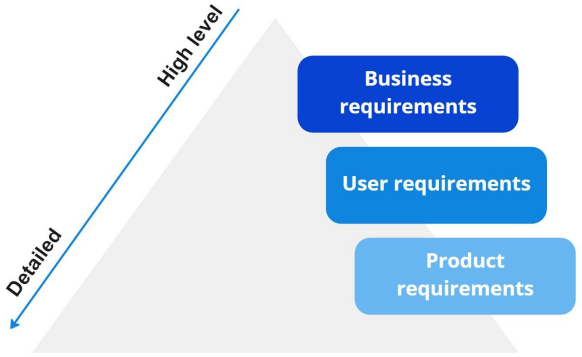


Figure 56: *The three areas that will be covered by the requirements document.*

Business requirements

Executive summary

Braedius Medical currently faces several challenges that are limiting the company's growth. Currently, the company makes enough money to keep afloat, but there is no budget left for adding staff or investing in other resources. The sales numbers of its products and services have not seen significant growth for the past years. The margins of the products and services are restricted by limited sales.
Braedius Medical needs to create a strategy to achieve sustainable financial growth.

Business objectives

By developing a new medical device for monitoring and observing the microcirculation of ICU patients, Braedius aims to achieve the following goals:

1. Create a novel product service solution that offers unique values and benefits to its target customers.
2. Diversify and grow revenue streams.
3. Enter a new market with a higher market potential.
4. Increase total revenue and profit.
5. Increase resources for R&D, marketing and employees.
6. Improve technology and knowledge portfolio.
7. Develop stronger branding.

The complete Business requirements can be found in Appendix G.

High-level user requirements

To summarize, the user, in this case, healthcare professionals working in the ICU setting, have the following needs:

- A solution that can visualise and analyse microcirculation in the skin automatically and continuously.
- Easy and quick to apply on the patient's body and also to remove.
- The patient does not have to be deeply sedated during video acquisition and monitoring.
- Video sample acquisition should be quick, easy and reliable: the device should prevent pressure and motion artefacts by design.
- Software is easy and intuitive to use. It should not complicate the usage, instead, it should help by guiding the users with the correct procedure and steps of operation.
- The interface displays the data in such a way that it can be interpreted at a glance and support the user with decision-making.
- Real-time, automated, and continuous monitoring/measurement is required and should be reliable and accurate. A delay of several minutes between the physiological occurrence and the display is acceptable.
- The solution is integrated into one system.
- Patient measurements and data need to be stored for longer periods of time, either locally or remotely.

High-level product requirements

- Hands-free operation
- Easy to clean with wipes
- Easy to apply on patient's body
- Easy to remove from patient's body
- Device can be left on the patient's body for multiple days
- Software guides user in the use-process (e.g. application of probe) to minimize mistakes
- Probe can be reapplied to the same exact location on the patient's body
- Data can be interpreted at a glance
- Does not get in the way of other devices in ICU
- Displays microcirculation on a cellular level with
    - High frame-rate (minimum of 95 fps)
    - High contrast (white background, black red blood cells)
    - Sharpness and clarity (defined object borders, no blurr)
- Measures and displays following quantitative biomarkers:
    - Total vascular density (TVD)
    - Proportion of perfused vessels (PPV)
    - Perfused vascular density (PVD)
    - Red blood cell flow velocity
    - Heterogeneity flow index
    - Tissue oxygenation
- Easy to store or put away when not in use

For all the detailed product requirements, please see Appendix H.

MDR safety regulations

A medical device's design must prioritise safety above all else. It is important for designers and manufacturers to take into account all potential risks and design devices to minimize these risks as much as possible.

Requirements are based on the following regulations or standards:

- Medical Device Regulation (EU MDR) 2017/745
- ISO 16142-1
- IEC 60601
- IEC 62366-1
- IEC 62366-2
- ISO 14971:2019

To determine the medical device class designation, we can use the following information:

Hardware: Class IIa

- Not used for in vitro diagnostics
- Non-invasive, placed on the skin for a duration of 60 min - 30 days
- Rule 10: Active devices intended for diagnosis and monitoring

Software: Class IIa

- Rule 11: Software intended to provide information which is used to take decisions with diagnosis or therapeutic purposes
- Software intended to monitor physiological processes

4.2 Concept design

Before starting the design phase for the concept, all the main insights are mapped onto an overview (Figure 57). It was used as a reference tool and to quickly communicate the project to other students who helped with the ideation phase.

Figure 57: *Overview of main analysis insights.*

Concept direction

It has been established that hands-free measurements of the underside of the forearm or thenar eminence will be one of the main features of the new concept design. However, a hands-free operation can be implemented in multiple ways. To save time and streamline the design process, this design choice is made early on.

Methods of fixation

A hands-free operation means the device is mounted or fixated so there is no additional support required from the user. For inspiration, other devices used in clinical applications were explored. Two potential solutions were found and a choice between the two was made by looking at their respective advantages and disadvantages.

Option 1: Articulating arm

A common way to have hands-free operation in clinical settings is to attach the camera or other type of tool to an articulating arm. Figures 30, 34, 35 and 58 show examples of this implementation. This arm can then be attached to the trolley, bed and ceiling. For this project the assumption is made to attach the arm to the trolley due to convenience and because the current hand-held camera is light and compact.

Option 2: Fixation onto the patient's body

Although not common for cameras, another typical way to mount sensors is to stick these directly on the patient's body. NIRS and Laser Doppler Flowmetry sensor probes are examples (Figures 28, 29, 33, 58).

The advantages and disadvantages of each option are shown in Figure 59.

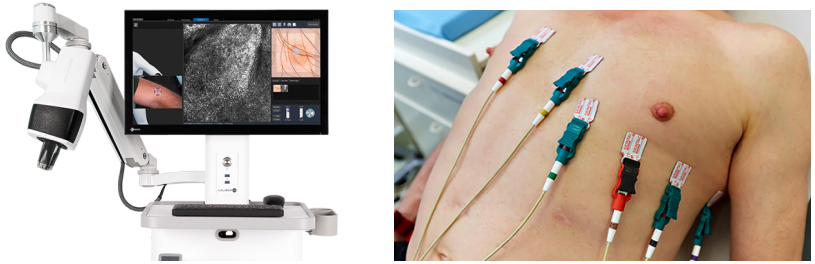


Figure 58: (Left) Articulating arm; (Right) Stick-on probe sensors.

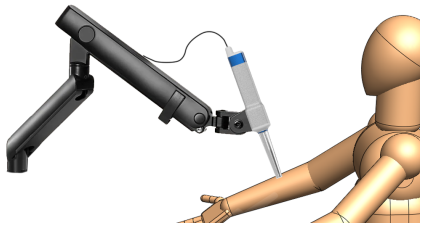
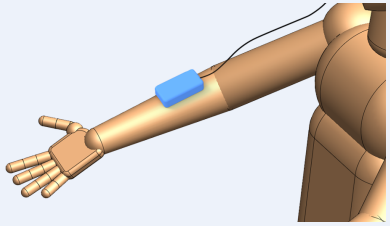
Articulating arm	**Stick-on fixation**
	
✓ Can re-use current CytoCam ✓ Lower development costs ✓ Shorter development time ✗ Patient can't move ✗ Setting the correct angle and pressure can be finicky	✓ Always stays on the same position relative to the skin ✓ No pressure artefacts ✓ No/minimal motion artefacts ✓ Easy application for user ✗ More elaborate and challenging development process

***Figure 59:** Comparing the advantages and disadvantages of the two fixation methods.*

Conclusion: Sticking the device directly onto the patient's body came out to be more favourable than attaching the camera to an arm. Therefore, a probe-like form factor was chosen to continue.

Ideation

After the direction of the concept has been chosen, a viable concept needs to be designed. To kick off the ideation phase, an inspiration board was made together with other students on Miro to explore existing solutions. This was then curated and edited afterwards (Appendix I).

Afterwards, the requirement documents were used to draft up a list of the questions that need to be solved in order to meet the requirements. These will be called Design Challenges. By working through these Design Challenges a viable concept will slowly be formed. Creating the list of Design Challenges was an iterative process and the order of the questions was continuously revised to represent the most logical and strategic chronological order of development. For the full list of Design Challenges and their respective sub-questions, please visit Appendix J.

Solving the Design Challenges

The main solutions that encompass clusters of the Design Challenges will be presented here. For an extended version with all the details such as all the found sub-solutions and choice argumentation, please visit Appendix K. The goal was to look for examples of existing solutions that were already proven for clinical application.

How to observe cutaneous microcirculation? (Covers DC1 - DC1c)

One of the key requirements for the feasibility of the chosen concept direction is to make videos of the microcirculation in the skin. This means the light needs to penetrate deeper into the tissue. The most straightforward solution was to use near-infrared light that resides in the optical window (covered in Chapter 2.3).

Steps taken:

- Talk with dr. ir. Ger de Graaf (TU Delft, faculty EEMCS), an expert in the field of optical spectroscopy for biomedical applications.
- Seek ouch which wavelengths are used in devices that investigate the microcirculation in the skin (Figure 60).
- Rudimentary tests with LEDs with different wavelengths (Figures 61 and 62).

Found wavelength [nm]	Based on	Source
685, 730, 770, 810, 870	LEDs used in NIRS tissue oximetry system by Edwards Scientific	Product brochure [88]
770 and 940	Respective peaks of deoxyhaemoglobin and oxyhaemoglobin within the near-infrared window.	Paper [89]
660 and 940	LEDs used in pulse oximeters. 660 nm for deoxyhaemoglobin and 940 nm for oxyhaemoglobin	Paper [90]

Figure 60: *Wavelengths used in various devices and found in literature.*

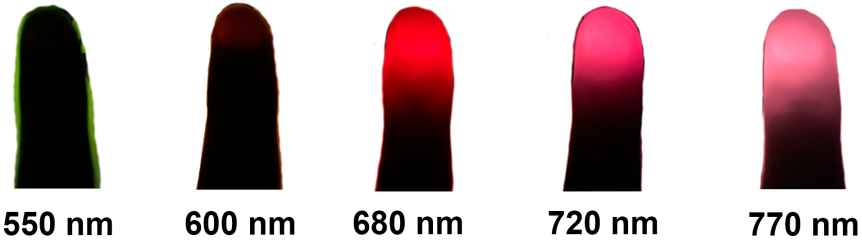


Figure 61: *Fingertips illuminated by LEDs with different wavelengths to see how much is passed through the tissue. Wavelengths above 800 nm were not picked up by the smartphone camera as it has an infrared filter. The longer wavelengths showed significantly better light transmission.*

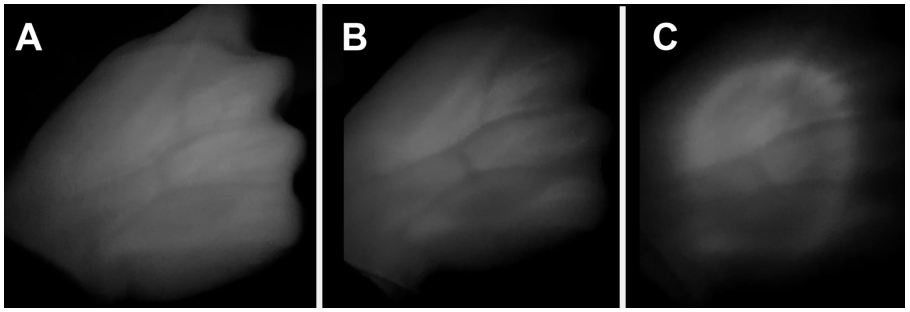


Figure 62: *The back of the hand was illuminated by LEDs with various wavelengths to see how well the veins would show. A: 680 nm, B: 720 nm, C: 770 nm. Unfortunately, 770 nm and up could not be well photographed by the smartphone. 720 nm (B) does show a significantly better contrast than 680 nm (A).*

No specific wavelengths could be narrowed down, but the conclusion from this study was to repeat this with the CytoCam to get a more representative result and also to be sure that the camera sensor can pick up near-infrared light.

What does the flow of data look like and how is it stored? (Covers DC2-DC4)

It is assumed the new concept uses the same core principle of the CytoCam system:

- A special microscope **camera** is used to acquire video samples of the microcirculation.
- The camera is powered and controlled by a **computer**, which also analyses the video samples made by the camera.
- The data output and interface are displayed on a **monitor**.

The microscope camera will be developed and manufactured by Braedius. The computer and display monitor can be sourced from other companies, but need to be carefully chosen to meet the high demands of the ICU environment. Features such as high processing power, dust-proof, fanless cooling, accurate colour display and medical-grade power supply should result in a dependable and safe system that can run continuously without maintenance.

Short-term data can be stored locally on the computer of the system. For long-term data storage, the system should be able to connect to the hospital's local network and upload the data to the servers. Figure 63 illustrates the system components and the data flow.

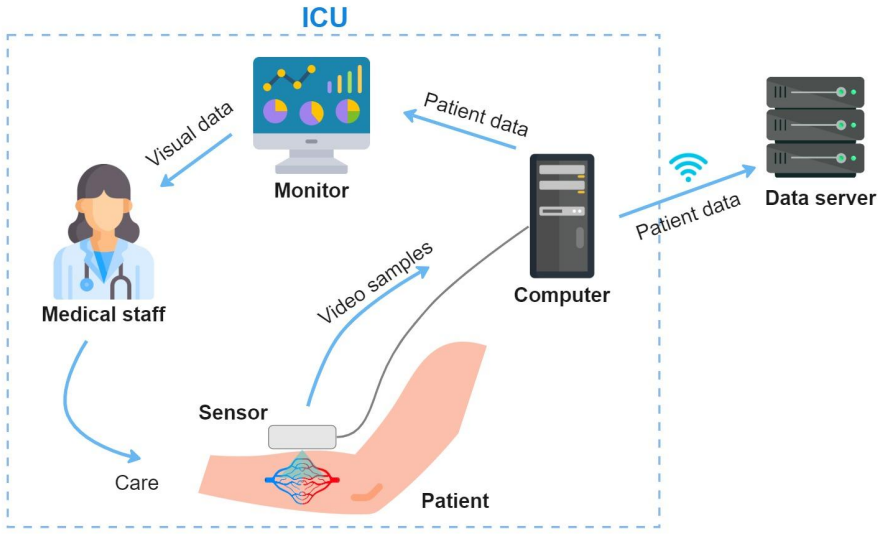


Figure 63: *Overview of the system components and the data streams.*

How to continuously monitor the skin microcirculation without heating up the skin? (Covers DC5-DC6)

Another key feature of the concept proposition is the ability to continuously acquire video samples and automatically analyse these for monitoring purposes. It is critical that the probe does not heat up the skin, as this will influence the perfusion of the microcirculation and therefore yield invalid data. Both the continuous video acquisition/analysis and heat management were solved by periodically filming short samples and optimising the time intervals. A representation can be seen in Figures 64 and 65.

Figure 64: *Proposed intervals of video capture. The red line represents the temperature change of the skin, which should be insignificant.*

Figure 65*: Timeline for the video capture, video analysis and data display output.*

How to fixate the probe onto the patient and facilitate reliable video acquisition? (Covers DC7-DC13)

One of the biggest challenges was to design a solution that reliably mounts the camera probe onto the patient's skin while eliminating video artefacts caused by movement, pressure and contaminants.

Prof. dr. Jenny Dankelman (Faculty 3ME, Biomechanical Engineering) helped with giving inspiration for possible methods on how to solve the sub-challenges.

Two solutions were chosen: Fixation by means of adhesion and by means of an adjustable strap (Figure 66). The probe itself is not directly mounted on the skin, but it will sit in a holder. This holder will be fixated onto the patient's skin allowing for easy removal and application of the probe while maintaining the same location of measurement.

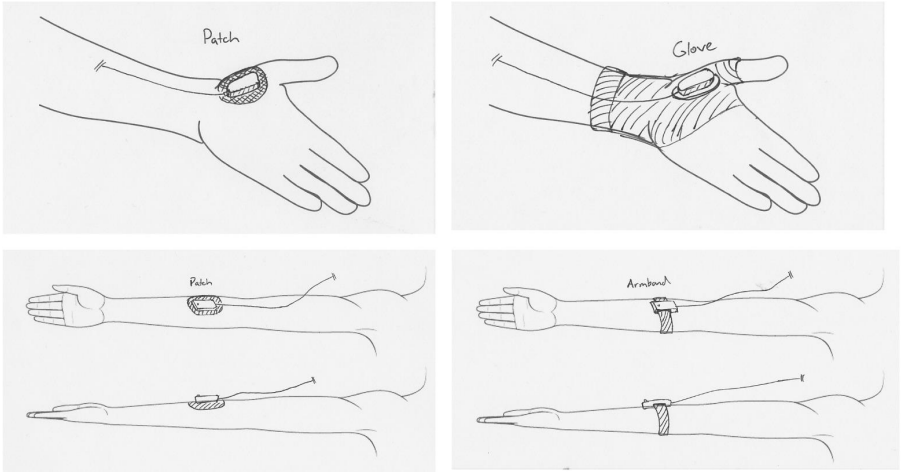


Figure 66: Adhesion and mechanic fixation.

A cleaning protocol for the skin and probe lens should remove unwanted contaminants and the probe holder will act as a barrier to seal off the entry for contaminants during monitoring.

Pressure artefacts are avoided by having the lens not touch the skin at all. Instead, it will utilise an immersion oil technique. The lens sits a fraction above the skin surface and paraffin oil is used as a transmission medium between the lens and skin to increase the aperture and prevent reflections from the skin. The lens is dome-shaped so possible air bubbles from the oil are moved aside, leaving no contaminants in the image.

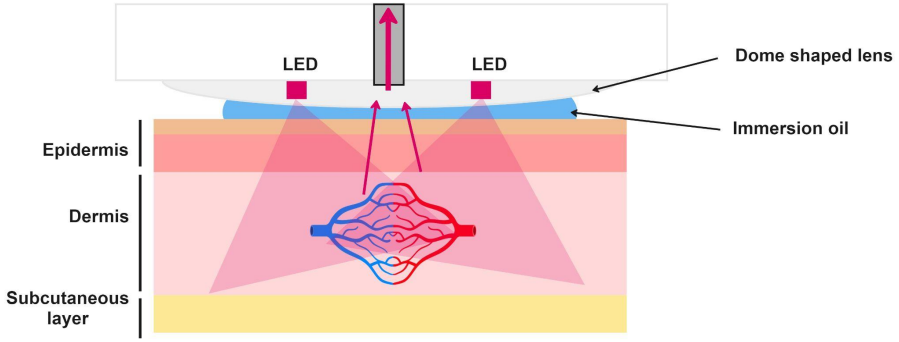


Figure 67: Detail of the camera probe interfacing with the skin tissue.

How to integrate the components into a compact probe? (Covers DC14-DC15)

Two implementations were made for the probe design (Figure 68). One variation has all the components in one bigger housing and the second variation divided the components into two housings: a very small one for the optical system and a bigger one for the PCB and other electronics. The latter implementation allowed for a much smaller sensor housing. The Classified Appendix shows the internal design.

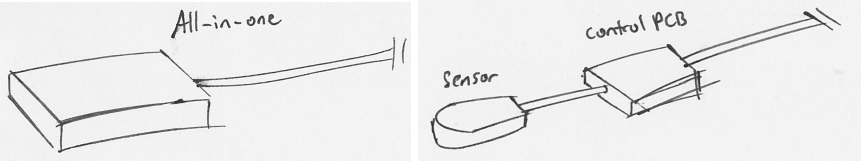


Figure 68: Two probe designs.

How to display the data and prevent user error? (Covers DC16-DC17)

By looking at existing interface designs for the ICU, a concept was designed for the software user interface. The main criteria were "at-a-glance" data interpretation and legibility from a distance (3 metres). Whether absolute values were important or rather trends monitoring were also taken into account for the visualisation of each parameter.

Next to being easy to use, the system should also guide the user through more involved steps or actions to prevent user error. Figures 69 and 70 show the screen designs.

How to integrate the system into the ICU? (Covers DC18-DC19)

A trolley system has been chosen to allow for a flexible solution that can be easily integrated into any type of ICU room layout. All components such as the display monitor, rugged computer and storage for the camera probes and accessories can be integrated into the trolley. There are various manufacturers such as Ergotron and Jansen Medicars that can provide medical trolleys suited for this purpose.

Figure 69: Data interface - healthy parameters.

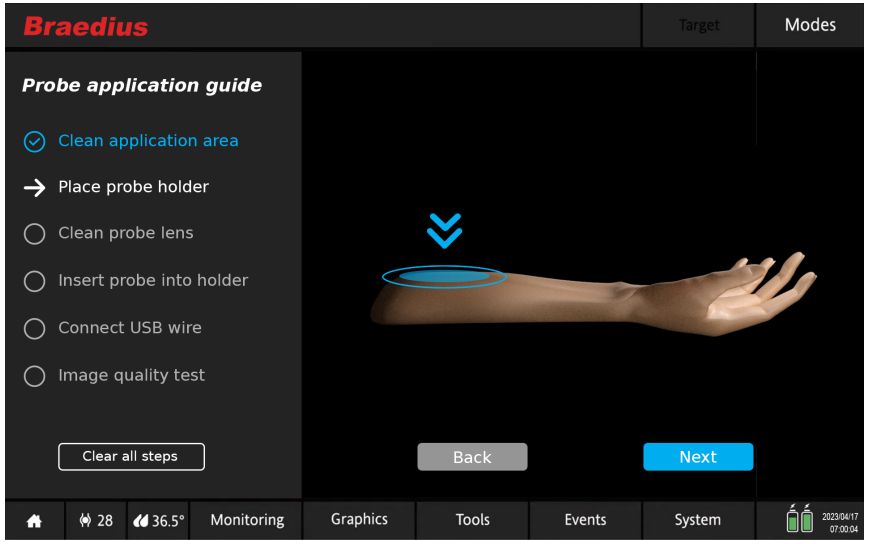


Figure 70: Software guides the user step-by-step to prevent user error.

Concept design

By integrating the solutions from the Design Challenges the following output was made:

- A trolley system design
- Two probe designs (Figure 71)

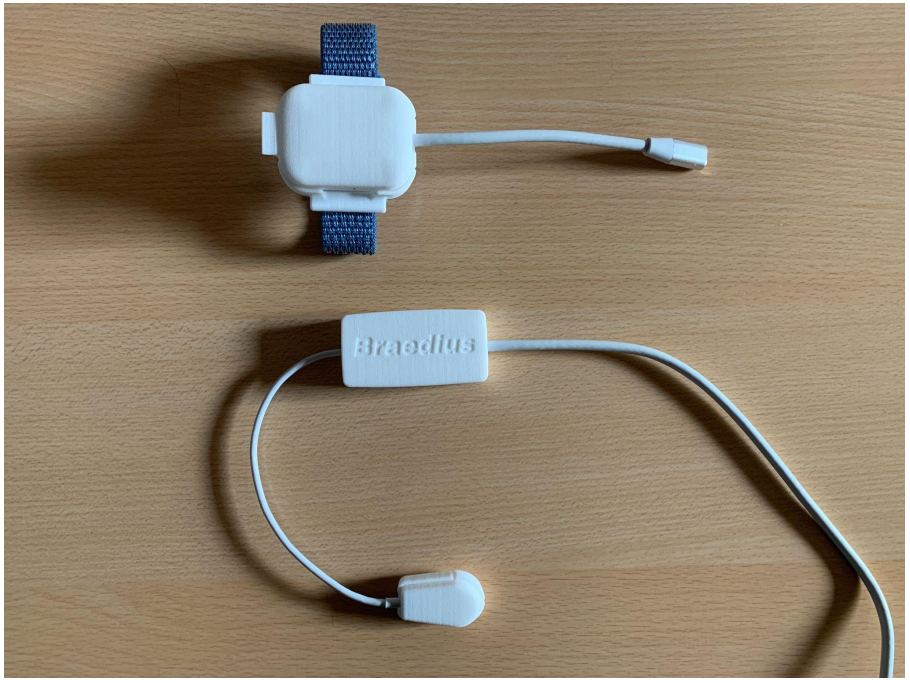


Figure 71: Prototypes of the two probe designs.

Concept choice

A small usability test was performed to see which of the two probe designs was easier to use.

Prof. dr. ir. Wouter Serdijn (Faculty EEMCS, Bioelectronics) and Frank Messie helped with advising on the feasibility of the electronic implementation of the probe designs. The advantages and disadvantages of each design are shown in Figure 72.

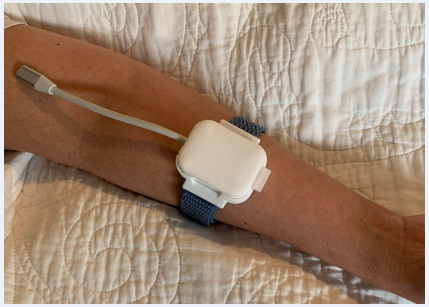
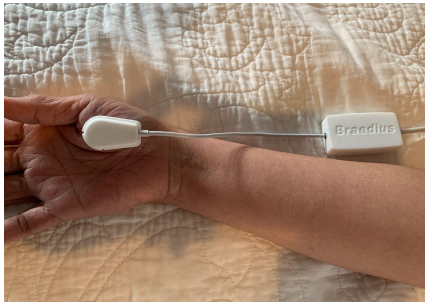
All-in-one	Separate housings
	
✓ Can re-use proven CytoCam optics and electronics ✓ Lower development costs ✓ Very easy to use ✓ Stays securely on its spot ✗ Difficult to place on the thenar eminence ✗ Takes up more space	✓ The smaller probe can be placed on the thenar eminence and forearm ✓ Takes up less space ✗ The small camera module is used in smartphones and is therefore not optimised for this application ✗ Having the electronic components in two separate housings is not advised and possibly not feasible ✗ The smaller probe was finicky to work with and the secondary PCB housing pulled on the sensor

Figure 72: Comparing the advantages and disadvantages of the two probe designs.

The all-in-one probe design was chosen due to its ease of use, stable fixation and requiring fewer development resources. One drawback of the chosen design is the larger size of the sensor probe which is difficult to place on the thenar eminence. However, the forearm is more favourable in terms of accessibility and superior vascular reactivity.

Final concept design

The final design of the trolley system and probe will be revealed here.

***Figure 73**: The trolley system.*

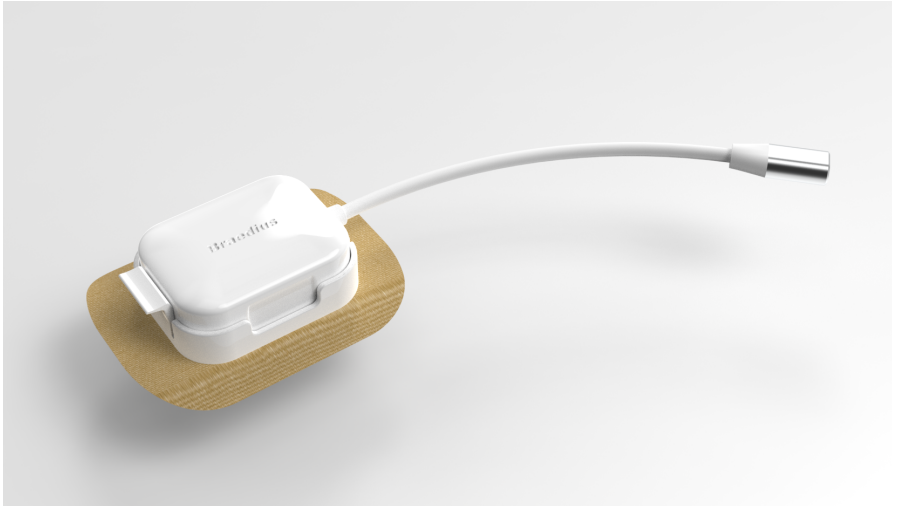


***Figure 74**: The probe latched into the stick-on holder.*

***Figure 75**: The probe latched into the holder with an adjustable strap.*

For more visuals and details, please visit Appendix L.

Placing the design into the context

To visualise the concept vision, the system was placed into an ICU environment (Figures 69-71).

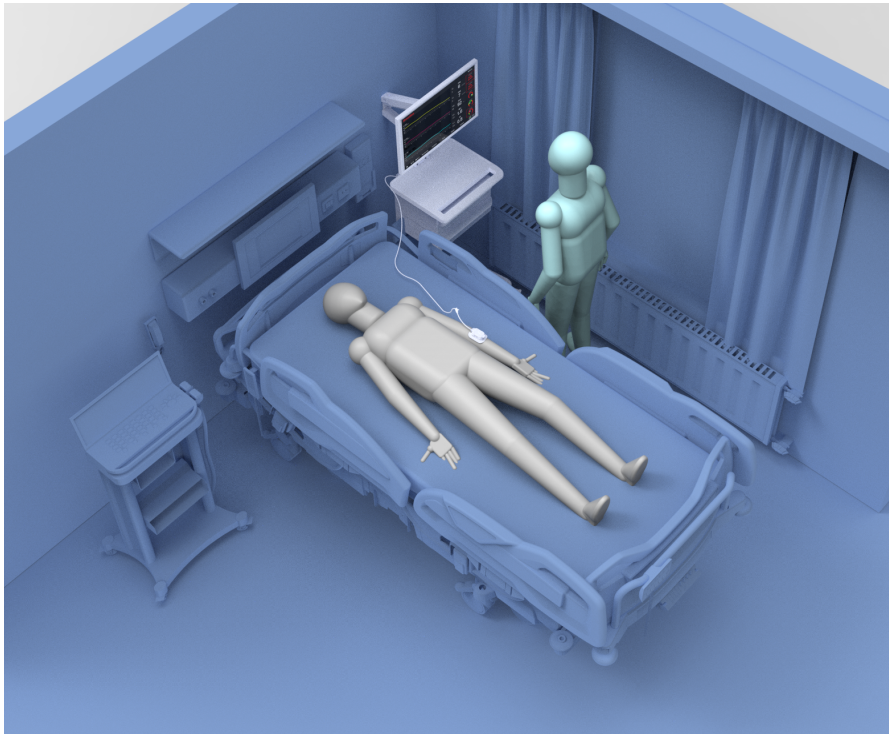


***Figure 76**: The system is placed into a mock ICU room. The system is monitoring a patient while a doctor is watching the data output.*

User scenario

To showcase the steps for application and removal of the probe (with both holder types) a demo video was made.

Please watch the Video Appendix file

***Figure 77**: The camera sensor is attached to a patient.*

***Figure 78**: Hands-free monitoring of cutaneous microcirculation in the ICU.*

For more visuals and details, please visit Appendix M.

4.3 Roadmapping

Now that the concept vision has been established (Figure 78), a strategic plan needs to be made to reach it. This will be done by creating a roadmap which defines the desired outcomes and includes the major steps or milestones. It will be used as a visual planning, alignment and communication tool for internal stakeholders (e.g. employees, managers) and external stakeholders (partners, prospective customers, investors). Inspiration was taken from the book Design Roadmapping (Lianne Simonse, 2018).

Approach

The goal of the roadmap is to create a feasible (can it be done?) and viable (will it survive?) long-term development strategy suited for Braedius Medical, which is a small company with limited resources.

The three horizons model was adapted for the roadmap design. Time pacing was defined based on the company's and competitor's research & development capacity. This should result in a manageable pace and competitive timing of the new innovations developed by Braedius. The overall strategy of each horizon will be covered next.

Horizon 1 - Design Value Enhancements
The first horizon focuses on enhancing the current products and services with features that can be transferred to the following horizons. This allows for funding of the technology required for the future vision by making it marketable at an early phase. For example, multiple customers have already communicated a need for observations of the microcirculation in other types of tissues such as the liver and skin.

Implementing new LEDs into the CytoCam should allow for new product variations and will give insight into which wavelengths will work best. Furthermore, ideas like the articulating arm (Figure 53) should be revisited as they can serve as intermediate solutions that will still improve the current usability.

Efforts to increase revenue and profit will also be done by optimising the business model. For example, the sales channels can be improved by creating a better website and putting more effort into customer acquisitions by e.g. hiring a (part-time) marketing personnel.

Horizon 2 - User-centered Value Creation
A proof of concept in the form of a minimal viable product will be developed in Horizon 2. The first iterations of the hardware and software of the concept vision will be made based on existing components of the CytoCam. These proofs of concepts will be used for testing, validating preconceived ideas, demonstration purposes and also to apply for approval by the regulatory bodies. This approval can take up to 14 months and will help with accelerating next-generation implementations. Even though these iterations are not perfect, they should be good enough to show the added value and to be eventually marketed. This can either be for research purposes or more transitional applications in the ICU.

Horizon 3 - Value Proposition Creation
Efforts in Horizon 3 will be made on optimising and maturing the technology and implementations of the previous horizon. For example, the probe will be made sleeker and smaller and the software will have more advanced features to aid in more effective healthcare. This phase will work towards the future vision as its endpoint.

***Figure 79**: Roadmap design.*

5 Concept evaluation

5.1 Viability Decision Canvas

The Viability Decision Canvas made by Dan-Stefan Florescu (Master thesis, supervised by Ir. Han van der Meer and Ir. Ehsan Baha) will be used as a framework to assess the concept. It works by answering questions regarding desirability, feasibility and suitability.

Desirability 1: Is the meaning supported by future trends?
Yes, there is a clear need for a bedside monitoring solution that can analyse the microcirculation which is expressed by current customers and also literature. By attending multiple webinars it was also made clear that precision medicine is a movement that the industry is working towards.

Desirability 2: Is it more meaningful than existing solutions?
Yes, the concept aims to eliminate the problems that exist in the current hand-held CytoCam device. Video acquisition and analysis are still too difficult and time-consuming to be able to use it for clinical applications. Other devices exist, but they are not capable of observing microcirculatory alterations such as flow heterogeneity. These can only observe regional oxygenation or flow, while cellular occurrence also needs to be analysed for a complete dataset.

Desirability 3: Is it meaningful for enough people?
Yes, the innovation is meant to improve patient care in the intensive care unit and possibly the hyperbaric oxygen therapy clinics. Not only does it help thousands of healthcare providers with their work, but it will also affect even more patients as they get better treatment.

The radical concept is Desirable.

Feasibility 1: Can it be done now?
No, more knowledge and resources are required to give tangible form to the new innovation.

Feasibility 2: Can it be done in [7] years?
Yes, the concept is based on existing technology and mostly proven solutions. A proof-of-concept and a minimum viable product should be viable in less time.

Feasibility 3: Can we adjust our operations to make it?
Yes, the realisation does requires growth and change to the current business operations, but these are well within the realm of possibility. The details can be seen in the roadmap (Figure 72).

The radical concept is Feasible.

Suitability 1: Does it fit our corporate strategy?
Yes, the aim of the concept is to increase revenue, profits, diversification and growth. These are in line with the goals of the company.

Suitability 2: Does it fit our innovation strategy?
Yes, the mission of Braedius Medical was always to develop a microcirculation analysis tool for clinical application.

Suitability 1: Does it fit our business strategy?
Yes, the company has always tried to be competitive by: 1) Striving to have the most innovative product or service and 2) having a technological advantage.

The radical concept is Suitable.

Viability: Should the radical innovation concept be adopted for further development?
Yes, the radical innovation should contribute to long-term profits, business growth and contributes by making a positive clinical impact.

The radical concept is Viable.

5.2 Validating the potential of clinical applications based on microcirculation

Before investing resources into this venture, it should be established that there is potential in the clinical application based on microcirculation. This will be underpinned with the help of a framework made by Monet et. al[91]. They state that there are three prerequisites for the clinical use of microcirculation monitoring:

I) Pathophysiology: "Does the microcirculation play a crucial role in the pathophysiology of shock?"
The microcirculation acts as the interface between the hemodynamic system and the tissue of organs. A compromised working of this interface inhibits oxygen and nutrient supply to the cells in the tissue and the depletion of waste molecules. This results in critical illness or death due to organ failure. Therefore, it is reasonable to say that the answer to this question is yes.

II) Technology: "Are the techniques to explore the microcirculation ready for routine clinical use?"
Currently, the answer is no. However, the goal of this project was to overcome the barriers and limitations that prevented the CytoCam from being able to use for routine clinical use. It can be seen as an opportunity for Braedius Medical as the first company to overcome this barrier. This will result in a first-mover advantage.

III) Therapy: "Does the assessment of the microcirculation trigger specific therapeutic interventions?"

Also here an opportunity can be seen. As there is still much research to be done to draft up and validate clinical therapies, developing a tool to easily acquire this data can be quite profitable. Not only will it help path the way to clinical implementation, but the technique and/or the company will also establish itself in the medical industry.

***Figure 80**: The prerequisites for the clinical use of microcirculation monitoring Adapted from Monet et. al[91].*

6 Recommendations and Reflection

Recommendations

This section will cover recommendations for activities that can be done after the project.

Concept validation by users

The concept design and vision can be validated by ICU staff (intensivists, anesthesiologists, nurses, and resident doctors) in the form of qualitative interviews and focus groups. This will allow for feedback on the design assumptions.

Usability testing

Simulations of user scenarios and actions can be done with ICU staff. Mock situations can be created by using the 3D-printed prototype and a prototyped version of the monitoring software. Figma is an example of a tool that allows for easy and quick interface prototypes. Another option is to create videos that are meant to simulate the data output of the monitoring system. This can be done with tools like Adobe After Effect. These videos are then played on a display monitor mounted on a trolley. Performance indicators can also be established. E.g. the time to apply a camera probe on a patient needs to be under a certain amount of time for it to be eligible for use in the ICU.

Functional prototype

When more data and insights have been gathered from the follow-up tests, a functional prototype can be made with parts from the CytoCam. This will serve as a proof of concept.

New website

Some of the recommendations of the Roadmap can be done in the near future. An example is making a new website. It would be interesting to see if this would result in more customer leads and sales.

Framework for standardisation

Very little standardisation has been established for microcirculatory videomicroscopy. These need to be resolved and validated. An example is the length of the video sample. Braedius recommends 5 seconds as the sweet spot, but some studies film for 20 minutes. We have found two potential translational medical researchers (EU and USA) who can help us with this. The goal is to have the results published. A list of these variables needs to be made and each item should be validated.

Protecting the IP

Options on how to protect the new innovation and its encompassing intellectual property should be considered.

Quality Management System for MDR and FDA approval

The hardware and software eventually need to be approved by regulatory bodies. To save time it is best that the required documentation is tracked and maintained from the very start. A QMS should be established. There are software solutions that can help with this such as Reqview.

Reflection

Process

This project has not only taught me a lot about the subjects covered in this thesis but also about project management and how I approach the process. One thing that I already knew about myself, but that came even more apparent in this project is that I have difficulties with switching my focus. For example, I tend to keep going into the depth of certain subjects or project phases. I am trying to chase answers or information that might not even be available yet. I also have difficulties with moving on to the next activity before I am completely satisfied. This often takes too much time. Sometimes I got lost in simply adding more information, while this didn't necessarily contribute to the end results. Luckily I can say that I gained a whole lot of new information and insight which I can use both for the short and long term.

For the next time, I am equipped with the knowledge of which steps to take for the analysis phase, which design or research tools are effective and how to efficiently draft a report. Some other good practices were learned such as how to keep track of all the source materials.

Even though looking back, I could have done a lot of things better, I am in a way happy I made these mistakes as they have taught me a lot of valuable lessons.

Results

Looking at the report, other deliverables, insight gathered and the prototypes I can say that I am happy with the quality of the results. The analysis has an adequate breadth and depth and I think the design choices have been well substantiated. I am also happy with all the visuals that I have made throughout the project.

Looking forward

After learning so much about the importance of the microcirculation and the potential impact it has on clinical applications I feel it would be a great mission to turn this concept vision into a reality.

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