Università Politecnica delle Marche
Scuola di Dottorato di Ricerca in Scienze dell'Ingegneria
Curriculum in Ingegneria Biomedica, Elettronica e delle Telecomunicazioni

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Development of a new medical device to detect the endothelial dysfunction

Ph.D. Dissertation of:
Chiara Calamanti

Advisor:
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XVII edition - new series

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Per quelli che han vissuto con la coscienza pura,
il cuore tenero e gli occhi contenti,
alla mia meravigliosa e libera *Zia*,
al mio caro e forte *Massimo*
al mio habibi e dolce *Khaled*

Abstract

The endothelium is the largest organ in the human body and covers all the vessels in the cardiovascular system (heart, arteries, veins, capillaries and lymphatic system). It plays a role of primary importance in the modulation of vessel tone and blood flow, as well as other numerous functions such as the regulation of inflammatory and immune processes and vascular permeability. The alteration of this organ leads to and endothelial dysfunction is known to be implicated in the pathogenesis and clinical course of all known cardiovascular diseases (CVDs). CVDs refer to several disorders of the heart and blood vessels and include coronary, cerebrovascular, rheumatic-heart diseases and other conditions that could lead to heart attacks and strokes, with consequent premature death. A possible strategy to prevent premature deaths is identifying the individuals at highest risk of Cardiovascular Diseases (preventive healthcare) to ensure that they receive appropriate treatment. The aim of this thesis it is develop a new medical screening device to detect the endothelial dysfunction. The main contributions of this Thesis can be summarised as follows:

- Design and development of a new medical device for ED screening;
- Design and development of data-driven approaches for the analysis of signals acquired with the new device;
- Design and development of a new Clinical Trial Study and Protocol for the ED device in the oncology context (IOT project).
- The new Clinical Decision Support Systems for ED clinical evaluation

The device design and development has been a complex process rife with regulations, specifications, application requirements, and end user needs and all of which are balanced and adhered to for a successful product.

Results prove the correctness of the design intuition trough the real device implementation, the effectiveness of the biomedical data processing technique and of the Clinical Decision Support System applied to a real dataset and real patients, using the proposed device. The application to Oncology Telecare is suitable and the use of the overall approach on real clinical trials will apply the proposed device and methodology to the oncological care follow-up.

Part of the research presented in this thesis was carried out at the Department of Biomedical Engineering of the University of Lund. The scientific contributions of this work have been presented at an international conference and one is being reviewed in an international journal. Other results are not presented because has been protected the intellectual property of this project, indeed the project is patent pending. For this reason, the non-disclosure of this work was requested for a period of 18 months. All the work described in this thesis was supervised by Strumedical s.r.l. who co-founded of this research project.

Sommario

L'endotelio è il più grande organo del corpo umano e ricopre tutti i vasi del sistema cardiovascolare (cuore, arterie, vene, capillari e sistema linfatico). Considerato in passato come semplice tessuto, svolge invece un ruolo di primaria importanza nella modulazione del tono vasale e del flusso ematico, oltre ad altre numerose funzioni come la regolazione dei processi infiammatori ed immunitari e la permeabilità vascolare. Un'alterazione dell'endotelio comporta una condizione patologica caratterizzata da una ridotta vasodilatazione, contribuendo a diverse alterazioni cardiovascolari come l'aterosclerosi, l'ipertensione e la trombosi. Tale condizione, prende il nome di disfunzione endoteliale ed è e alla base di numerosi fattori di rischio cardiovascolare come il fumo, la dislipidemia, il diabete, l'obesità, il sedentarismo, oltre ad essere presente in alcune patologie cardiovascolari come la cardiopatia ischemica e lo scompenso cardiaco. La diagnosi precoce della disfunzione endoteliale, può giocare un ruolo fondamentale nella prevenzione di eventi cardiovascolari. Ad oggi la metodica gold standard, oltre ad essere costosa ed altamente operatore dipendente, richiede l'impiego di personale specializzato, limiti che la rendono molto lontana dall'essere considerata una metodica di screening.

Partendo da questa premessa, questa tesi mira a sviluppare un nuovo dispositivo di screening per valutare la funzione endoteliale. L'ambizione finale è quella di rivolgere l'utilizzo del dispositivo a tutta la popolazione, così da agevolare le azioni di prevenzione nel ridurre gli eventi cardiovascolari, rendendo quindi l'esame più accessibile alla pratica clinica.

L'attenzione è stata rivolta allo sviluppo del dispositivo con tecnologia affidabile e riproducibile e allo sviluppo di algoritmi sofisticati per valutare la funzione endoteliale. Questo lavoro intende fornire uno strumento medicale da poter testare e validare in un ambiente ospedaliero, anche in campi ad oggi sconosciuti. Proprio rispetto a quest'ultimo punto, un'applicazione altamente innovativa è l'utilizzo del nuovo dispositivo sui pazienti oncologici per monitorare l'effetto dei farmaci chemioterapici. Questo aspetto è stato affrontato nel contesto di un progetto regionale chiamato Intelligent Oncology Telecare (IOT), dove il dispositivo in questione svolge un ruolo centrale del sistema di monitoraggio del paziente oncologico.

Per la progettazione del dispositivo medicale sono stati eseguiti i seguenti passaggi: (a) studio delle tecnologie normalmente adoperate per lo studio della disfunzione endoteliale, (b) scelta della tecnologia, (c) definizione di tutte le specifiche a livello hardware, software e di design, (d) sviluppo di un sistema di supporto alle decisioni con applicazione basate su tecniche di "Machine Learning" (f) sviluppo degli algoritmi per rilevare dal segnale pletismografico biomedico la disfunzione endoteliale.

Contestualmente, è stata seguita tutta l'attività di ricerca relativa al dispositivo nel contesto del progetto IOT, che ha permesso lo sviluppo del primo prototipo che verrà testato e validato presso l'ospedale di Fabriano. Parte dell'attività di ricerca presentata in questa tesi è stata svolta presso il Dipartimento di Ingegneria Biomedica dell'Università di Lund. I due contributi scientifici prodotti da questo lavoro sono stati presentati uno a conferenza internazionale ed uno è in revisione in una rivista internazionale. Altri risultati saranno presentati una volta tutelata la proprietà intellettuale di questo progetto, a questo scopo il progetto è patent pending. Per questo motivo è stato richiesto, per un periodo di 18 mesi, la non divulgazione di questo lavoro. Tutto il lavoro descritto in questa tesi è stato supervisionato dalla Strumedical s.r.l. che ha cofinanziato questo progetto di ricerca.

Indice

Elenco delle figure

Elenco delle tabelle

Abbreviations

The following abbreviations are used in this manuscript:

BMI	Body Mass Index
CDSS	Clinical Decision Support Systems
CMs	Confusion Matrices
CV	Cross Validation
CVDs	Cardiovascular Diseases
DT	Decision Tree
ED	Endothelial Dysfunction
EDD	Endothelial Dysfunction Dataset
EHRs	Electronic Health Records
FAST	Function Analysis System Technique
FMD	Flow Mediated Dilatation
I_RH	Hyperaemic Reactive Index
IOT	Intelligent Oncology Telecare
IPA	Pulse Area
KNN	K-Nearest Neighbor
LLO	Leave-One-Out
ML	Machine Learning
NED	Not Endothelial Dysfunction
NO	Nitric Oxide
PI	Pulse interval
PP	Pulse Pressure
PPG	Photoplethysmography
QFD	Quality Function Deployment (QFD)
RF	Random Forest
SA	Systolic Amplitude
SI	Large Artery Stiffness Index
$Prec$	Precision
Rec	Recall
RT	Recovery Time
SVMs	Support vector machines
US	Ultrasound

Capitolo 1

Introduction

1.1 Objective

In 2017, the European Heart Network (EHN) affirmed that Cardiovascular Diseases (CVDs) cause 3.9 million deaths in Europe and over 1.8 million deaths in the European Union (EU) and it costs the EU economy 210 billion Euro a year [4]. CVDs refer to several disorders of the heart and blood vessels and include coronary, cerebrovascular, rheumatic-heart diseases and other conditions that could lead to heart attacks and strokes, with consequent premature death. A possible strategy to prevent premature deaths is identifying the individuals at highest risk of CVDs (preventive healthcare) to ensure that they receive appropriate treatment.

In this context, Endothelial Dysfunction (ED) is achieving increasing importance, because it may improve the identification of individuals at risk: in Widlansky et al. [5], the endothelial function is defined a "barometer" for cardiovascular health. ED is observed in the early stage of most CVDs, atherosclerosis or other disorders, and for this reason an effective screening and earlier diagnosis of ED is extremely important.

There are several (both invasive and non-invasive) techniques for endothelial assessment (Sec. 2.2), with limitations such as high incisiveness and/or costs, not being suitable for screening purposes. For example, the Eco-Doppler method, which is considered the gold standard among the non-invasive techniques, is operator dependent, expensive and requires a skilled medical specialist. The EndoPAT^{TM}, (Itamar Medical, Israel) is an innovative device that tries to overcome some of these issues [6], [7], but still presents several limitations: the probes are disposables, which implicates high costs, and it is neither automated or standalone.

To date, a device that satisfy all the requirements of an ideal screening device to detect the ED does not exist and the state of the art does not reports fully automated data processing and Clinical Decision Support Systems the ED diagnosis.

The purpose of this Ph.D. work is to develop and test a new screening device to detect the ED, this idea was inspired by Doctor Mario Rabuini (Cardiologist, Italy) and Eng. Massimo Pergolesi (Strumedical s.r.l.)[1].

Hence, this work is based on the development of an ideal screening device which is able to fulfil all the following requirements:

- Non-invasive ;
- Cheap ;
- Safe ;
- Automated ;
- Repeatable ;
- Operator-independent ;
- Portable ;
- Stand-alone ;
- Printer-integrated to release immediately the report ;
- Usable in home care ;
- Usable by any operator (medical doctors, nurses, pharmacists), not only by cardiologists.

The device may contribute to the early detection of ED, preventing cardiovascular complications and lowering the number of premature deaths, using also a novel data processing method inside a Clinical Decision Support System for assisted diagnosis.

The device may contribute to the early detection of ED, preventing cardiovascular complications and lowering the number of premature deaths, using also a novel data processing method inside a Clinical Decision Support System for assisted diagnosis. Although the device is designed to be used for this application, the project has also been extended to an oncological context. The innovative idea consists in the use of the new device on cancer patients to monitor the action of chemotherapeutic drugs. In this way, it is possible to follow the cancer treatments also from the cardiology perspective. Indeed the toxic effects caused by cancer treatments may lead to endothelium alteration which may result in cardiovascular complications. For this reason, the design of the device, object of this thesis, has been included in the regional project Intelligent Oncology Telecare (IOT).

This Ph.D. work is included in the Italian Intelligent Oncology Telecare (IOT) project (Chapter 3). IOT is co-funded by the Marche Region program POR-FESR 2014-2020, with ten cooperatating companies, two departments of research of the "Università Politecnica Delle Marche", one department of the "Università Degli Studi di Camerino" and the local health authority "Azienda Sanitaria Unica Regionale Marche".

[1]Strumedical s.r.l. is a company specialized in selling, assistance, importing and marketing electromedical equipment for diagnosis and monitoring. It is situated in Via Tambroni, 28, 62010 Montecassiano (MC), Italy

1.2 Thesis structure

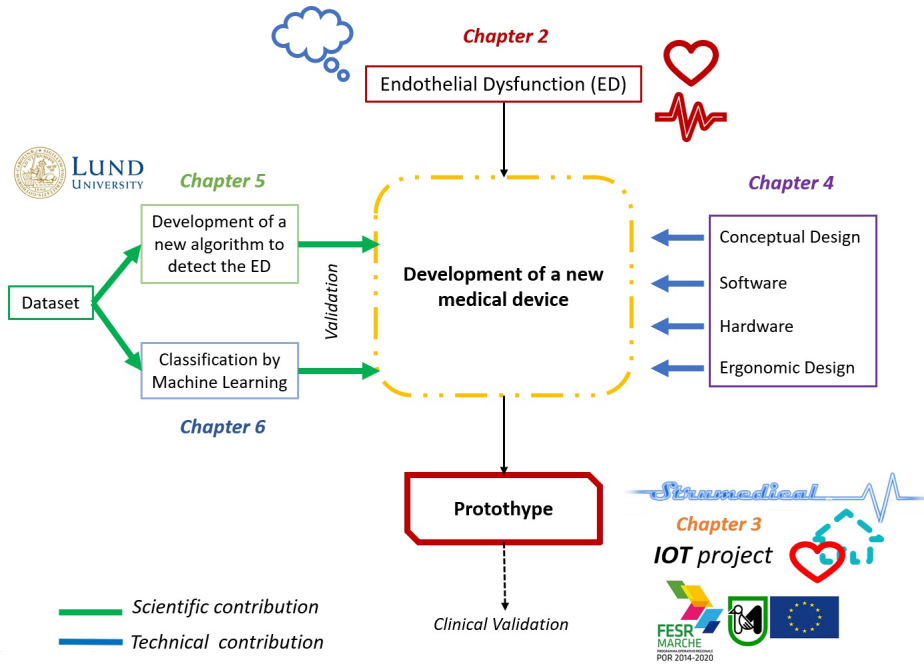

Figura 1.1: *Graphical map of Ph.D. thesis, the background of endothelium in the Chapter 2 (red),the IOT project and the phases of the design in the Chapter 3 (red). The Chapter 4 (purple) describe the development of the hardware and software about the device. The Chapter 5 (green) explain the algorithm to detect the endothelial dysfunction, while the classification of the dataset by Machine Learning approach will be describe in the Chapter 6 (blue). Moreover, with the green arrows are indicated the scientific contributions and in blue the technical contributions. Finally are reported the logos about the co-financiers, Strumedical s.r.l. (company that it is the owner of the new medical device and co-financier of the this doctorate), IOT that is the project co-funded by the Marche region program POR-FESR 2014-2020 explain in the Chapter 3.*

Figure 1.1 shows the Ph.D. thesis structure and emphasises the scientific and technical contributions of this thesis.
The thesis is organised in seven chapters, which describe the design and development of the new medical device to detect ED. **Chapter 2** explains the endothelium and reviews the state-of-the-art techniques for assessing ED and their limitations. **Chapter 3** briefly describes the ED in the oncology context and the IOT project **Chapter 4** describe the phases to develop the device (conceptual design, analysis and design of software and hardware, including the investigation of the ergonomic design of the device and the assembly of

all components). **Chapter 5** describes the development of the new index to discriminate the presence of the ED and the new algorithm to define the fiducial points useful for the parameters calculation from the PPG. **Chapter 6** explains the machine learning approaches to analyse and improve the diagnosis of ED. Finally, conclusions are reported in **Chapter 7** , as well as some future research directions.

1.3 Thesis contribution

The main contributions of this Thesis can be summarised as follows:

- Design and development of a new medical device for ED screening;
- Design and development of data-driven approaches for the analysis of signals acquired with the new device;
- Design and development of a new Clinical Trial Study and Protocol for the ED device in the oncology context (IOT project).
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Capitolo 2

Background of Endothelium

This chapter is mainly focused on the endothelium functions and anatomy to better understand the overall project focus and the specific bio-medical mechanism that are the base of the project design and data driven methodologies that are the main results of this thesis.

In the last decades, the endothelium was considered a simple barrier between the circulating blood and the vascular wall. It is now considered, instead, a predominant player in the control of blood fluidity, platelet aggregation and vascular tone, and it is recognised as the most important autocrine organ for the regulation of pathogenesis of thrombosis and atherosclerosis[8],[9].

The endothelium is a mono-layer of endothelial cells covering the lumen of blood vessels (arteries, veins and capillaries) and the lymphatic system, and therefore is in direct contact with the blood or lymph and the circulating cells[10]. In 1865 [11], the Swiss anatomist, Wilhelm His, introduced the term **endothelium** to define the barrier between the blood and the other tissues . At the end of the 70's, thanks to the advent of new techniques how electron microscopy and the culture of tissues, Florey and collaborators give the new foundations to study the morphology and the function of endothelial cells [12]. Since then, several discoveries have occurred, in particular the endothelium vasculature modulating function and its specific agent, nitric oxide. In 1998 Drs. Furchgott, Ignarro, and Murad received the Nobel Prize for their discovery of the role of nitric oxide in cardiovascular regulation[13][14][15]. To understand the importance of endothelium and its functions, it is necessary to start with anatomy and physiology of it.

2.1 The Vascular Endothelium

The vascular endothelium is an extensive network of cells covering the entire cardiovascular system. The essential components of the human cardiovascular system are the heart, blood and blood vessels. The hearth is the system's pump and the blood is carried through the body via blood vessels (Figure 2.1). There are three major types of blood vessels:

- the arteries, which carries blood away from the hearth where it branches into smaller vessels
- the capillaries where nutrients, wastes and gases are exchanged between the blood and the tissues
- the veins which carry blood from capillaries to the heart.

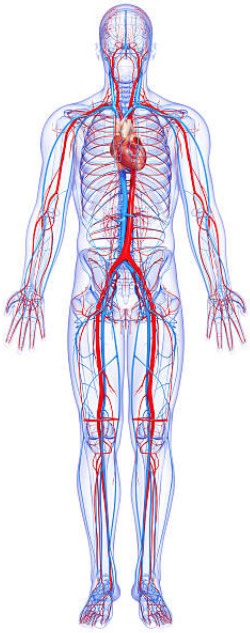


Figura 2.1: *Cardio Vascular System*

The arteries and veins share the same general features, have three distinct tissue layers from the most interior layer called tunics, the most interior is the tunica intima, then there is the tunica media and the outer is the tunica adventitia (Figure 2.2). Each tunica has different characteristics, as follows:

- Tunica adventitia: it is mainly composed of collagen and surrounded by an external elastic lamina to anchor vessels with surrounding tissues.

- Tunica media: it is made up of smooth muscle cells, elastic tissue and collagen.

- Tunica intima: it is the thinnest layer it is made up of one continuous layer of endothelial cells that are in direct contact with the blood flow. This layer is supported by a subendothelial connective tissue and then is surrounded by a thin membrane comprised of elastic fibres running parallel to the vessel.

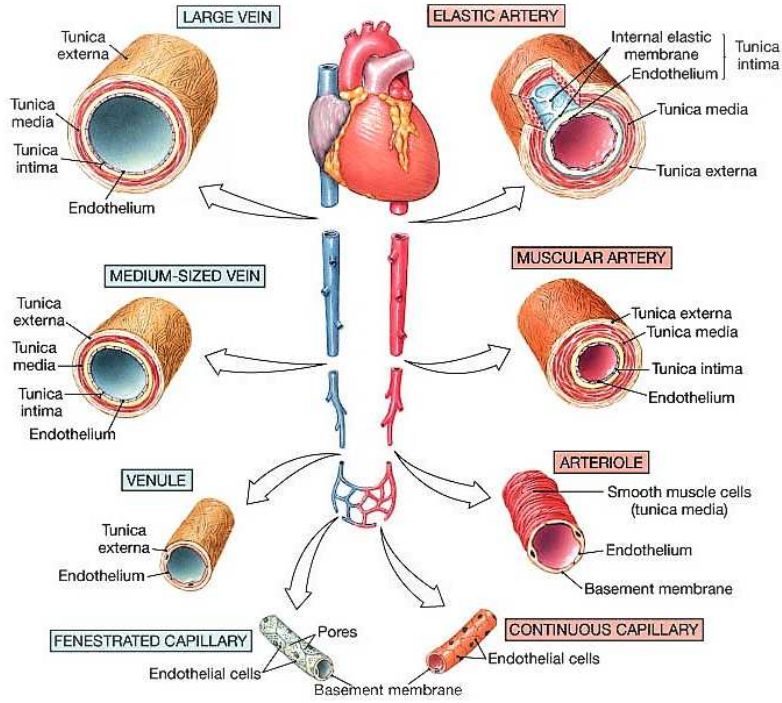


Figura 2.2: *Blood vessel structure, where are displayed the tunica intima, media and adventitia for arteries, veins and capillaries (image from [1]).*

The capillaries walls consist of a single layer of endothelial cells and the smallest have a single endothelial cell wrapped around to join with itself.

Therefore lining the tunica intima is the squamous endothelial cells (called the endothelium), which is continuous throughout the entire vascular system, including the lining of the chambers of the endocardium (the innermost layer of the heart) and the lymphatic vessels (that carry lymph).

The endothelial cells are not all alike, in fact, the shape of the cells varies across the vascular tree, normally they are thin and slightly elongated, 50 -

70 μm long, 10 - 30 μm wide and 0.1 - 10 μm thick. In the blood vessel wall, endothelial cells are orientated along the axis of the vessel, minimizing the shear stress forces exerted by the flowing blood. In the adult human, the endothelium is composed of approximately 10 to 60 x 10^{12} endothelial cells that occupy a surface (blood/endothelium interface) measuring approximately 300 to 1000 m^2. For this reason the endothelium it is considered the largest organ in the human body [10].

2.1.1 Endothelial function

Endothelial cells act to maintain vascular homeostasis through multiple complex interactions with cells in the vessels wall and lumen including [10]:

- **Barrier function** - The endothelium forms a semi-selective barrier between the vessel lumen and surrounding tissue, controlling the passage of materials.

- **Leukocyte trafficking** - The interaction between leukocytes and the vascular endothelium is a physiological and pathophysiological process. The endothelium regulates the passage of white blood cells into and out of the bloodstream. Excessive or prolonged increases in permeability of the endothelial mono-layer, as in cases of chronic inflammation, may lead to tissue edema/swelling.

- **Hemostasis** - The hemostasis processes do not involve only the formation of platelets, but also the fibrin formation or blood coagulation, even if both processes strongly interact. When the integrity of the vascular endothelium is interrupted, the subendothelial matrix and the collagen fibres are exposed, consequently, the circulating platelets adhere to these structures and start the hemostatic process.

- **Balancing blood fluidity** (thrombosis and fibrinolysis) - The endothelium prevent adhesion, aggregation and activation of platelets and promote platelet de-aggregation. Instance normally the endothelium provides a non-thrombogenic surface because it contains, for example, heparan sulfate which acts as a cofactor for activating antithrombin, a protease that inactivates several factors in the coagulation cascade.

- **Metabolism and catabolism** - The endothelium can metabolize or conversely activate many circulating factors and have essential roles during vessel formations, such as glycolysis, fatty acid oxidation, polypeptide hormones, amines, nucleotides, lipoproteins, metabolites of arachidonic acid and reactive oxygen species.

- **Regulate smooth muscle cell growth** - The endothelium it is able to stimulate or inhibit the proliferation of the underlying smooth muscle cells.
- **Regulate the immune response** - The endothelium play a key role in the regulation of immune response.
- **Control of the vascular inflammatory process** - the endothelium has the capacity to produce cytokines and adhesion molecules that regulate and direct the inflammatory process.
- **Control of blood pressure** - The endothelium plays an important role in the control of blood pressure through the regulation of vascular tone.
- **Regulation of Vascular Tone** - The endothelium regulates vascular tone by balancing the production of vasodilators including nitric oxide (NO), prostaciclina (PGI2) e l'endothelium derived hyperpolarizing factor, and vasoconstrictors.

As this PhD thesis mainly deals with the assessment of endothelial function based on the capacity of the blood vessels to self-regulate vascular tone, the regulation of it will be discussed more in detail hereafter.

The role of Nitric Oxide in the regulation of vascular tone

In the 1980 Furchgott and Zawadski, discovered that the endothelium is able to produce the vasodilatation substance that called the endothelium-derived-relaxing-factor (EDRF) [13]. Later researches identify this vasodilator with the Nitric Oxide (NO), that play a crucial role in the regulation of vascular tone. NO is a soluble gas continuously released by the endothelium with a half-life of 630 s, synthesized from the amino acid L-arginine in endothelial cells by the constitutive calcium-calmodulin- dependent enzyme nitric oxide synthesis (NOS)[16][17][18][19][20].

The production of this enzyme may be induced by many stimuli that operate on specific receptor situated on the surface of endothelial cells, and consist of different endogenous substance such as acetylcholine, bradykinin, Substance P, Histamine and the serotonin. However, the principal stimulus for the NOS and release from the endothelium is a physical stimulus, in particular the shear stress of blood flowing over the surface of the vessel by a non-receptor-dependent mechanics [21][22][23][24].

Regardless of the stimulus, when the Nitric Oxide is released, spreading through the membrane of endothelial cells and inside in the smooth muscle cells where the NO stimulus soluble guanylyl cyclase, producing an increased concentration of cyclic guanosine monophosphate (GMP) that regulate many

functions, such as the relaxation of the vascular smooth muscle and the platelet function[25][8].

To summarize, the main roles of NO are vasomotor action, inflammation process, antioxidant activity, and has multiple beneficial effects including, maintain vascular homeostasis, regulation of local cell growth, inhibition of leukocyte adhesion, and protection of the vessel from platelets whole and cells circulating in the blood [10][26]. A limited production of the NO and a reduced bioavailability of NO, it is the early anatomical alteration of endothelium due to the atherosclerotic process and consequently may induce other cardiovascular diseases.

2.1.2 Endothelial dysfunction

Under normal conditions, the endothelium preserves normal vascular tone and blood fluidity and all the endothelial functions are balanced. When cardiovascular risk factors appear, a chronic inflammatory process starts. Disease conditions could worsen and provoke a loss of vasodilator and anti-thrombotic factors and an increase in vasoconstrictor and pro-thrombotic products. This situation implies an unbalanced condition of the normal endothelial functions and, in the first stages, the principal endothelial alteration is solely at the anatomical level [5][27]. In this conditions, the defence mechanism of vascular endothelium is compromised, and the endothelium is liable to Endothelial Dysfunction (ED).

ED leads to atherosclerotic lesion formation, inflammation, hypertension, heart failure and is strongly correlated with classical and novel risk factors for CVDs [28]. Commonly-recognized risk factors are ageing, smoking, dyslipidemia, diabetes, postmenopause state, hypertension, to which novel risk factors are added, e.g. obesity, homocysteine, infection or inflammation, physical inactivity, post-prandial state [5][29].

An endothelium characterized by a dysfunction (maybe due to the presence of risk factors) is marked by a decrease of the NO bioavailability, and other protective substances. In addition, the endothelium may transform into a harmful organ because it is induced to synthesize mainly vasoconstricting, pro-aggregating, pro-inflammatory substances. The first consequence is the beginning of atherosclerotic or thrombosis processes. Furthermore, patients with diabetes, obesity, dyslipidemia and hypertension are characterised by ED. There are many interventations to limit these complications, some of these may contribute to the reverse of endothelial dysfunction. Thus for instance antioxidant therapy (typically vitamin C, vitamin E), dietary modifications, lifestyle modification, reduction of cholesterol, quitting smoking and the assumption of some substances to improve the NO synthase.

2.2 Method of evaluating the Endothelial Function

During the last years, several techniques have been developed to evaluate the endothelial function, both invasive (that are considered the gold standard for early detection of endothelial dysfunction) and non-invasive (that are giving promising results and show good reproducibility)[30][31][32].

2.2.1 Invasive technique

- Intracoronary Infusions:
  This method consists of the intracoronary infusion of some vasodilatory substances (such as acetylcholine) to measure the changes in vessel diameter using quantitative coronary angiography. The aim is checking how the coronary arteries dilate after the infusion, to quantify the endothelial function. In particular, in presence of endothelial dysfunction, the acetylcholine may lead to a decreased vasodilatory response, on the other hand, the arteries dilate in a dose-dependent way. This technique is invasive, more expensive. Moreover there are some risks correlated with the catheterisation and for these limitations it is not be considered a screening procedure.

- Intrabrachial Infusions:
  In this technique, the infusion it is more accessible than the coronary because it is applied in the brachial artery. This procedure like the previous method gives a direct quantification of endothelial function (at the level of brachial artery) and it consists in the evaluation of dose-response relations of endothelial agonists and antagonists. This method is higher reproducible and the catheterisation may be less complicated but may be dangerous for the median nerve. Nevertheless, it is invasive and expensive and can causes infections.

2.2.2 Non Invasive technique

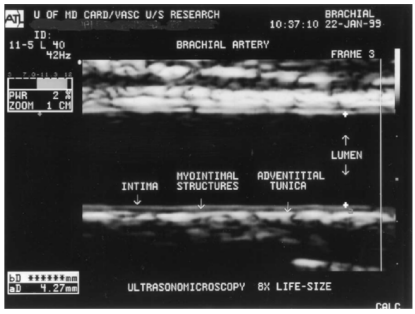
Flow Mediated Dilatation

In 1992, Celermajer et al. developed a new non-invasive method to evaluate the endothelial function [33], called Flow Mediated Dilatation (FMD) that describes the increase of the arterial diameter, as a consequence of the reactive hyperemia, and is comparing it with the baseline diameter and expressed simply as a percentage of this baseline diameter (% FMD). The exam is conducted with the ultrasound system by a highly specialised doctor, usually a cardiologist. The procedure in detail is reported in the "Guidelines for the

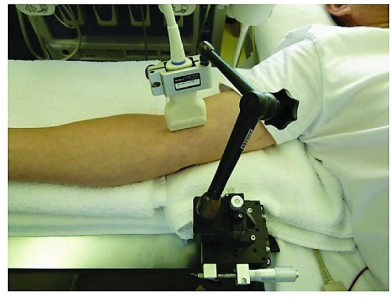
Ultrasound Assessment of Endothelial-Dependent Flow-Mediated Vasodilation of the Brachial Artery" wrote by CORRETTI et al. [34].

Once the patient is ready, and he is lying supine with his arms at his side, in a comfortable position, the doctor places:

- The cuff of a normal manual sphygmomanometer on the arm (left or right depending on the dominant limb) above the bend of the elbow.
- The linear transducer above the arm at the brachial artery level, in the longitudinal plane above the antecubital fossa, attempting to select the distal segment where the intimal faces between the lumen and vascular wall are better distinguishable. (The best procedure it is with the use of a mechanical support for the probe that reduces the probe's movements, thus limiting the bias introduced by the operator) 2.3.
- The cardiac electrodes are positioned on the patient's chest to obtain an adequate electrocardiographic trace.



(a) *Measuring of the brachial diameter based on the ultrasound image (Image from [34])*



(b) *Position of the probe on the brachial artery. To reduce the movement of the probe it is recommended the use of the mechanical support. (Image from [35])*

Figura 2.3: *Flow Mediated Dilatation procedure*

The recording phases are [36]:

1. **Basal phase**: To allow the patient to relax the duration of the phase it is about 5 minutes. In the penultimate minute, video recording starts for 1 minute and actually the 5 measurements of the brachial artery diameter (in the longitudinal plane) were obtained, each measurement it was taken during the tele-diastole coinciding with the R wave of the ECG. After that, the mean of the 5 measurements was calculated to define the Baseline Diameter.

2. **Compressive phase**: This phase lasts 5 minutes and consists in the inflation of the sleeve with a pressure of at least 50 mmHg above the systolic blood pressure, in any case, not exceeding 200 mmHg.

3. **Post-compressive or hyperaemic phase**: This phase lasts 5 minutes and starts immediately after the quick deflation of the sleeve. After the first minute, the video recording begins for 1 minute with the reference ECG and with the positioning of the sample volume of the pulsed Doppler in the centre of the brachial artery (always on the longitudinal plane with correction of the angle lower than 60 degree) to highlight the hyper flow blood. The measurements of the arterial diameter in 5 samples, in telediastole, coinciding with the R wave of the ECG. The average of these 5 measurements, will be considered as the Post Hyperaemia Diameter.

FMD is calculated as a percentage increase in the diameter of the artery during the reactive hyperemia phase compared to baseline values, how the ratio:

$$FMD = \frac{PostHyperemiaDiameter - BaselineDiameter}{BaselineDiameter} * 100 \qquad (2.1)$$

The patient with normal endothelial function has an FMD greater than 7% while the patient with endothelial dysfunction less than that value.

Pulse Wave Velocity

Aortic Pulse Wave Velocity (PWV) is considered an index of aortic stiffness, and is defined as the velocity of pressure pulse wave, generated by the systolic contraction of the heart, propagate along the arterial tree. PWV is normally measured between the carotid and femoral artery calculating the distance from the arrival of the pressure pulse wave in these two places. The pulse waves travel through the arteries and its velocity depends on the vessel. Indeed, all the factors including the endothelial dysfunction may lead to the arterial stiffness and therefore the lower vessel dilatation and compliance [37][38][39].Typically, the pulse wave is detected by pressure transducers or arterial tonometry.

Peripheral Arterial Tone

The Peripheral Arterial Tone (PAT) signal is a proprietary technology measured by the EndoPAT^{TM}Israel device (Itamar Medical) and represents the arterial tone changed in peripheral arterial vessels. In detail, EndoPAT^{TM}is a non-invasive device for endothelial function assessment, is approved by the Federal Drug Administration and it was developed and distributed by Itamar Medical, Israel. The device (Figure 2.4) records the PAT by unique photoelectric fingertips, different from the normal photoplethysmography sensors because

they are provided by an external casing that containing inflatable chambers. This solution is thought to apply uniform pressure to the surface of the distal finger, to excluded the venous flow. The exam follows the same procedure of the FMD method. In detail, the exam consists in the application of two fingertips one for the hand that will be subjected to the transient ischemia (created by a normal pressure cuff situated on the upper arm) and one in the other hand for control. To assess endothelial function, the blood flow after occlusion (hyperemic condition) is compared to the baseline flow and the ratio is computed by the EndoPAT^{TM}software that gives the EndoPAT index, called also RHI-PAT [6],[40][41][42] [43][44].

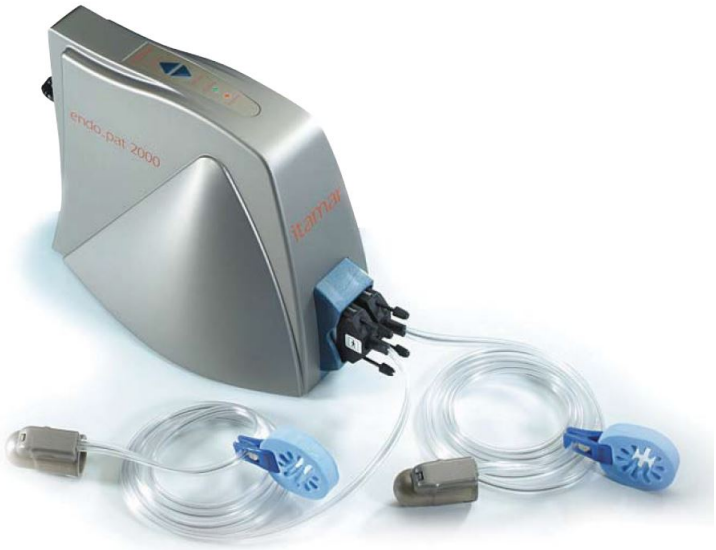


Figura 2.4: *EndoPAT^{TM}, Itamar Medical, Israel*

2.2.3 Limitation of the assessment of endothelial function

Table 2.1 summarises the advantages and disadvantages of both the invasive and non-invasive procedures".

It is worth noticing that these techniques are time-expensive, require both manual intervention (from specialized heathcare operators) and expensive devices, that are not standalone. All these disadvantages make it difficult to consider these devices suitable for the screening and prevention, and indeed they are not easily included in the routine examination.

Starting from such a premise, this thesis addresses the topic of developing a new medical device to assessment the endothelial function, to prevent the

cardiovascular complications. Following are reported some requirements: non-invasive, cheap, safe, automated, repeatable, operator-independent, portable, stand-alone, printer integrated to release immediately the report, usable in home-care, usable from any operator (medical doctors, nurses, pharmacists), not only cardiologists.

Techniques	Advantages	Disadvantages
Intracoronary infusion	- direct quantification of endothelial function in the coronary arteries - direct connection with the infusion of nitric oxide	- invasive - expensive - risk associated with the catheterisation infection, vascular injury,stroke - not screening test
Intrabrachial infusion	- brachial artery is easily accessible then the coronary arteries - cannulation has less complications	- invasive - expensive - risk associated with the catheterisation (infection, vascular injury) - risk of median nerve - not screening test
FMD	- non invasive - safer - faster then the other techniques	- highly operator-dependent - expensive - variability in measurements - the arteries smaller than 2,5 mm in diameter are difficult to measure - requires a skilled operator - size of the equipment
Pulse Wave Velocity	- non invasive - safer -requiring less training - operator independent	- it is not stand alone - variability in measurements
PAT*	- non invasive - safer - new technology - operator-independent	- expensive - probes can be used only one time - it is not standalone - not automated - size of the equipment

Tabella 2.1: *Advantages and Disadvantages of the most commonly used techniques to evaluate the Endothelial Function.* EndoPAT device*

2.3 A new approach for the assessment of the Endothelial Dysfunction

This paragraph describe the technique used to develop a new medical device. Although each of the many functions performed by the endothelium can be examined to detect the endothelial dysfunction, the one that is simpler to evaluate, and which appear more standardized, is the regulation of vascular tone (the same issue evaluated by the FMD and EndoPAT)[34][45]. When endothelial damage occurs the vascular tone is the first function that can be compromised because may depend by the anatomical alteration of endothelial cells, and therefore useful to detect previously. For this reason, the study of volume-blood changes was identified as a possible method to detect the endothelial dysfunction.

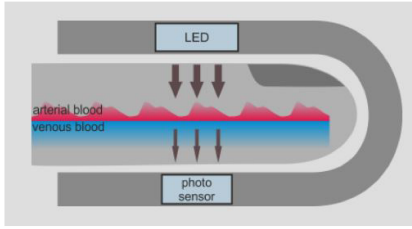
Among the different methodologies to assesment the endothelial function, the attention was focused on the photoplethysmography. There are several studies that were conducted to investigate the utility and efficacy of the photoplethysmographic signals in the assessing of endothelial function. In particular, some of these were conducted to investigate if there is any comparison with the gold standard (Doppler ultrasound via flow-mediated dilatation)[3],[46],[47],[48],[49]. Based on these results, that show the high correlation between the exams of ED by PPG and the gold standard and considering the limitations of the normal techniques that have already been explained, to satisfy all the requirements of the new medical device the PPG method was chosen.

2.3.1 Photoplethysmography

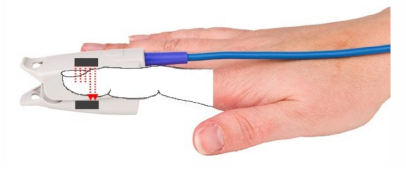
Photoplethysmography (PPG) is a noninvasive, optical technique that can be used to determine the changes in blood volume as a function of time, in the microvascular bed of tissue. To obtain a PPG signal, a light emitting diode (LED) illuminates tissue with two different wavelengths (red and infrared) and a photodiode on the other side of the tissues measures the intensity of the non-absorbed light at each wavelength, Figure 2.5. This technique was developed by Takuo Aoyagi and is an indispensable clinical tool for non-invasive monitoring of blood oxygen levels. The technology it is based on two principles:

- Light absorbance is different for oxygenated and non-oxygenated haemoglobin at the two wavelengths used
- Based on the wavelengths there are two components (Figure 2.6)
  - The absorbance has a pulsatile (AC) component which reflects the pulsations from the cardiac cycle, indeed represent the changes in the blood volume that occurs between the systolic and diastolic phases.

– the non-pulsatile component (DC) of the PPG signal depends on the structure of the tissue, indeed represent the absorption from the tissue and bones as well as static blood absorption (arterial, venous and in smaller amounts, capillary).



(a) *The transmission mode of PPG sensor (image from the MEDIS company website[1]))*



(b) *Finger clip PPG sensor (image from the Mind Media website [2])*

Figura 2.5: *PPG sensors placed on finger*

The PPG enables to measure the arterial oxygen saturation (SpO2) using the ratios of AC and DC components of the red and infrared PPG signals and in standard clinical setting, the PPG signal is usually seen in the monitors with the Hearth rate (HR) that is excracted from the PPG. In this work, the application of the PPG it used to study the PPG morphology insofar useful to study the ED.

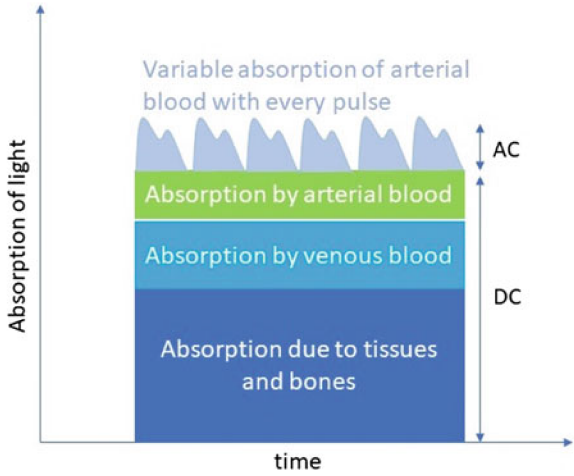


Figura 2.6: *Pulse oximetry waveform illustrating pulsatile and non-pulsatile absorption components (image from [2])*

2.3.2 PPG and ED

As mentioned in the paragraph 2.3, in literature different studies demonstrated that there is a correlation between the PPG and the Flow Mediated Dilatation (gold standard) to assessment the ED [3],[46],[47],[48],[49]. In particular, Zahedi et al. [3] [50] demonstrated a significant association between PPG amplitude and the FMD to evaluate the endothelial function, they applied the same procedure of the Flow Mediated Dilatation with the acquisition of PPG. In detail, for measuring the PPG signal, they recorded three minutes in the baseline condition, four minutes during the occlusion of the brachial artery (by the cuff placed above the elbow), five minutes during the hyperaemia. The figure 2.7 takes from the paper Zahedi et al,[3] represents the PPG wave respect the FMD wave measured with Eco-Doppler of a healthy patient.

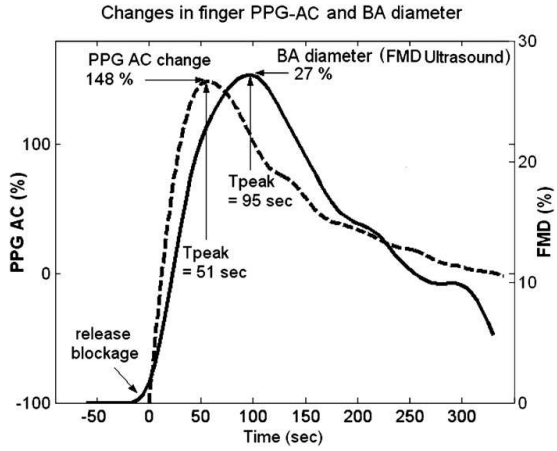


Figura 2.7: *Percentage changes in the brachial artery diameter with the PPG signal (dotted) and the FMD (solid line) in the healthy patient during the hyperaemia phase (images from[3]).*

It was thus decided to develop a new medical device to detect the endothelial dysfunction based on photoplethysmography technology, for the following advantages:

- There is the correlation between the PPG and FMD (gold standard)
- Less expensive respect the other methods
- Possibility to extract some morphological features
- Non-Invasive

Capitolo 3

ED in the oncology context

In recent years, thanks to advances in early diagnosis and above all substantial improvements in therapy, there has been a noticeable prolongation of patients survival affected by neoplasms. However, cancer patients showed some cardiovascular complications which represent an increasing problem in modern cardiology and oncology clinic practice. In particular, ventricular dysfunction and heart failure are the adverse effects common to many categories of cancer drugs. For this reason, a careful assessment of the patient's risk profile through close cooperation between doctors and patient monitoring is necessary for successful treatments, in a way to prevent and control complications. In this context, the idea is follow cancer patients during chemotherapeutic treatments, with the new medical device, objective of this thesis. The introduction of this device allow to identify previously the ED which, has some studies have shown, may be caused by the toxic effects that comes from the assumption of cancer drugs. At this purpose a project called IOT has been developed with the aim to constantly monitor patients following chemotherapy treatments with the ED detection tool.

3.1 Introduction and scopes of the IOT project

The project **Intelligent Oncology Telecare** (IOT) integrated the research activities of this thesis. IOT is a project co-funded by indirect Europoean Commission funding managed by the Marche Region under the program POR-FESR 2014-2020. In the project are involved ten companies, three university departments and the local public health authority.

The IOT project targets the development of a new management model for chronically illness oncology, through the development and testing of advanced technological systems that allow home management of the sick under the supervision of qualified medical team that works remotely through a control centre. Today the improvement of efficiency and optimization of the health system requires of the decision-makers that they respond to a growing demand for services while maintaining the same level of service. In Italy the number

of cancer patients are increasing (in 2014 there were 365,000 malignant tumor diagnoses, in the latest ISTAT data (2012) there were 1322 cases in the Marche Region) and at the same time the mortality rate of this disease is actually decreasing, so that today the term "chronic" allows for living with the disease for a longer and longer period, engaging more therapeutic resources, through both hospital and domestic care since several studies conducted show that the treatment administered to chronic patients is far more effective if administered at the patient home. As a matter of fact, experimental studies only 4% undergoing domiciliary palliative care resort to hospital admissions. The innovative organisational and management model of home care for the cancer sick will be through the development of new telecare devices and technological communication infrastructure for the continuous monitoring of the patient, controlled drug intake, psychological and clinical care as well as the creation of a data sharing environment related to the particular regime of treatment. From the point of view of hardware new SMART devices will be developed that will cause a paradigm shift in the quality of life of a terminal cancer patient enabling treatment at home with all the required medical and technological support. The system will avail of devices for the detection of important physiological parameters to determine the patient's health that can be easily deployed in the home environment. In addition, the cancer patient would have to undergo diagnostic tests to check for side effects of a therapy, which leaves scope in this project for the design and development of such innovative devices (System for evaluation of endothelial dysfunction and electrocardiograph) that will allow examinations at home with analysis and reporting conducted through authorized doctors remotely. In patient management oncology at home the project will also produce a device for the administration of drugs according to appropriate protocols through a smart dispenser that is an innovation compared to the current scientific and technical state of the art. The release of the drug will be processed automatically by generating alarms at two levels: the first is effected through a simple acoustic reminder mechanism and / or voice. Failing this warning the device is able to alert a caregiver that the medicine has not been taken through the delivery of a push message. The use of this device safeguards the patient against a loss of the correct prescribed care, without interruption of family life at a difficult time. It also simultaneously facilitates the optimization of cost and management of delivered health care. The monitoring and diagnostic devices integrated constantly send all the medical information in encrypted form to a Cloud facility that will allow it to be available in real time. Furthermore, this same data and can be integrated with the regional health records, a facility not available today. In this way it will effectively permit the creation of a real home control centre of the physiological parameters required to assess the state of health of the patient by carrying out "remote

visits" to the clinician who will be able to evaluate the effects of the drug use via the dispenser, thus providing a totally innovative, immediately accessible mode of administration. The scientific information produced by research combined with those produced in real time and transmitted from the devices on the network from the dispenser, generate large amounts of data, the complexity of the phenomenon, requires the development of a inferential semantic system for oncology. The system is designed as a powerful and effective innovative tool to be used by the clinician or physician to acquire, integrate, develop, make available and enhance an impressive wealth of knowledge, based on the integration and correlation with multiple levels of both clinical and scientific grounds, both real and experimental. The architectural solution will be service oriented (REST), in order to offer to the user community, in a short time, an innovative and advanced service, which can be continually improved on the basis of its own results.

IOT partnership

The project leader is the VIVISOL Srl, one of the leading European groups operating in home healthcare, that through the means of this project intends to invest in research and development of new models of specialized care for cancer patients, and thus enter into a new market. The rest of the partnership consists of a pool of highly competent knowledge based companies working intensively for years in the field of medical and electromedical devices. Aditech, Systemic and Strumendical are involved in the project for the construction of new monitoring devices of physiological parameters, home diagnostic devices and the new dispenser thereby taking the opportunity to introduce new products in the healthcare market. Ataena, manufacturer of machinery for the packaging of the drug, recognizes the potential of the dispenser by intervening in the development of a new packaging format for drugs in order to reduce waste. Again with reference to the dispenser design, the intervention of AV Consulting will provide the project with valuable experience in the area of biomedical design. The software for the device will instead be drawn up by companies Win Italia and On Demand. Charry Lab will provide for communication between the different devices in order to enhance the character of interoperability allowing the sharing of data and warnings that are managed by a web platform developed by Bookerang that has already participated in other projects in the health sector and intends to go to market with a developed product product. In the partnership, taking the role of consulting will be three public research companies (Unicam, UNIVPM and further to these in the same role one public-private company (Meccano). The main competitive advantage attained by companies is expected be the definition of a model of care of cancer patients standardized and normalised so that it can be replicated and exported on a national and

international scale. This represents a real opportunity for companies to enter their systems and devices within standardized protocols that can be sold as a single system or package. Further, entire territories might adopt on a trial basis such systems to provide certain types of users (from the chronically ill) who may come from abroad to choose a type certified nursing which enables high standards of quality and comfort. In addition, companies will be able to look out at a potential market which is offered through the involvement of private investigators. The companies will commit to producing products in 18 months, with the exception of the endothelial device that requires more time for the certification of the biomedical device and this is expected to release at month 24. In any case, the duration will be from 18 to 12 months. The experimental phase of the project will be conducted on ASUR AREA VASTA 2, the territorial zone of Fabriano and Senigallia (Italy), will validate the clinical aspect making it possible to identify a business model and measurement of the ROI of such technologies within the public and private health systems. This is thanks to the involvement of VIVISOL, which will handle the technological validation.

IOT Clinical Trial

The trial will be carried out thanks to the voluntary cooperation of 100 cancer patients treated at the Medical Oncology Unit of Fabriano and Senigallia. The population will be composed of individuals who show a higher cure prospective greater than six months, sub categorized through a sufficiently representative sample by age, tumour type and treatment. The purpose is to validate a social welfare model of cancer patients through a trial that compares two groups of patients. In fact the first half of the sample (approximately 50 subjects) will be treated through an evolved care model with all the instrumentation developed within the project, the other half will only be treated with a traditional home care system with the aim of putting comparing the results obtained in terms of cost benefit. This assessment, which will be realized through statistical studies, will be based on symptom control and the quality of life of patients, the use of hospital resources in the active treatment phase and the end of life, the acceptability of the technologies by patients and their family members.

IOT goals

The benefits that this new model would bring the needs of the community are manyfold and all aimed at improving home care resulting in more efficient public spending: i) greater comfort for care received in the home environment will lead to a reduction in hospital admissions and emergency calls; ii) through the platform and the sensors it will be possible to provide new daily data available to the general practitioner and clinical staff allowing them to evaluate and to appropriate care prescribed based on the extensive monitoring by reducing hospital admissions and facilitating optimisation of drug consumption.

The project started in 2017 and will last three years. The idea is to propose a new and efficient home-based management system for the oncologist to improve the quality of care through an innovative tele-care devices and the use of advanced data methods.

The main project goals related to this thesis are (figure 3.1):

- overseeing the cancer patients every hour at home with a new, low cost and easy to use screening device (object of this thesis) and collect a list of other basic health parameters and data (electrocardiogram, blood pressure, etc) to a cloud infrastructure.

- design a data driven decision support system (DSS) on a cloud computing architecture concerning oncologist medicine, to facilitate the sharing of health data and coordinate their streams.

- give the possibility to the clinical team, to administrate the drugs, check the action of the chemotherapeutic treatment identify previously the toxic effects and eventually change the therapies, based on the DSS.

In this context, the new screening device to detect endothelial dysfunction plays a key role: it should follow the patients during the cancer treatment, monitoring the action of chemotherapeutic agents. In this way, it is possible to follow the cancer treatment also from the cardiology perspective. Previous studies linked the toxic effects caused by the radiotherapy (RT) and/or anthracycline-containing chemotherapy and the endothelium alteration. This may result in an increased risk of cardiovascular complications, as coronary heart disease, valvular heart disease, and heart failure (HF) in survivors of tumours [51] [52] [53][54][55][56].

The following paragraphs describe all the activities of the IOT project correlated with the development of the new medical device. Whereas, all the following phases, are coordinated and supervised from the undersigned that has covered the role of project manager. All these activities are coordinated by the collaboration of Strumedical s.r.l. [1] (the owner of the device) and the

[1] Strumedical s.r.l. Via Tambroni, 28, 62010 - Montecassiano (MC).

Department of Information Engineering , Università Politecnica Delle Marche [2].

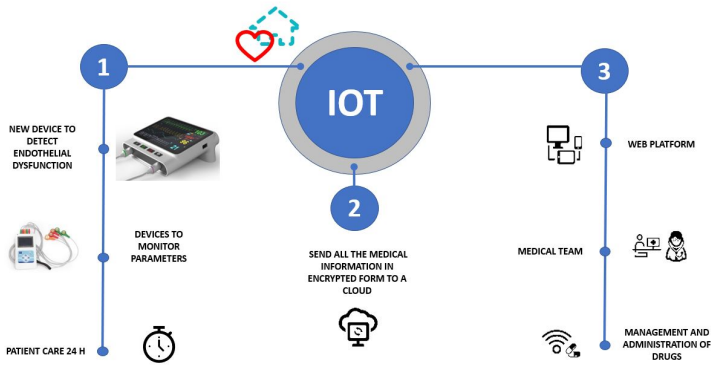


Figura 3.1: *IOT project schema*

[2] Department of Information Engineering, DII, Università Politecnica delle Marche, Ancona (AN)

3.2 IOT Design Activities

The IOT project is divided into two main activities: The development of the prototypes, and the clinical trial for the bio-medical technique validation. The following list reports all the project activities with the specific partners involved:

- Design and development of the device prototype, in cooperation with:
  - Department of Industrial Engineering and Mathematical Sciences, Università Politecnica Delle Marche[3] for the conceptual design (described in the paragraph 4.1).
  - KUNST Engineering s.r.l. [4] company to design and produce the hardware and firmware (described in the paragraph 4.2).
  - Department of Informatics of the "Università di Camerino" (UNICAM) [5] and the Department of Information Engineering , Università Politecnica Delle Marche (UNIVPM) [6] to develop the software and the Electronic Health Record (described in the paragraph 4.3).
  - Eng. Raul Frolla [7] and the TECNE 90 s.p.a.[8]company for the industrial design and the 3D printing models respectively (described in the paragraph 4.4).

- Clinical Trial: The aim of this step is to compare the results from the device to the gold standard, i.e. the Flow-Mediated-Dilatation by Eco-Color-Doppler exam. For this part, it became necessary to contribute to defining the statistical analysis and the correct way to compare the two exams. Moreover, it was necessary describing in detail the new medical device, as the exam procedure, the algorithm implemented and other features to define the clinical investigation plan, used by the Ethics Committee and Ministry of Health. This phase is obligatory to validate the algorithm and the device, and fundamental eventually for the next step, otherwise the EC certificate according to the Directive 92/42 EEC. Schematically the clinical trial is reported in the Appendix (Figure 1). In this task are involved the following structures:

[3]Department of Industrial Engineering and Mathematical Sciences, Università Politecnica Delle Marche Via Brecce Bianche, polo Monte Dago, 60121 - Ancona (AN)
[4]KUNST Engineering s.r.l. Via Remo Stortoni, 20, 62019 - Recanati (MC)
[5]Department of Mathematics and Computer Science, University of Camerino - Camerino (MC)
[6]Department of Information Engineering, DII, Università Politecnica delle Marche, Ancona (AN)
[7]Eng. Raul Frolla, Via Vittorio Veneto, 9 , 63839 - Servigliano (FM)
[8]TECNE 90 s.p.a., Via Firmino Giulietti, 3, 62010 - Montelupone (MC)

- Hospital of Fabriano [9], where the clinical trial will start in January and after six month will be concluded, the study will be supervised by local health authority "Azienda Sanitaria Unica Regionale Marche".

- VIVISOL s.p.a. [10] (a SOL group company), operates in the framework of home care in the health care setting by managing medical and curative therapies at home. They will be follow part of the Clinical trial in the Hospital and then they will replicate the procedure in the home care environment.

- MECCANO s.p.a. [11] expert in the sector of the device certification process, they supported all the activities necessary to obtain the CE Marking.

Furthermore, has been necessary for this project add some technical requirements respect the first version of the device because were necessary some integrations, how the communication with health platform (provide clinical health care from a distance) and the interconnection with other devices as the blood pressure monitor. For this part, it is involved the Department of Information Engineering (UNIVPM), and the Department of Informatics (UNICAM). After this phase, when the measure will be validated, begins the second phase the monitoring of cancer patients at home with the device to detect the ED. For this phase will be necessary to continuously monitor the patients involved by providing them with a basic technological infrastructure for the detection of physiological parameters. For this purpose, the work that Vivisol (a SOL group company, operates in the framework of home care in the health care setting by managing medical and curative therapies at home) makes at the patient's home it is crucial, thanks to the constant nursing medical support, were collected all the measurements of physiological parameters. At the same time, the ASUR Marche with the oncology associations follows the home care service to the cancer patient's home. Finally, the monitoring and diagnostic devices that are used at patient's home, constantly send all the medical information in encrypted form to a Cloud, to be available in real time the patient's data to the clinician.

[9] "E. Profili" Hospital, Intensive Care Unit, 60044 - Fabriano (AN).
[10] VIVISOL, Via Agostino Novello 1, 60035 - Jesi (AN)
[11] Meccano s.p.a., Via G. Ceresani, 1, 60044 - Fabriano (AN)

3.3 Impact of the IOT project and future prospective

The major impact of the project on competitiveness is that the new medical device to detect the endothelial dysfunction is innovative compare the markets devices. Moreover, the study of the ED in the oncologist patient is a novelty, it is important to highlight as some chemotherapeutics agents may be lead an endothelium alteration, and consequently in the cardiovascular complications. Indeed, sometimes the cancer survivors may face cardiovascular complications [57]. A different perspective is about the impact in the local area, in the regional manufacturing sector. From an industrial point of view, the development of this project involves :

- Create a new industrial district for the development of medical systems for personal care. This field is in perfect harmony with the regional policies that already for years provide for an industrial conversion on the assisted home automation technologies;
- The specialization of industrial companies about the issues of certification and validation of the medical devices, which sometimes represents a real barrier to entry to the market;
- The possibility for small and micro companies to tap into a lucrative and potential market, reducing the economic risks of testing times and very long validations.

These results will be achieved through the synergy between large and small companies, the involvement of the researching partners and the regional Health system. Based on these considerations, it is clear that the project has direct effects on the Smart Specialization of the Marche Region, contributing to the achievement of the strategic objectives set by the POR - FESR 2014/2020 program in the different thematic areas as:

- Ambient Assisted Living: through the use of advanced technological solutions integrated into home care. In particular, the use of medical devices dedicated to the detection of physiological parameters to assess the well-being of the patient, that are interconnected thanks to the development of communication protocols.
- Health and wellness: all the data from the devices are collected and shared on a cloud-based architecture data with an intensive effort on privacy and data security on open and interoperable standards in synergy with those developed by the Marche Region.
- Mechatronic: for the new medical device, some microelectronics and advanced materials will be studied and developed in according to the specifications imposed by the various medical device certification standards.

Furthermore, the adherence of the project to the regional strategy will be measured according to two main parameters:

- use by the user-end of the product device
- increase in the production of technological devices for the elderly and non-self-sufficient people.

Capitolo 4

Conceptual Design, Hardware e Software

This chapter describes the hardware and software design, together the user interfaces and the ergonomic human machine interface (HMI). For every module of the device project design detailed results about the implementation is presented, together with main novelties and barriers. This part is one of the main contribution of this thesis: the conceptual, hardware and software engineering of the novel Endothelial Dysfunction device and its comparison with the state of the art.

4.1 Conceptual Design

The first stage of the design it is a deep analysis of all issues, clarification of tasks, define the requirements list to take in account the demands and the wishes of the customer, therefore to define all these aspects it is important to involve different figures (clients, users, engineers, marketers, other experts). To follow these steps it was used the Quality Function Deployment (QFD) method [58]. This approach it was used to identify critical customer attributes and to create a specific link between customer attributes and design parameters.

The main utility of this approach is that the design it is oriented to the client and to satisfy his needs, and these requirements based on the priority are transformed in quality characteristics, including also the analysis of the weaknesses of the product with that of the competition. Moreover, other advantages with the QFD, it is a reduction in the time required for product design as well as a reduction in those costs associated with the process. This is possible because the design alternatives are realised much earlier in the process, thus lessening the number of corrections and design errors.

Furthermore, a higher level of clarity for decision making is gained through the use of this tool. The organising framework for the QFD process is a planning tool called the " House of Quality" it is a kind of conceptual map that promotes the management of the flow of information, thus provides the means for cross-functional planning and communications. In the diagram 4.1 are described the phases to obtain the matrix table of the "House of Quality"[59]. After that, were defined all the the connections between the tasks and functions by the Function Analysis System Technique (FAST) and the abstraction process. For the Conceptual Design, the study and the modelling of the chassis have collaborated Eng. Alma Leopardi, PhD student in Department of Industrial Engineering and Mathematical Sciences, Università Politecnica Delle Marche. [1]

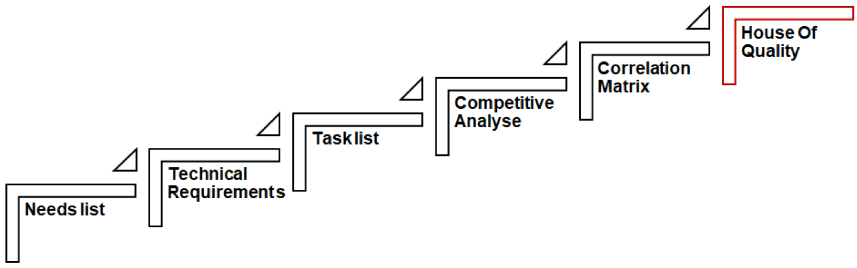


Figura 4.1: *Basic steps to obtain the House of Quality*

[1] Eng. Alma Leopardi, PhD Student in Department of Industrial Engineering and Mathematical Sciences, Università Politecnica Delle Marche Via Brecce Bianche, polo Monte Dago, 60121 - Ancona, a.leopardi@pm.univpm.it

4.1.1 Hardware and Software design: materials and methods

Requirements list and technical specifications

The requirements list it was structured identified, first of all, the needs of the client, i.e. the medical doctors. After that, they expressed the weight for every need by a numerical value from one (less important) to five (most important), as is highlighted in the table 4.1. Then the obstacles were recognised during the analysis of the context of use of the device.

User needs	Weight	Obstacles
CE marking	5	-
Class II medical device	5	-
Portable	4	size and weight too high
User-friendly	4	hard to use also by specialised operator
Real-time results	4	absence of paper report
Power supply connected or battery power	3	there aren't device that allow both the solutions
Washable	5	
Automatic device to block the blood flow in the brachial artery	5	sphygmomanometer is always separated from the device, and is not automatic
Non-invasive	5	PPG for single use
Touchscreen	3	screen to small
Physical keyboard	3	lack of physical buttons for quick actions
Clear user interface	4	complex user interface
Independent from other devices	4	they aren't the stand-alone devices
Connect the device to computer	3	communication problems with other devices
Connect the device to external monitor	3	viewing problems
Personal data	5	problem associated to the use of the small screen
Resistant	4	
Adhering to the supporting surface	3	slippery on support surface
Waterproof	4	
Easy to read on-screen	4	problem associated to read the screen (sitting position)
Blood pressure measurement	2	the other devices do not measure the blood pressure
Extract fiscal code from the reader	2	it is an accessory that facilitate the data entry

Tabella 4.1: *User needs, weight from 1 to 5 for each need (defined by the users) and the obstacles recognised during the analysis of the context of use of the product*

Based on the previous information, technical and functional requirements were defined, as reported in the table 4.2. The basic requirements are implicit requests, namely not defined by the customers.

While the technical requirements are explicated by the customer, these were used and selected to compare the proposed system with similar devices currently in the market. Finally, the attractiveness requirements are a list of implicit requests, wthat make the difference on buying or not a device (colour, shape, material, user interface). Also a user-task table is reported to show how the evaluation was processed. starting from the above mentioned data (Table 4.3).

	Requests	
Basic requirements	**Technical requirements**	**Attractive requirements**
1) Safety for patients and Operators	1) Satisfy all the characteristics to CE marked	1) Manageable shape
2) Indication of intend use	2) Material easy to clean and disinfect	2) Anti-slip surface
3) Non-invasive	3) Hypoallergenic material	3) Transportation case
4) Class II device	4) PPG sensor reusable	4) Intuitive interface
5) Portable	5) Acoustic sound for the start and end of measurement	5) Bright screen
6) Weight less of 5 Kg	6) relatively small size and height	6) Un-squared shape
7) Robust	7) Thermal printer	
8) Staple on the support surface	8) USB ports (min.2)	
9) Waterproof	9) Ethernet port	
	10) Automatic sphygmomanometer	
	11) HDMI port	
	12) Battery life ∼2h	
	13) Touch Screen monitor: 10”	
	14) Resistive Touchscreen	
	15) Internal memory	
	16) Monitor inclined stand (20 degrees)	
	17) Blood pressure device included	
	18) Reader for extract fiscal code	
	19) Timer	

Tabella 4.2: *The list of requirements divided in basic,technical and attractive*

TASK
1. Use of the device in Europe
2. Use of the device completely in safety
3. Portable, useful also in home care
4. Start the measurement, print the report and switch off the device, easily and quickly
5. Obtain the exam report immediately also printed
6. The device is able to do the measurements by battery power or power supply
7. Use the device even by several people,guaranteed the hygiene standards
8. The automatic sphygmomanometer starting simultaneously with the measurement
9. After the exam the PPG sensors are ready for the next exam, the sensors are reusable
10. By the touchscreen it is possible to read the results and other information about the patient
11. Rapid commands troughs the physical keyboard
12. Reading speeds
13. Automatic measure
14. Device able to collect all the data in external memory
15. Device able to show the results in a big screen
16. Use of simple user interface and touch screen
17. In the event of falls the device do not break
18. The device it is fixed on the work surface
19. Waterproof
20. The screen is able to give a good read in the seated or in the orthogonal position
21. Device able to give the blood pressure measurement
22. Quick insertion of patient data

Tabella 4.3: *List of tasks that the user can perform thanks to the help of the device, that covering the implicit and explicit needs identified*

House of Quality

Once these features and technical requirements have been determined a "House of Quality" was constructed (Figure 4.2). This correlation matrix determines the relationship between different design factors [59]. The output of the house of quality is a matrix with customer requirements on one dimension and correlated nonfunctional requirements on the other dimension. The cells of the matrix table are filled with three different weights: one (less important), three (important), five (more important) assigned to the characteristics. The table is composed by thirty-eight columns (on the bottom) and twenty-one rows. In detail for the columns:

- The first two columns represent the needs importance
- from three thirty-two are the device's characteristics
- thirty-three is the sum of the weight for each row
- from thirty-four to thirty-eight are the planning steps
- the last two columns are the weights attribute for the devices selected as main competitors (EndoPat, Endothelix)

Finally for the following rows:

- from column one to twenty-three customer's needs are reported
- the last three rows are the automatic calculations that are useful to describe which features are more important related to the needs.

Starting from the "House of quality" several information were extracted. For instance, as reported in green cells in the columns dedicated at the "planning", the most important tasks are the class of the device, guarantee the hygiene standard and the waterproof, furthermore the device must be able to do the measurements by battery power or power supply and able to give the blood pressure measurement. Moreover, the requirements that result have greater weight than the other features are a big and useful touch screen, lightweight, the device must be non-invasive and operator-independent, that can be identify in the last three rows. At the end, were identified in the same table other features that can be implemented at a later stages or that can be considered how accessories, how reader for extract fiscal code or acoustic signal, and the timer. From this considerations were extracted the principal functions, and we proceeded with the abstraction process.

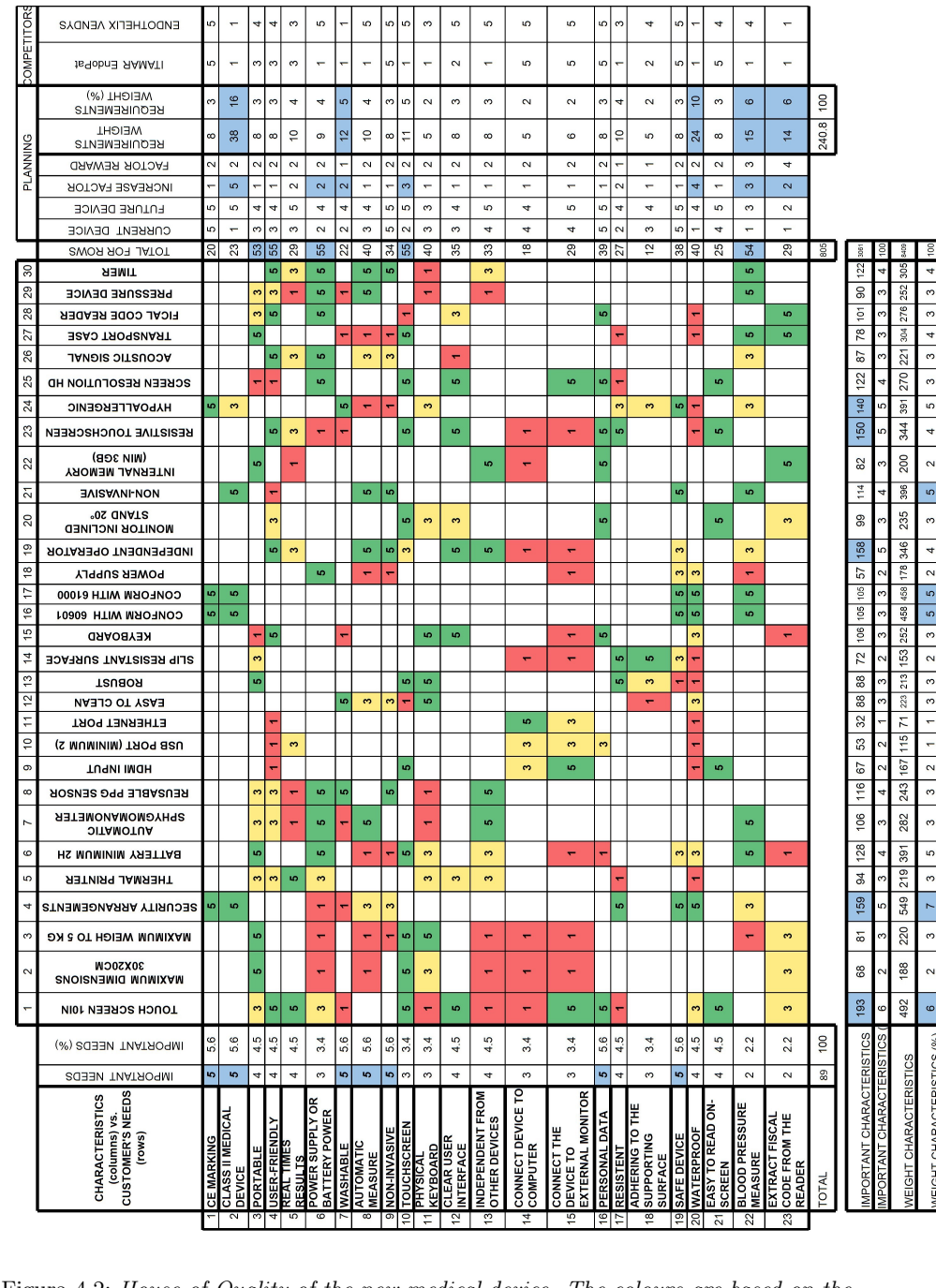


Figura 4.2: *House of Quality of the new medical device. The colours are based on the weights given for each characteristic, green (weights ¿ 3), yellow (weights ¿1) and red (weights=1). The blue colour indicates the most important information extracted from the House of Quality.*

Once the the requirements list was completed, it was elaborated by a competitive analysis layer, useful to compare the main features of the new device with respect to the competitors.

This phase, finally, evaluated the strengths and weaknesses of the competitor's devices to formulate the benefits and disadvantages of the new device. For this study are considered two different devices that are similar with the new device, in particular, the EndoPAT^{TM}(described in the previous paragraph 2.2.2) is the major competitor and the VENDYS II by Endothelix ®.

Functional Analysis and Abstraction in Conceptual Design Process

In the conceptual design process, one part is dedicated to the abstraction of the prototype. This step is fundamental to capture the essence of the functions, requirements, performance for the development of a new medical device. Initially was applied the Function Analysis System Technique (FAST) to identify the logical connections between the tasks and functions. From the following questions, it was possible to extrapolate the sub functions from the base function.

- How is this function performed?
- Why is this function performed?

Answering the first question, the sub-function about the base functions was determined, while the second answer, verified the correctness of the logical path (Appendix 2 reports the full results of this process).

After that we proceeded with the abstraction of the project, following these steps [60]:

- remove all the personal preference
- leave out the requests that are not connected directly with the base functions
- transform the quantitative data in qualitative data and reduce them to essential instructions
- generalise the results of the previous steps
- formulate the problem in a neutral way

Afterwards, were identified the central point of the project problems, it possible define the base function of the device (Figure 4.3).

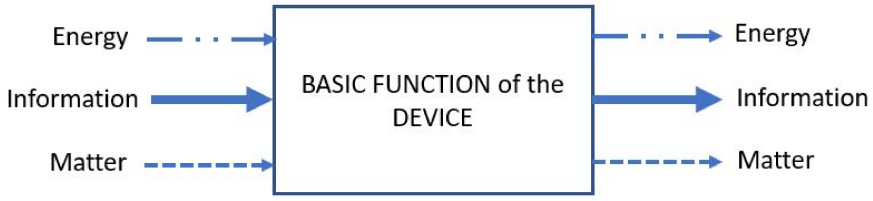


Figura 4.3: *Abstraction process*

Applying this approach in our device we started with the block show in the figure 4.4) which represents the overall view of the device with all the inputs and outputs. Subsequently this method was applied for each function.

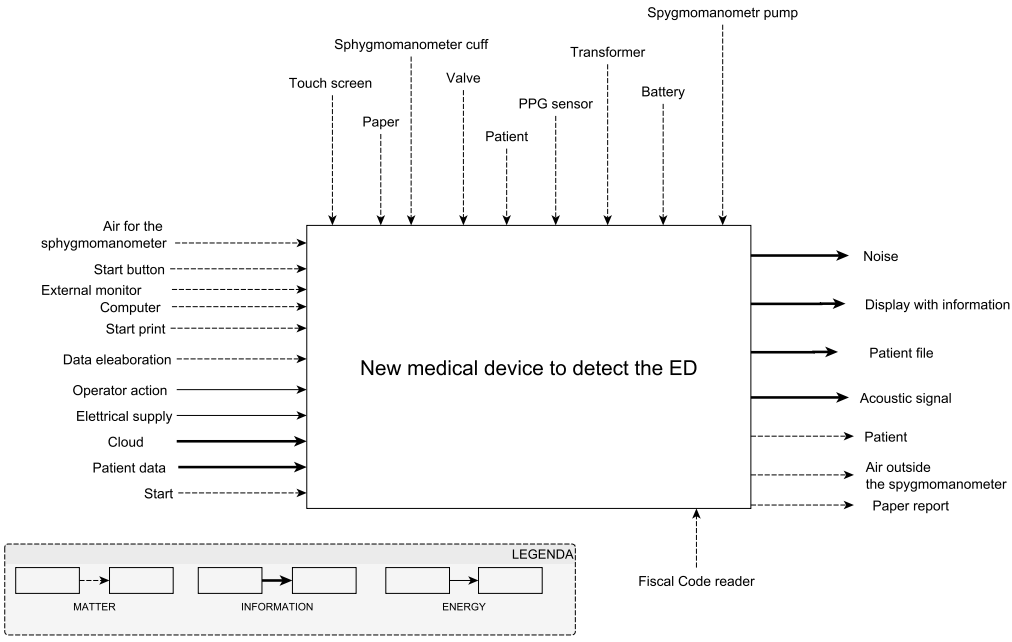


Figura 4.4: *Abstraction base level*

For the complexity and high quantity of device functions, the procedure was divided into four different levels. The first level of abstraction is shown in the figure 4.5; the seven blocks represent the most important function for this level: power supply, switch on and switch off the device, measurement, information management, printer function and the display of information. For each block, were defined inputs and outputs. After that, the second level of abstraction were developed: from the previous blocks twenty new blocks were extrapolated. For example, from the measurement block was extrapolated other five functions, sensor positioning, the start of a new measurement, sample photoplethysmography signal, occlusion of the brachial artery by the sphygmomanometer's cuff, stop the measurement. For each function, all the connections with the other features were defined. Finally, the third level and the fourth level were designed (Results of the whole process are reported in the Appendix).

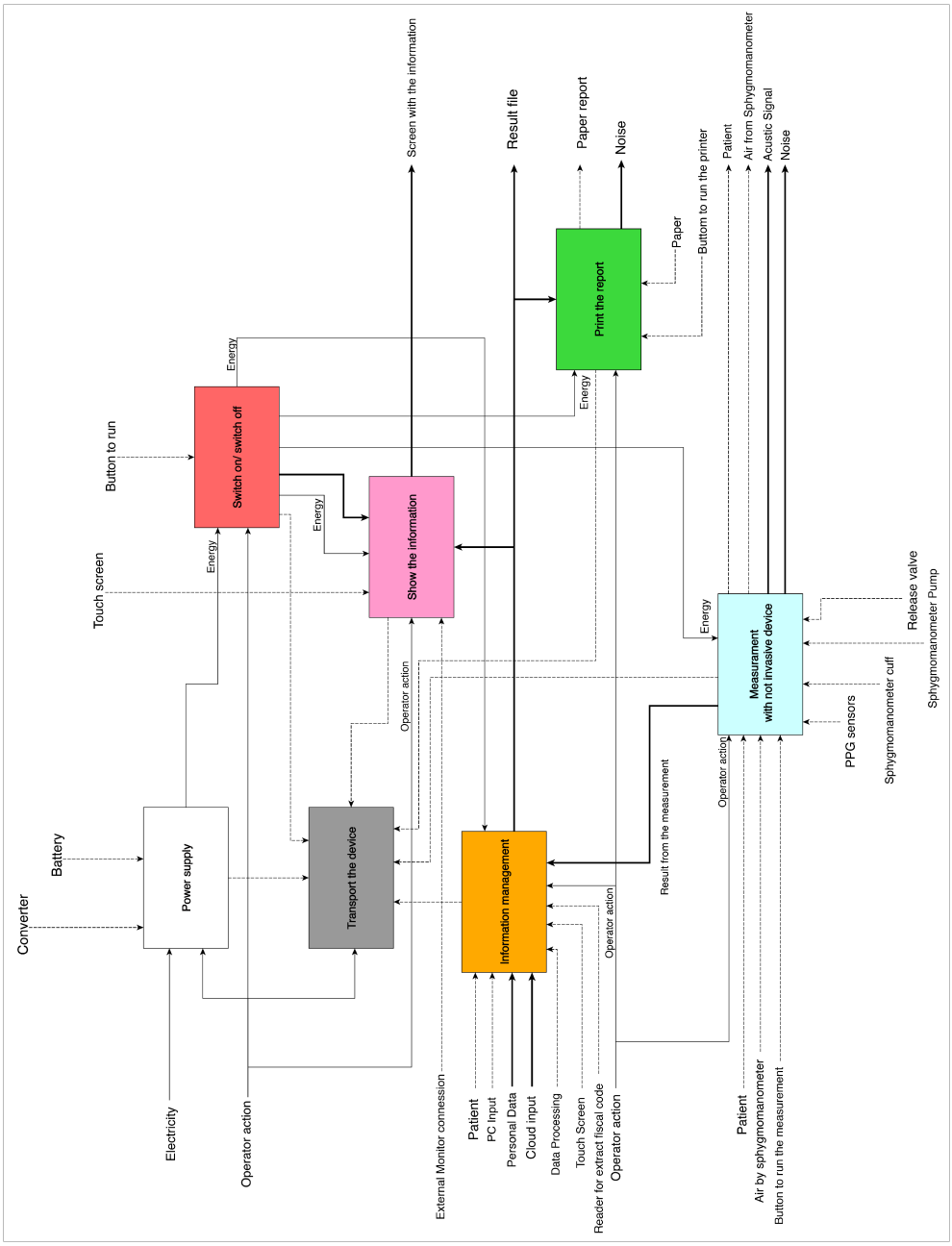


Figura 4.5: *Abstraction process first level*

4.2 Hardware Design

4.2.1 Introduction

This part will focus on the technical aspects of the device, considering all of the mechanical and design issues already fixed at this stage of the project. We will therefore put our attention on the measure system and on the electronics needed to perform the required functions. This part was develop in collaboration with the KUNST Engineering s.r.l. [2].

The design of the hardware will be derived by three main sources:

1. Project Requirements. Have been defined in the previous paragraph 4.1, and reported in the table 4.2.

2. The regulation requirements for medical device design and manufacturing. The device is an electronic system for used for screening, therefore has to be included in the "active medical device" category. The intended use is for both hospital and home-care, configured as a portable device (battery powered) that can operate also grid connected. The exact list of all the annex and the section that can apply to the device is still under analysis, but as stated during the first meetings with the notified body engineers, it is mandatory the application of the IEC 60601 (as general requirements for safety, EMC etc.) and, as new requirement also the application of the IEC 62304 for software lifetime management.

3. The physics and physiology of both measure and pathology

The device is based on the PPG signal analysis and its reaction to an external pressure alteration, the system will therefore consist of two main functional units:

1. A cuff (a sphygmomanometer type) controlled by a pneumatic system

2. A PPG analyser

The project have to face two main issues:

- Safety: involving the pneumatic cuff, being the instrument applied also to oncologic and/or paediatric patients often in long stay hospitalization, where both skin and circulatory system are extremely fragile.

- Reading accuracy and easiness of operation: the instrument is intended to be used by trained operators but in condition (i.e. home-care) where there is the need to perform a reliable reading in a limited amount of time. The instrument should give a reliable reading within the minimum number

[2]KUNST Engineering s.r.l. Via Remo Stortoni, 20, 62019 - Recanati (MC)

of attempts (ideally 1) to avoid over-stress to the circulatory system of the patient. The sensor for the PPG should also be able to react to compensate the different room light conditions and possibly the different condition of both the peripheral circulation and the skin integrity.

4.2.2 Material and methods

Device structure

Analysing the device main features, it is clear that it can be divided in three main units (see Figure 1):

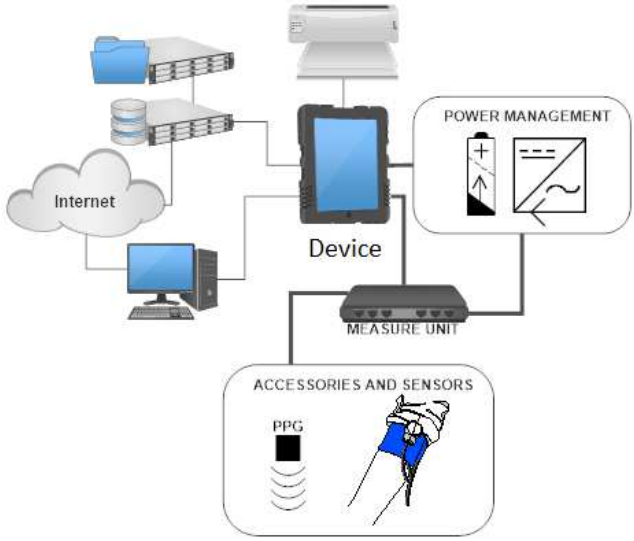


Figura 4.6: *Hardware device units*

- An interface system
- A measure unit
- A power management plus accessories and external sensors.

The user interface will have the possibility to connect to the external world through several standard protocol, and therefore a complete OS will be required in order to guarantee the possibility of integration on existing infrastructures. The interface is a bridge between the real instrument (measure unit + sensors) and the real world (users and other machines), we can than divide the interface in two sub-units:

- UI (user interface): composed by a graphical output (display), several input devices (pointing devices, push buttons, keyboards etc.) and the software needed to interact with the user

- SI (system interface): all the hardware and software needed to connect the instrument to other devices (i.e. network adapters, USB, HDMI etc..)

The role of the power management unit is to handle the battery charge, discharge, fuel gauging and to perform online power switching between self-powered and grid-connected operating condition. It is an independent system that can communicate with the interface to allow the user to acquire all the information about the power supply working status. The measure unit is the core of the instrument, all the information on the patient biometric parameters under analysis are handled by this unit. The unit con be divided in three main sub-unit:

- A sphygmomanometer (with its sensors and actuators)

- A PPG analyser: a chain of sensors, sources and electronics for signal conditioning to capture PPG signals from the patient

- A measurement control unit: a uC electronic to manage the required measurement and all the physical signals. This unit is also responsible to manage the communication protocol with the interface for data exchange.

Directly involved in the measure chain and connected to the measure unit there are two external devices (accessories and sensors):

- A PPG sensor, which is a set of coupled led and photodiodes, used to estimate absorbency or transmittance on the capillaries

- A sphygmomanometer cuff to perform vessels constriction and pressure measurement

These two devices, even if part of the measurement unit, are considered as independent items being commercial parts and therefore out of our design process.

4.3 Software Design

4.3.1 Introduction

The first version of the software was developed in collaboration with Eng. Fabio Pagnotta, PhD student in University of Camerino, [3]. For the design, we followed these steps: requirements list, analysis of them and definition of the uses case.

4.3.2 Material and Methods

Technical requirements, Analysis and User Case

Initially to evaluate functional and aesthetic features and to obtain feedback from potential users of the device, software prototyping was performed with simple images. With this prototype, the doctors, nurses and operators have been involved in some suggestions and changes. From this prototype, the technical requirements of the software have been defined. The advantage of this approach is to involve different users, refine the specific needs of the project and improve the usability of the software device and to reduce development time and costs. In addition to these specifications, all the items of the questionnaire that is submitted before each examination to the patient have been defined in detail. This information is of fundamental importance for a subsequent cross-analysis of the data with the exam and for integrating the patient's electronic medical record. Specifically, the information requested from the patient in the questionnaire are: Age, Sex, Height, Weight, BMI (calculated automatically, Fasting, Smokers, Not Smokers, Ex-Smokers, number of cigarettes, Drug, Antioxidants, Period of Menstrual Cycle, Influenza, Physical activity, Diabetes, Hypertension, Family History.

All the requirements are important, but they are prioritized to deliver the greatest and most immediate benefits early. For this reason was applied a fast analysis of the requirements with the MoSCoW method [61],[62]. How reported in the table 4.4 for each requirement was defined the weight importance. Briefly, the MoSCow analysis divides the requirements based on these categories:

- Must Have: the requirements are essential. Without these, the project fails and the software won't be usable.

- Should Have: the requirements are important but not necessary to use the software. They have a high priority but may be implemented in the second moment.

[3] Eng. Fabio Pagnotta, PhD Department of Mathematics and Computer Science, University of Camerino - Camerino, fabio.pagnotta@unicam.it

- Could have: the requirements are desirable but not necessary, could improve the user experience or customer satisfaction.
- Won't Have: the requirements for the future.

Once the necessary access levels have been defined, was identified all the user activities, that are contained in the figure 4.7.

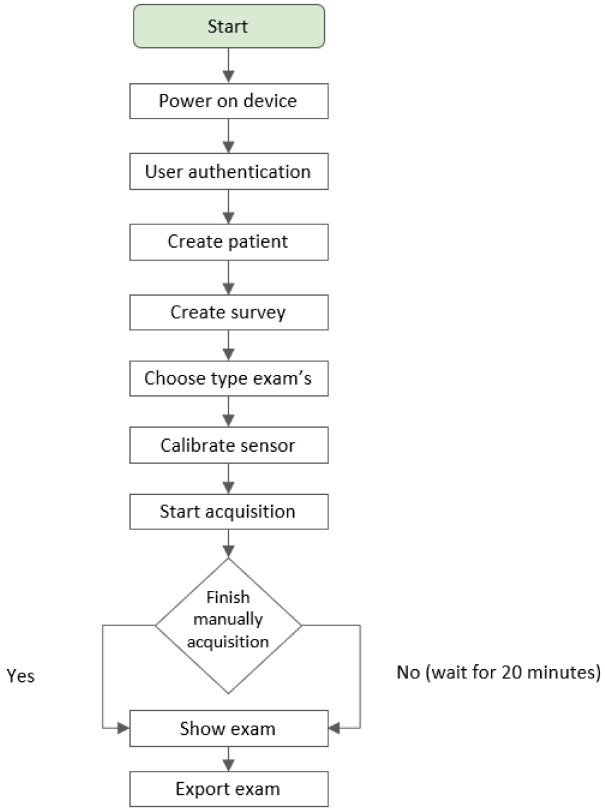


Figura 4.7: *Activity diagram with a series of actions and the flow control of the device.*

Suddenly the access levels were identified (Figure 4.8):

- Admin: User with the highest privileges can create and modify all the data. Furthermore, the admin is able to create the user credential for the other users.
- Doctor: this user can create, modify or examine the patient, export the data.
- External user (Operator): This user may visualize only the exam information.

ID	Description	MoSCoW
1	The software should be portable and easy to use	MUST HAVE
2	The device monitor the biomedical signal	MUST HAVE
3	There are the different user: Admin, Doctor, Operator	MUST HAVE
4	Each authenticated user must provide authentication credentials through username and password	MUST HAVE
5	Credentials of the admin or of the doctor must be saved securely	MUST HAVE
6	After succeed in the access, the device will have to identify the user as admin or doctor	MUST HAVE
7	The doctor can create and eliminate the patient's exams	MUST HAVE
8	The doctor can create/modify/eliminate and visualize the patients	MUST HAVE
9	The patient can be anonymous	MUST HAVE
10	The patient will be characterized by: id patient, name, surname, date and place of birth, address of residence, height (centimetres), weight (kilograms), gender, fiscal code, description and nationality	MUST HAVE
11	Automatic calculation of Body Mass Index	SHOULD HAVE
12	The acquisition of the fiscal code is done through an appropriate reader	COULD HAVE
13	The doctor can fill in a questionnaire	SHOULD HAVE
14	The questionnaire is composed by the following items: frequency of physical activity (never, 1 time, 2-3 times, more than 3 times) smoke (yes/no/ex), number of cigarettes (in the case of is a current smoker), year of the smoking suspension (if the patient stopped to smoke), last menstruation date (only for female gender: now, about 7 days ago, about 14 days ago, about 21 days ago, about 30 days ago, menopause), fasting before the exam (yes/no), physical activity before the exam (yes/no), influenza before 2 weeks (yes/no), diabetes (no/type 1/type 2), cholesterol (>=200mg/dl, <200mg/dl), hypertension (yes/no), consumption of antibiotics (yes and which one/no) consumption of antioxidants (yes and which one/no) current illnesses and familiar history.	MUST HAVE
15	Chose two type of exams: standard or trial	SHOULD HAVE
16	A standard exam require 20 minutes	MUST HAVE
17	For the trial exam the time is not predictable	SHOULD HAVE
18	The exam is divided into two phases: calibration and acquisition	MUST HAVE
19	The device will read 20 triple of values per second	MUST HAVE

20	The device has two sensors a Photoplethysmography(PPG) and a sphygmomanometer	MUST HAVE
21	The measurement will be displayed on a graph	MUST HAVE
22	The doctor can conclude the exam at any moment	MUST HAVE
23	The device will give an evaluation to the exam on the basis of an algorithm which takes into consideration the patient's data and the data acquired with the exam	MUST HAVE
24	At the end of the exam the doctor will be able to : eliminate, read, view, export and comment the exam	MUST HAVE
25	Data Format should be JSON and PDF	SHOULD HAVE
26	The device can export data in DICOM format	COULD HAVE
27	The device can export in a removable device (such as a pen drive, hardisk..) or in a server	MUST HAVE
28	The doctor can view the patients exam results in the screen "Patient results"	MUST HAVE
29	The doctor can view the daily exams on the screen "List of the daily exams"	MUST HAVE
30	The software should be set in a way that can be used on mobile devices	SHOULD HAVE
31	The software will have a virtual keyboard	MUST HAVE
32	The software will have a navigation bar for each screen	SHOULD HAVE
33	The taskbar must be summarized all the information linked to the device as date, time, percentage of battery and connection state	MUST HAVE
34	The taskbar will contains information regarding the selected patient and the registered doctor	MUST HAVE
35	The device will be able to provide a CE certification	MUST HAVE
36	The device will have a touch screen display, an internal battery, an ethernet port, one or more USB port and 4 physical buttons to be used by the doctor	MUST HAVE
37	There are 4 buttons on the device, to switch on and off, to start the exam, to print the exam, to stope the exam at any moment	MUST HAVE
38	Only the admin can create, modify and eliminate the doctor profiles	MUST HAVE
39	The admin can create, modify and eliminate the admin	MUST HAVE
40	In the plot of the exam, will show on the cartesian system the horizontal axis with the time (from 0 to 20 minutes) and the vertical axis with the blood volume changes (from -10 to +10)	MUST HAVE

Tabella 4.4: *List of the technical requirements and relative MoSCow analysis*

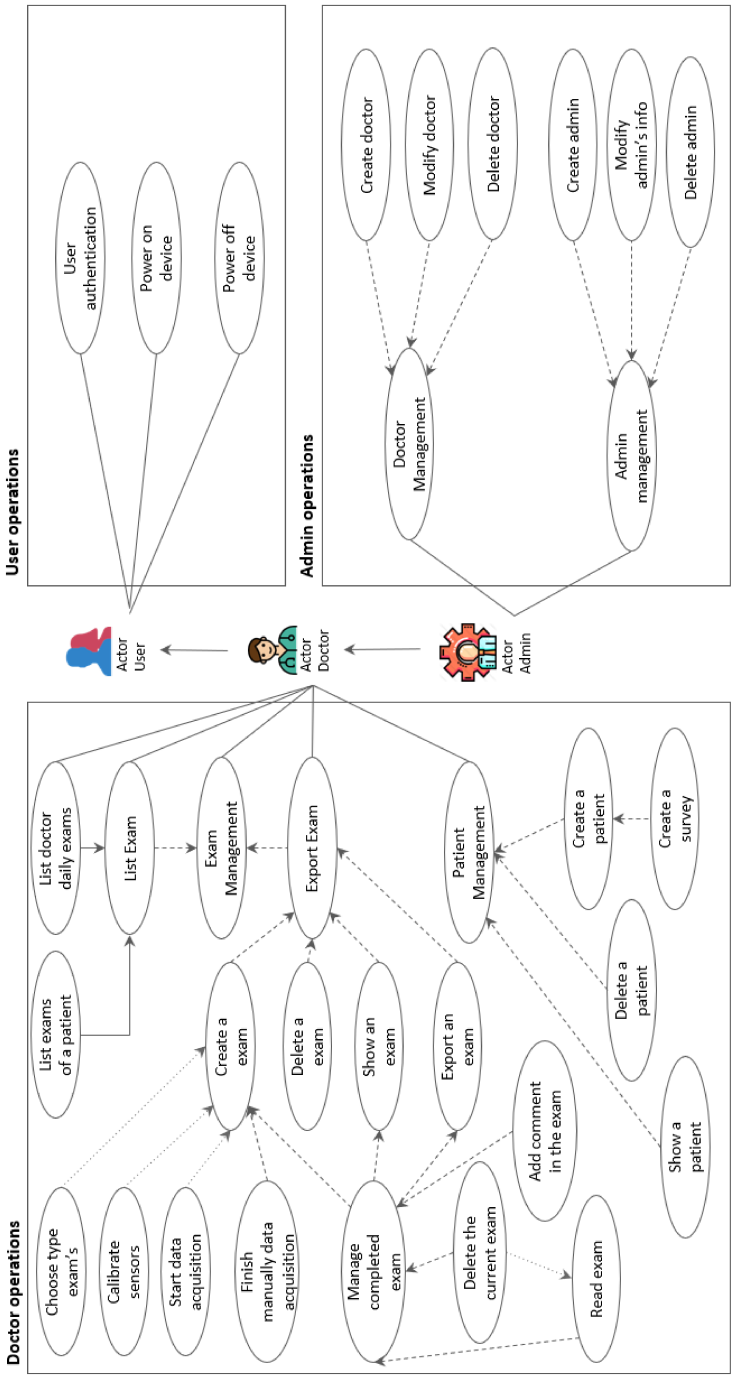
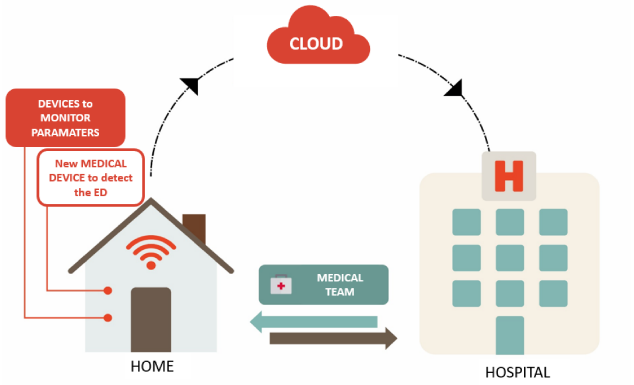
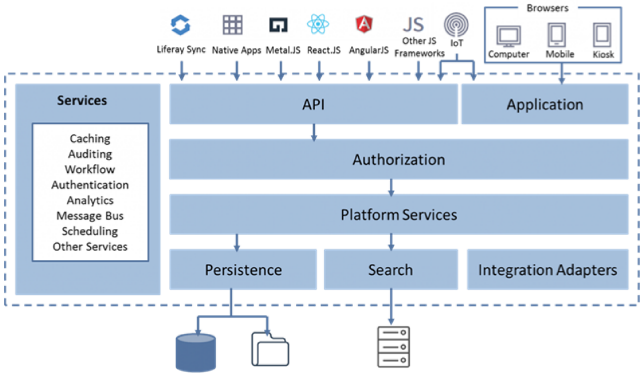


Figura 4.8: *Use case diagram where are describe a set of actions (use cases) for the different users: Admin, Doctor and Operator and their collaborations.*

4.3.3 IOT cloud-based healthcare architecture



(a) *The cycle of the transmission patient data, from the medical devices at home, to the cloud structure and at the end to the hospital. The infrastructure is finalised to give at the medical team the information of the health patient at distance at any moment*



(b) *The Data Architecture, that allows the developing and the deploying of the process automation of data collection, storage, processing and distribution through a medical device network that uses cloud computing*

Figura 4.9: *The cloud-based healthcare infrastructure*

According to the definition of the International Organization for Standardization (ISO) the Electronic Health Care (EHR) is a repository of patient data in digital form, stored and exchanged securely, and accessible by multiple authorized users [63]. The interaction with different clinicians, hospital wards and other structures produce several patient information that must be collected in the EHR for many reasons as facilitate the vision of data patient, to create a personal clinical history, to assemble the prescriptions, consultations

and medical reports[64]. A system that manages the EHR must be able to meet three main demands:

- the integration of data from different sources (e.g. hospitals, private clinics, health care professionals);
- the correct acquisition of data;
- support for clinical decisions.

In this context, for the IOT project, in order to collect all the information from different devices, we are implementing a system architecture that allows the developing and the deploying of the process automation of data collection, storage, processing and distribution through a medical device network that uses cloud computing (Figure 4.9) . The data from medical devices are imported in the cloud database through a system of WebServices (WSDL in XML format, according to the SOAP protocol) which guarantees the procedures for importing data and access to the database are encrypted and accessed, using "strong" credentials as well as other medical authorities (or other health professions, as far as relevant information about an individual is concerned) authorized by the physician.

4.4 Results

Following the steps described above, the study of the conceptual design, the hardware development and the software interface we have concluded the first prototype.

Hardware implementation

In this section we will describe the implementation of the hardware.

The main units are:

- The **main computer board**: can be seen as an embedded PC based on a multicore ARM processor. It is based on a Broadcom 2837 SoC, which integrates a quad core ARM A53 64bit processor and a quad core GPU capable of hardware graphic acceleration. The processor chipset is placed on a SODIMM200 board to allow replacement and easy upgrade if available.
- The **display**: The display is an industrial grade LCD with LED backlight. The display has been chosen following the same principles of reliability and performance, keeping the power consumptions as low as possible. The weight and dimensions for this display are among the best

available on the market for hard coated industrial product. To allow the deposition of a mylar film to increase ESD immunity and cleanability the resistive touch-panel has been chosen. The LED backlight will ensure lower consumptions and longer lifetime. The LVDS interface will help to reduce EMI while the extended temperature range for this display will increase the usability in different environment, especially in regions and periods of the years with higher temperature swings (Figure 4.10).

- The **interfaces** can use different input devices, we will not consider external common input devices (i.e. USB keyboard and mouse) even if always available as "plug and play" accessories. There are two main input devices the user will interact with when working with the device, the first one is the touch-panel of the display, which is a direct input device to control the device software (Figure 4.11). The second one is the pushbutton interface, this is an indirect input device, it is used just to control the device operations and, for safety and reliability reasons, if has been connected directly to the measure unit controller, the status of the pushbutton will then be transmitted to the interface through the communication protocol. Each pushbutton is also equipped with an LED to allow back lighting of the commands when the device is used in dark environments (i.e. ICU, night monitoring etc..) (Figure 4.11).

- The **OS and the Software**: In order to obtain the maximum performances from the device without having to increase power requirements, it has been chosen Linux as OS. In addition to the power vs. performances consideration, the development of applications on this OS is easy and reliable and widely used by the academic developers. Moreover Linux give an easy access to all hardware peripherals configurations and controls. The software will be developer natively under Linux, probably the first development of the application will be implemented using the Python programming language.

- **Measure unite**: where are implemented the dual channel PPG analyser and sphygmomanometer (Figure 4.12).

- **Power Management Unit**: It has been required to the device that could be operated both battery-powered and grid-connected. This means that we must have on-board two main power sources the Battery and DC power supply (Figure 4.13).

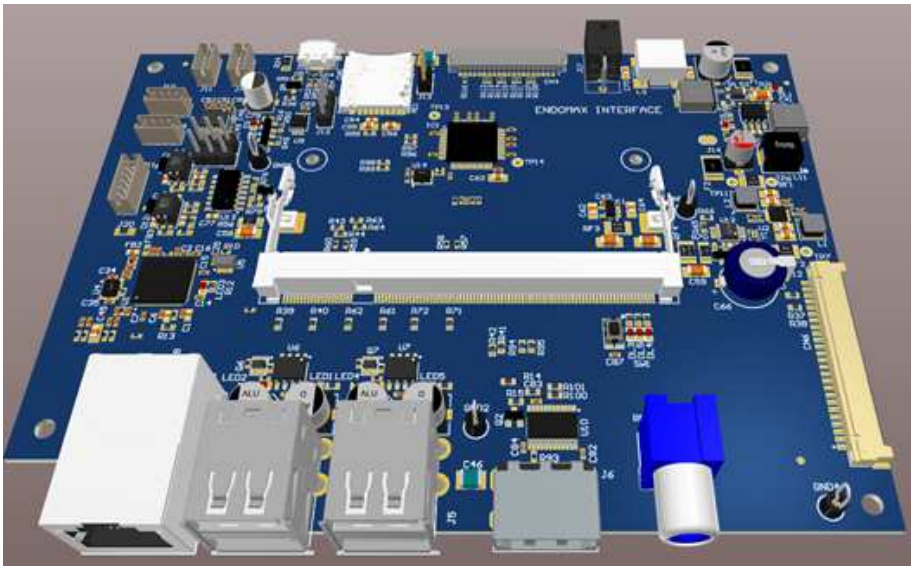


Figura 4.10: *The main computer board*

(a) *Touch Panel of the display*

(b) *Pushbutton Interface*

Figura 4.11: *The interfaces*

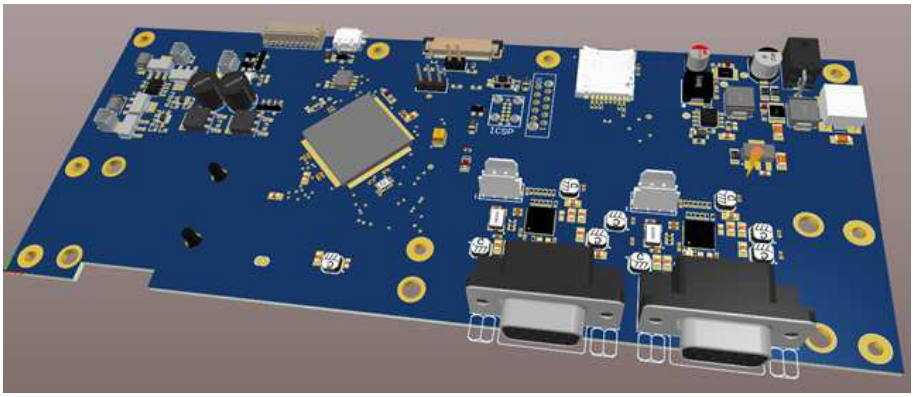


Figura 4.12: *Measure Unit*

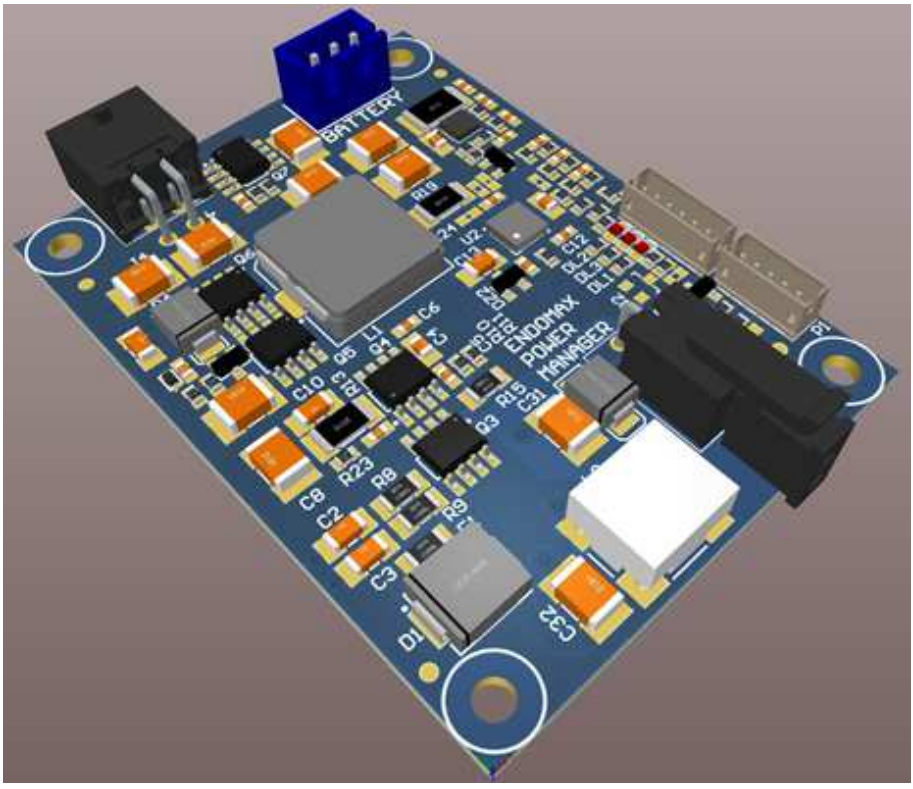
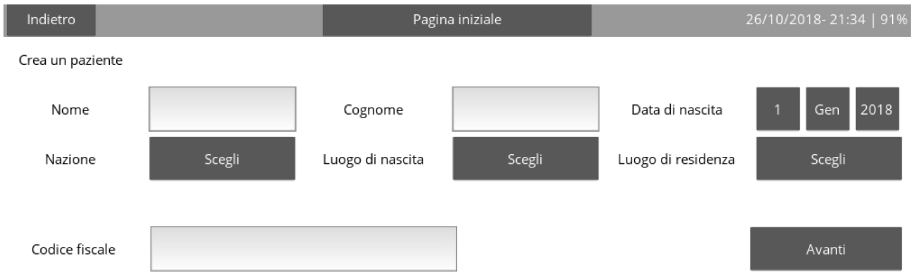


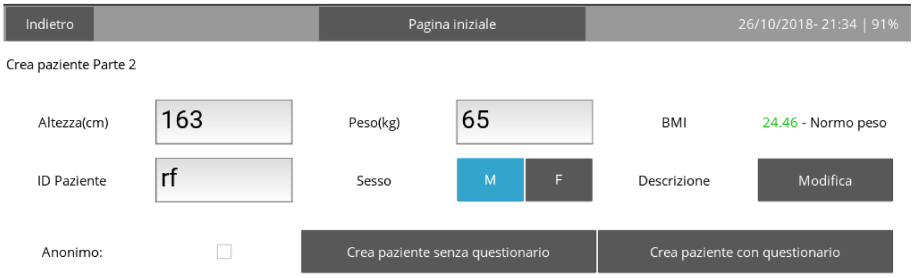
Figura 4.13: *Power Management Unit*

Software Interface

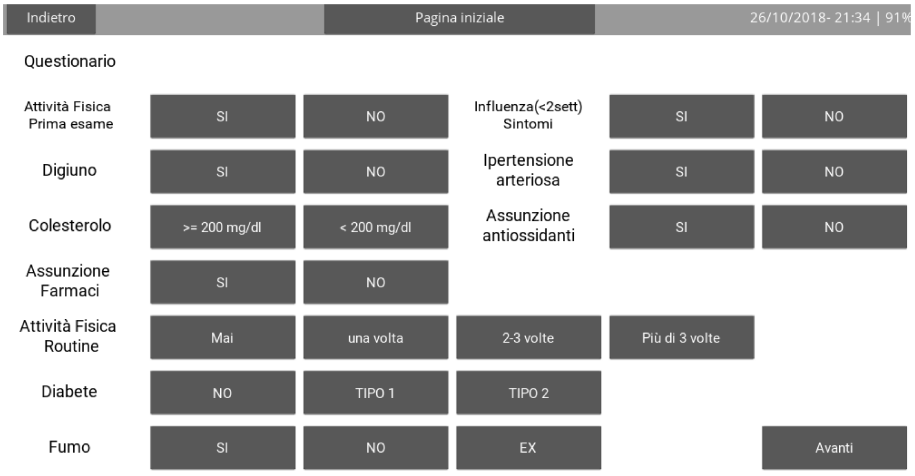
After the analysis of the requirements, the first version of the software was developed by the PhD student Fabio Pagnotta by Python and Kiwi for the graphical framework. To complete all the phases are show four screen-shoot of the software (Figure 4.14). In this phase, for the first prototype, it was not necessary for the study of user experience and usability.



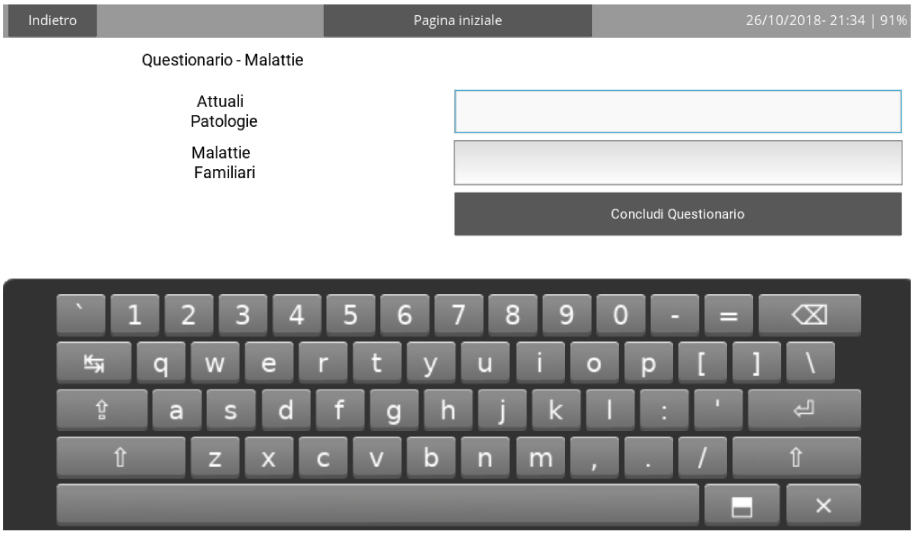
(a) *Screen to insert the first data patient*



(b) *Screen to insert the second data patient*



(a) *Questionnaire first part*



(b) *Questionnaire second part*

Figura 4.14: *Some screenshot about the first version of the software in the new medical device to detect the ED*

Ergonomic Design and 3D print

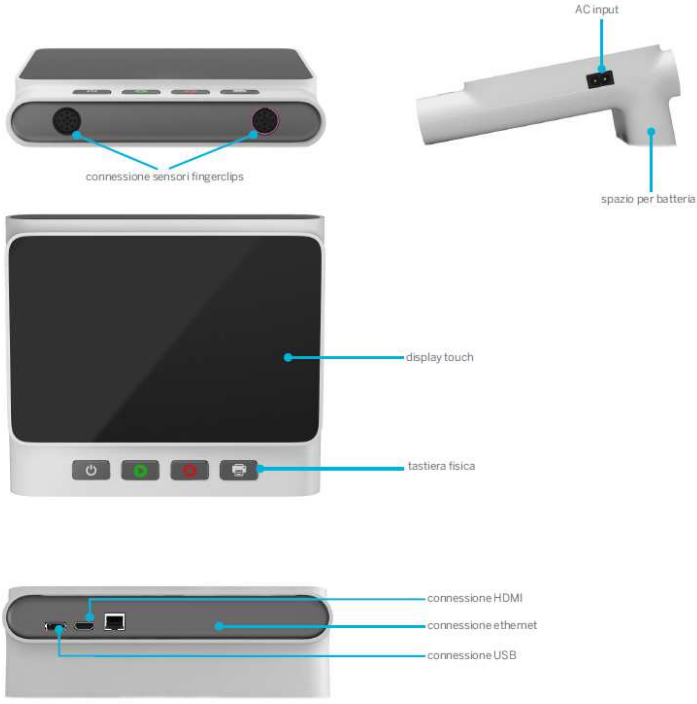
After defining the requirements of the device, the hardware components, have been identified the volumes, weights and other features of the device that was necessary to perform a study of ergonomics, usability, and material for the new device. The designer Eng. Raul Frolla expert in industrial design based on the indications provided by the PhD student propose four different solutions and the figure 4.15 4.16 show the chosen design. Therefore, the model was developed by Eng. Alma Leopardi, PhD student in Department of Industrial Engineering and Mathematical Sciences, Università Politecnica Delle Marche. [4] and printed by TECNE 90 s.p.a.[5] through the 3D printer. The figure about the chassis it is reported in Appendix.

Figura 4.15: *Design Concept*

[4]Eng. Alma Leopardi, PhD Student in Department of Industrial Engineering and Mathematical Sciences, Università Politecnica Delle Marche Via Brecce Bianche, polo Monte Dago, 60121 - Ancona, a.leopardi@pm.univpm.it

[5]TECNE 90 s.p.a., Via Firmino Giulietti, 3, 62010 - Montelupone (MC)

(a) *Ergonomic Design*



(b) *Model of the new medical device*

Figura 4.16: *Design of the new medical device*

Capitolo 5

Development of a novel algorithm for detect endothelial dysfunction

This chapter presents the PPG analysis of data coming from the previously described devices. The signal processing and the mathematical process used to filter data and define novel evaluation indexes are presented and evaluated on a novel dataset collected on real patients. This data processing method is another main contribution of the theses.

5.1 Introduction

In this chapter, the PPG analysis will be described in order to develop a new tool to detect the Endothelial Dysfunction (ED). The aim is to lay the groundwork to explore those features that will be useful to study the ED by analysing the PPG signal. The main novelties are:

(i) a new index, which discriminates the presence of ED, based only on the timing of discrete components of the PPG.

(ii) a new algorithm to automatically detect the fiducial points from the PPG wave, that will contribute to the definition of some parameters that may be correlated with the ED.

The prototype, which is the object of this thesis, will test and implement this algorithm during the clinical trial described in the Chapter 3. To validate the new index, to define the threshold and to evaluate whether there are some parameters that can be correlated with the ED and the definition of its severity. This work was conducted at Lund University with the collaboration of the Department of Biomedical Engineering [1].

The chapter is organised as follows: The section 5.2.1 gives details on the training dataset used for the PPG analysis and the PPG and FMD experimental protocols respectively (Sub-Section: 5.2.1 and 5.2.1). In the section

[1]Department of Biomedical Engineering, Faculty of Engineering, Lund University, Lund Sweden

5.3 are describe the steps to analyse the PPG signal in particular are shown the following steps the preprocessing (Sub-section: 5.3.1) the new method to detect the ED in the section 5.3.2, followed by the section 5.3.3 with the new algorithm for the identification of the fiducial points; final sections present the results (Section 5.4).

5.2 Material and methods

5.2.1 Data collection

Equipment

- **VenoScreen**: the photoplethysmography (PPG) signal has been recocorded by the medical device called VenoScreen®(MEDIS company, Ilmenau[2]), Figure 5.1. Normally, it is used with two photo-optical sensors based on Light Reflection Rheography (LRR) that allow measuring the venous filling to evaluate the venous function. This device choice is due because it allows to carry out another examination with two photo-optical sensors based on PPG. However, in this case, it is adopte to examine the peripheral pulse wave as well as the functional circulatory disorders. The measurement system is composed by the measuring unit VenoScreen and the CardioVascular Lab software package (MEDIS company, Ilmenau). The measuring unit has been connected via a USB interface to the computer. The software verifies the measuring, evaluates the measurement signals and displays the results. Furthermore, it is possible to export the raw PPG data in CSV format. This last function has been implemented by the Medis Company only for this study. In particular, this kind of device has been chosen for this partnership.

- **Aneroid sphygmomanometer**: to induce the hyperaemia (blockage of the blood flow) the Prakticus II by F.Bosch has been used (Figure 5.1).

- **Ultrasound System (US)**: The US used to detect the FMD must be equipped with two-dimensional (2D) imaging, color and spectral Doppler and a high-frequency vascular linear array transducer (multiple frequency: 7-12 MHz) and finally ad internal electrocardiogram (ECG). For this study, it has been used the M-Turbo Sonosite Ultrasound System with the HFL38x linear transducer Figure 5.1.

All participants has been informed and they have provided their written agreement in accordance with the Declaration of Helsinki. They were all volunteered and the study protocol has been approved by the medical group. It is clarified that the same procedure has been submitted to Ethics Committee in "Comitato Etico Regionale Marche, Ancona" for future validation and testing of the medical device in the hospital.

The Endothelial Dysfunction Dataset (EDD) has been built selecting fifty-nine patients. Thirty-one healthy subjects (F/M=28/31) aged 39 ± 16 (range 17-79) years. The population is heterogeneous and well matched for age, gender

[2]MEDIS Medizinische GmbH, Ilmenau, Germany

(a) *VenoScreen®, MEDIS company, Ilmenau*[3]

(b) *Sphygmomanometer, Prakticus II, F.Bosch*

(c) *Ultrasound System, M-Turbo, Sonosite*

Figura 5.1: *Experimental setup*

and body mass index (BMI). Moreover, they are Caucasian and their medical history is known. The characteristics of the data collection are listed in Table 5.1. As mentioned in the previous paragraph, the endothelial function influences the CVDs risk factors. By the way, genetic predisposition or temporarily factors (stress, drugs, diet) may contribute to endothelium alteration. Before the exam, the subjects completed a questionnaire about the presence of these factors. It consists of 16 questions, where 14 have multiple choice and only 2 open questions related to family history and patient conditions. In this way, for each patient was recorded the following information: age, sex, weight, height, the fasting conditions, taking antioxidant supplements, smoking (how many cigarettes), drugs, menstrual period, flu, physical activity before the

exam, physical activity times for week, dyslipidemia, diabetes,hypertension. The data collected by the questionnaire are listed in Table 5.1. Besides, for each subject, the Body Mass Index (BMI) was calculated as weight (Kg) divided by height (m^2). Subjects with BMI greater than or equal to 30 BMI ($Kg = m^2$) are considered obese.

Features	**Analysed subjects**	**Mean + SD**
Total	59	
Anthropometrics		
Age,years		39 ± 16
Sex, female	28	
Sex, male	31	
Height, meter		$1,73 \pm 0,1$
Weight, Kg		$76,25 \pm 15,11$
BMI, (Kg/m2)		$25,70 \pm 4,93$
Questionnaire data		
Fasting (at least 8 hours)	33	
Smokers	9	
Not smokers	44	
Ex smokers	6	
Antioxidants	6	
Drugs	11	
Menopause	8	
Influenza	3	
Physical activity	29	
Hypercholesterolemia (cholesterol >200 mg/dl)	13	
Diabetes	2	
Hypertension	6	

Tabella 5.1: *EDD description*

Patient preparation

Different factors as temperature, food and drugs can influence the exam. For this reason, the exams were carried out in the morning in an environment with comfortable temperature, in absence of noise. The subject was in the room at least half an hour before the exam permitting the body to adapt to temperature. Moreover, the patients before the exam should be:

- complete fasting for at least 8 hours (liquids are admitted with the exception of coffee or tea);
- without taking medicines in the previous 6 hours (the only exception is hypertension therapy);
- without smoking in the previous 6 hours cigarettes or similar (such as, electronic cigarette, pipe, cigar, etc.);
- without doing intense physical activity in the hours immediately preceding the exam;
- without nail polish

PPG experimental protocol

The experimental protocol follows exactly the gold standard protocol as the FMD exam by ultrasound system, as described by Corretti et al. [34]. In this study, PPG signals of fifty-nine patients were recorded using VenoScreen (MEDIS company, Ilmenau). Its software "CardioVascular Lab" (MEDIS company, Ilmenau) was pre-installed to a personal computer for data acquisition and for exporting the data in CSV format for the subsequent signal analysis by Matlab R2018a (The MathWorks, Inc., Natick, MA, USA)

Two PPG sensors has been used to record PPG signals from index fingers of the RA (right arm) and LA (left arm) for fifteen minutes at a sampling rate of 200 Hz. When the participant was seated at rest, was applied the blood pressure cuff of sphygmomanometer above the elbow on the subject's left arm to induce the ischemia (during the occlusion phase) (Figure 5.2).

After that, it has been applied the PPG sensors on the tip of each index finger. Pulse waves were displayed and if the signal was without artefacts, the PPG traces were ready to be acquired. For fifteen minutes, the PPG was recorded, following three phases (Figure 5.3):

- Pre-Occlusion: the first five minutes represent the baseline condition (before cuff pressure).

- Occlusion: five minutes during the blood flow blockage, with the inflation of the sleeve with a pressure of at least 50 mmHg above the systolic blood pressure, in any case, without exceeding 200 mmHg (ischemia).

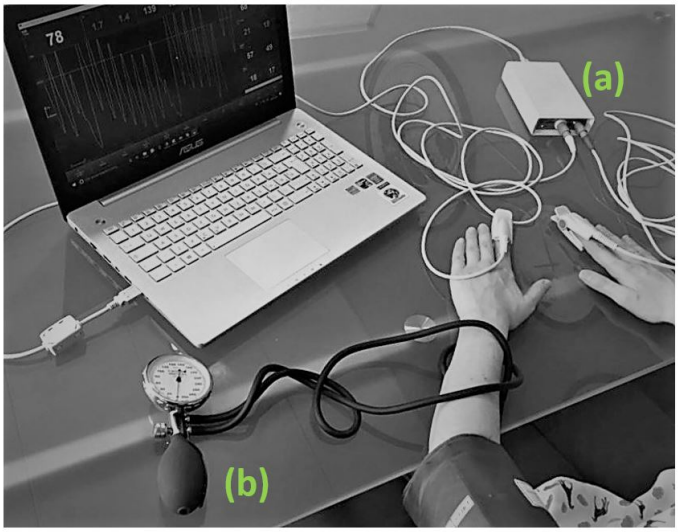


Figura 5.2: *PPG-signal acquisition setup: (a) VenoScreen®(medis) with two photoplethysmography sensors and (b) sphygmomanometer with cuff. Acquired signals were processed by the VenoScreen®(medis) software.*

- Post-Occlusion: five minutes after the release of blockage, (reactive hyperaemia).

The procedure is based on the endothelial release of Nitric Oxide (NO) and other endothelium-derived relaxing factors in response to an increase in shear stress. For this reason, it is created a period of transient ischemia, after that during the deflation of the cuff the increased flow results in shear stress, which activates endothelial NO synthase to release NO via the L-arginine pathway. The NO diffuses to the smooth muscle cells, causing them to relax, resulting in vasodilation [31].

Figura 5.3: *Example of PPG signal recorded for a subject. Follow the procedure three phases are highlighted: pre-occlusion (normal blood flow), occlusion (flow is occluded), post-occlusion (restore of the flow).*

FMD experimental protocol

Only fifteen patients of the fifty-nine patients described in the previous paragraph have been subjected to the flow-mediated-dilatation exam 5.2. The cardiologist follow the standard guidelines described by Corretti et al. [34]. The procedure is detailed in the paragraph 2.2.2. Briefly, the diameter of the brachial artery has been measured in the baseline condition and after the release of cuff pressure with the probe of the ultrasound system. Subsequently was calculated the FMD as describe in the formule 2.1.

PZ	**Age (years)**	**Sex**	**FMD (%)**	**ED - NED**
1	70	M	3,6	ED
2	62	M	9,2	NED
3	39	F	10,2	NED
4	44	F	10,9	NED
5	30	M	13,4	NED
6	41	M	6,5	ED
7	70	M	5,4	ED
8	26	M	8,2	ED
9	28	M	10,4	NED
10	70	M	4,8	ED
11	22	M	8,8	NED
12	53	F	6,9	NED
13	59	F	9,2	NED
14	36	M	10,4	NED
15	40	F	13,2	NED

Tabella 5.2: *Dataset with fifteen patients and relative FMD. ED indicate patients with Endothelial Dysfunction, NED the healthy patients.*

The intention of this dataset it is a trial dataset where design and test the algorithm to detect the ED based on only the PPG signal. Moreover, the dataset will be used to test the algorithm to study the morphological features of the PPG to extract features may be useful to define the severity of the disease.

5.3 PPG analysis

The steps to analyse the PPG signal are: Pre-Processing, Feature Extraction and Classification (Figure 5.4).

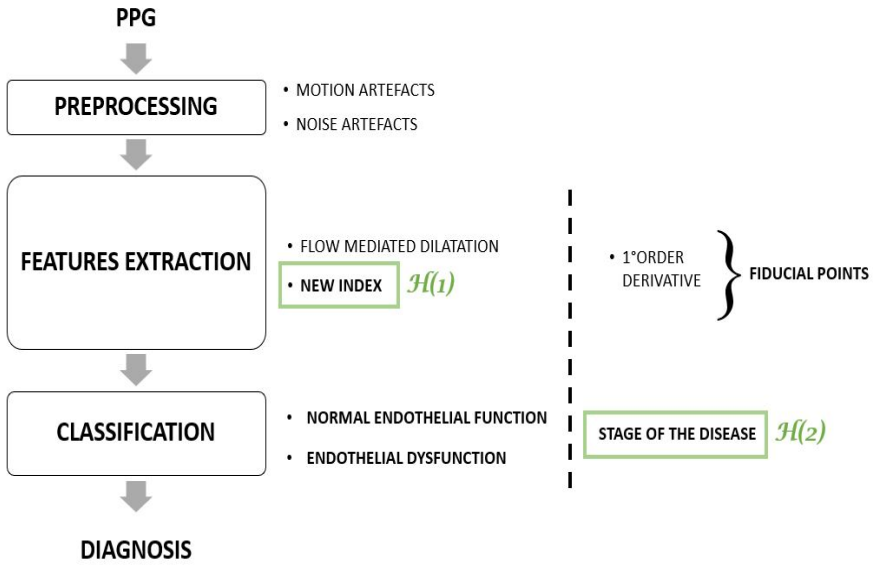


Figura 5.4: *The block diagram about the procedure to develop the new algorithm*

5.3.1 Preprocessing

The PPG signal, described in Chapter 2.3.1, can be obtained by measuring infrared light passing through the tissue (i. e. skin) of the finger. An LED light is diffused through the human tissue and then detected by a photo-detector located at the opposite side of the LED. The transmittance varies over time in accordance with variations in the blood volume. The device that records the PPG signal provide two different type of information: the signal that represents the light that is detected by a photo-detector (light transmitted) and the transmittance, which is the proportion of the incident (approaching) light that travels through the tissue to the photo-detector. For this reason, it was necessary to divide the raw signal by the transmittance 5.1. Figure 5.5 shows the raw PPG signal, the Transmittance (Z_0) and the signal obtained from the equation 5.1.

$$X_{PPG}(t) = \frac{X_{RAWppg}(t)}{Z_0(t)} \tag{5.1}$$

where *(t)* is the time.

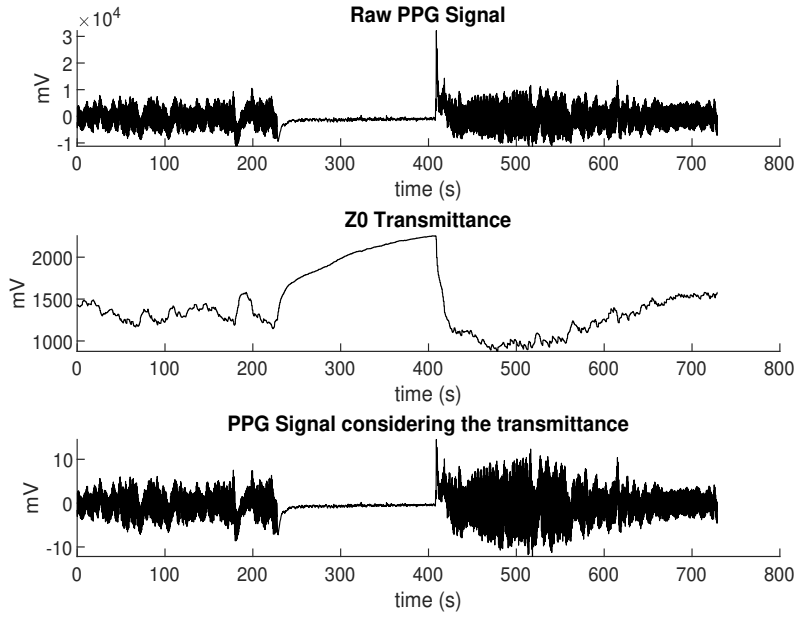


Figura 5.5: *Example of raw signal for a patient (top), the transmittance of the sensor that change in the time (middle) and the signal considering the transmittance*

The PPG signal is modulated by each cardiac cycle and may be influenced by several factors such as breathing and movements. Moreover, the PPG signals may vary according to blood oxygen saturation, skin temperatures, skin structure and external factors such as light in the environment. The aim of the pre-processing phase is reducing the distortions of PPG, that may be observed in the wave profiles and may influence the features extraction, thus negatively impacting the subsequent phases of signal processing and the final diagnosis. As reported in the block diagram 5.6, the main challenges of preprocessing are remove the:

- **noise**: Inevitably the signal contains high-frequency noise which is the mixture of the ambient light, thermal noise and other unclassified noise. Furthermore, the power line represents another noise source in the PPG; it is normally characterized by 50 Hz sinusoidal interference, probably accompanied by a number of harmonics [65]. To remove this noise a simple approach was applied, the low pass filter with 20dB attenuation at 8 Hz[66].

Figura 5.6: *The block diagram shows the process of the preprocessing of the PPG signal. At the first stage we remove the powerline interface, then the Butterworth filter is applied to remove the motion artefact, and after that the Moving Average Algorithm is applied for baseline drift removal, at the end the specific algorithm is performed to remove the outliers.*

- **baseline wander**: is required in order to minimize changes in beat morphology, which do not have cardiac origin [65]. The technique employed to remove it was obtained by down-sampling the PPG signal to 2 Hz, followed by forward/ backwards filtering, using a second-order low-pass Butterworth filter with a cut-off frequency of 0.5Hz [67]. After that, the signal is unsampled and subtracted from the original PPG signal.

- **outliers**: features extraction requires an accurate detection of the peak and others fiducial points. For this reason, it is necessary to remove the outliers from the signal. In this case the "isoutlier" function (The MathWorks, Inc., Natick, MA, USA), was applied to the signal. The outlier is defined as a value that is more than three scaled median absolute deviations (MAD) away from the median. Every 10 seconds the outliers were detected and they were normalized to the mean value calculated in the same interval.

The result of this filtering for a particular signal is shown in Figure: 5.7.

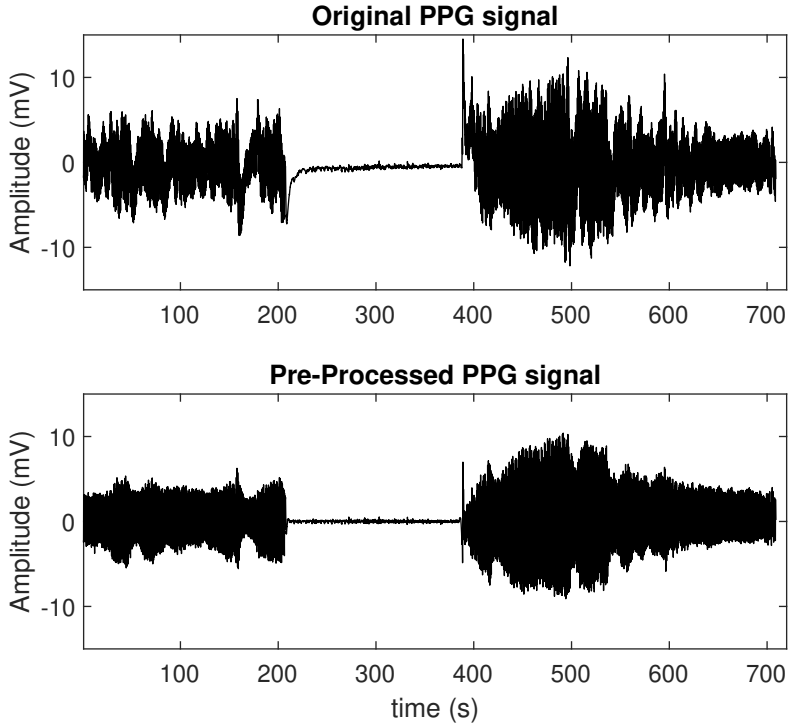


Figura 5.7: *Noise filtering. The original PPG signal (top), the output signal after the pre-processing steps (bottom).*

5.3.2 Algorithm 1: New method for assessment of ED based on PPG

Several studies demonstrate that it is possible to evaluate the endothelial function on the basis of the PPG signal. As described by Kuznetsova et al. [48] a method to calculate the index to detect the ED could be computed as follows: it divides the ratio of the average of the post-occlusion PPG pulse amplitude to the pre-occlusion amplitude of the hyperaemic finger by the same ratio about the control finger. The same approach is used by Zahedi et al. [3], but they normalized the variables dividing the Pulse Amplitude value by the mean of the Pulse Amplitude in the same interval.
On the other hand, the EndoPAT give an index that is calculated in the same way, but on the basis of the Peripheral Arterial Tonometry (PAT) signal. EndoPAT is a proprietary technology owned by the EndoPAT^{TM}Israel device (Itamar Medical) and it appears to be the only technology available on the market that it measures the arterial tone changes in peripheral arterial vessels with a special PPG sensor (described in the paragraph 2.2.2). Its algorithm

and the method are validated by different studies and approved by the Food and Drug Administration (FDA).

The new approach is based on the methods described above, in particular, the KUZNETSOVA et al. approach, but calculating the area based on the envelope and not the mean of PPG signal 5.8.

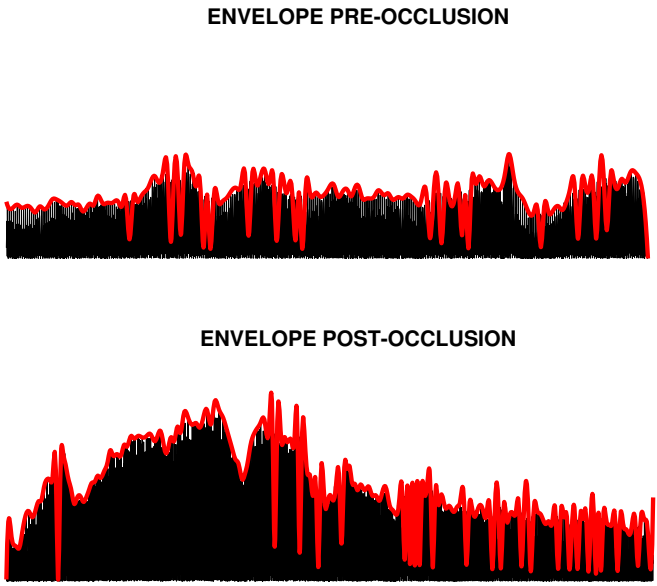


Figura 5.8: *Envelope of the waveform during the pre-occlusion (top) and envelope of the waveform during the post-occlusion (bottom).*

After evaluating the envelope of the absolute PPG signal during the pre-occlusion and the post-occlusion (Figure 5.8), the new index called I_RH will be calculated as:

$$I_{RH} = \frac{\frac{A_B}{A_A}}{\frac{A_D}{A_C}} \tag{5.2}$$

Where:

- A_A= Area of the PPG signal for one minute during the pre-occlusion in the arm blocked, excluded the first 90 seconds.

- A_B= Area of the PPG signal for one minute during the post-occlusion in the arm blocked, excluded the first 90 seconds.

- A_C= Area of the PPG signal for one minute during the pre-occlusion in the arm unblocked without hyperaemic stress, excluded the first 90 seconds.

- A_D= Area of the PPG during for one minute during the post-occlusion in the arm unblocked without hyperaemic stress, excluded the first 90 seconds.

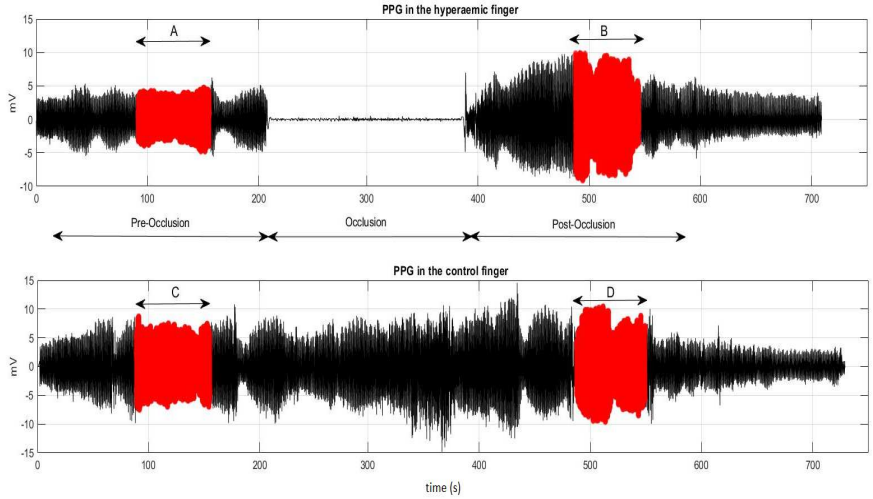


Figura 5.9: *PPG signal in the hyperaemic stress (top) and in the arm unblocked (bottom).*

Envelop choice is motivated because from the area more physiological information may be extracted as the "recovery time". The recovery time it a new parameter calculated during the post-occlusion. This interval indicates how many seconds are necessary for the signal to come back in the baseline condition (Figure 5.10) that may be useful to sudy it in correlation with the ED.

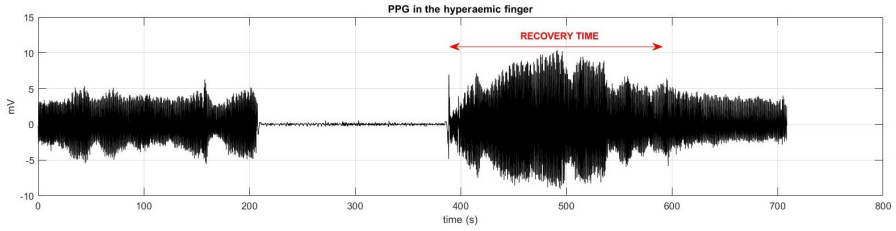


Figura 5.10: *Parameters extracted from the morphological analysis of PPG.*

Considering that this algorithm will be implemented in the new device (where the owner is Strumedical srl), some aspects and other related issues are patent pending.

5.3.3 Algorithm 2: Semi-Automatic identification of fiducial points

PPG features and correlation with Endothelial Dysfunction

The main purpose of this section is to identify some features that can help in the diagnosis of ED and the definition of its severity. As described in many studies, there are different features that can be extracted from the PPG signal that may be correlated with the cardiovascular diseases (Systolic Amplitude, Pulse width, Pulse Area, Peak to Peak Interval, Augmentation Index, Large Artery Stiffness Index and Crest time) [68].

The PPG reflects the blood flow in the vessel during the time of measurement. Figure 5.11 shows a pulse wave, where we can see the systolic and diastolic phases of the cardiac cycle; the rising component represents the systole of the hearth, while, the falling component it is the diastole and wave reflections in the periphery. Sometimes it is possible to individuate the dicrotic notch that expresses the closure of aortic valve (more visible in young healthy patients).

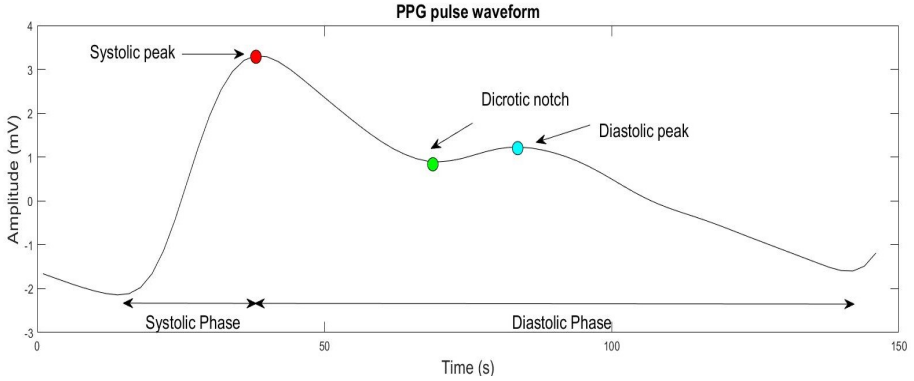


Figura 5.11: *Example of PPG: a pulse wave from a PPG signal, where the Systolic Peak, the Diastolic Peak and the Dicrotic Notch can be easily identified. The signal includes two different cardiac cycle phases, the systolic and diastolic phases.*

From the study of PPG morphology, some parameters were defined with the aim to study the correlation with the ED. These morphological features were extracted resorting on the analysis of the time of the PPG, in this case only with the signal before the occlusion.

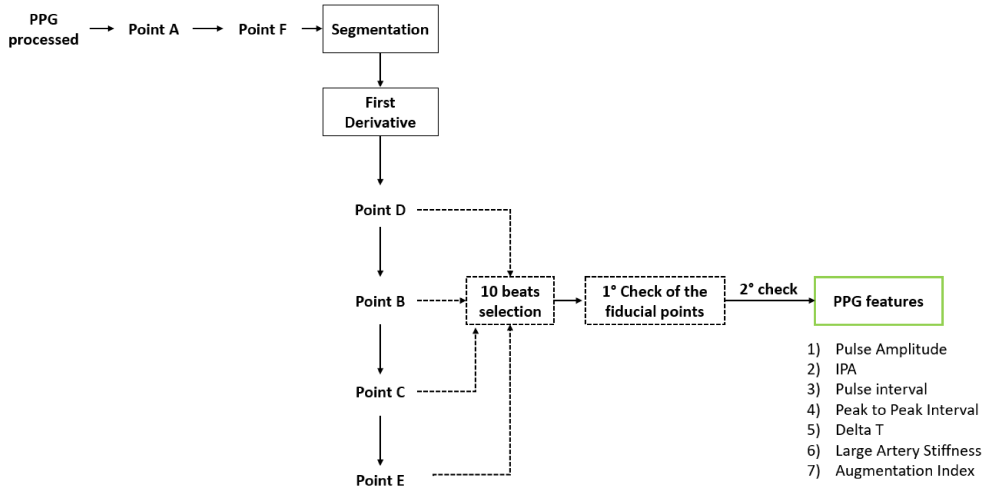


Figura 5.12: *Scheme of the proposed fiducial points detection methodology*

The proposed methodology for the automatic detection of fiducial points consists of the steps reported in the chart (5.12): (a) identification of Systolic Point (Point A), (b) identification of Diastolic Point (Point F), (c) segmentation, (d) extraction of fiducial points B,C,D,E, (e) randomly selection of ten beats, (f) automatic check of the points detected, (g) manual check of the same points and (e) finally the calculation of the morphological features.

The first step it was identified the systolic point as the maximum value (point A) and the last point of the beat as the minimum value (point F) indicated in the figure5.13, in this way we define the segment $\overline{AF}$.

The other characteristic points were analysed by the first derivative, that is calculated for each segment5.13. The first characteristic point that was calculated it is the D point, this choice it was justified after tried several approaches. Indeed, between all the characteristics points, it was found that the best identification of the exact location of a certain characteristic point on the waveform, based on only the first derivative, was the D point. For this reason, we started with the identification of that point like the maximum of the absolute value of the first derivative in the $\overline{AF}$ interval. Subsequently, we identified the B point like the maximum value of the first derivative between the point A and point D. Then from this last point, we identified the point C like the number of smaller approximation close to zero always in the first derivative in the interval $\overline{BD}$. This point represents the dicrotic notch. It is important to specify that sometimes, the identification of this point it is really complicated, especially for aged patients. Finally, from the C to F point we calculated the E point as the smaller number close to zero, this point is the Diastolic Peak.

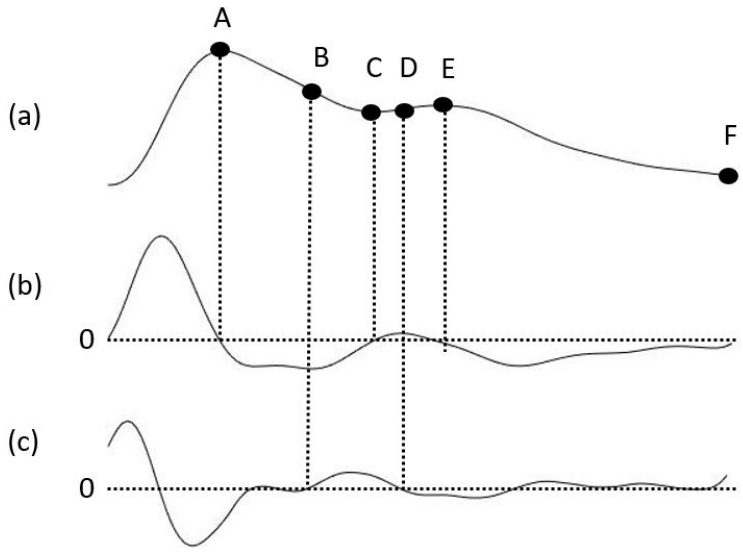


Figura 5.13: *PPG waveform and derivatives for a patient. (a) PPG original waveform, (b) first derivative wave, (c) second derivative wave. From the first derivative it is possible to identify automatically the following fiducial points: A,B,C,D,E. Where A it is the Systolic Peak, C is the Dicrotic Notch and E it is the Diastolic Peak.*

In Figure 5.14 the fiducial points identified for one beat of the patient are reported. For some patients (and sometimes for different beats in the same patient), the PPG contour becomes more rounded and otherwise the dicrotic notch is less pronounced; this situation is typical in older patients 5.15 [69]. In this case, based on only morphological characteristics, it is impossible to identify the dicrotic notch (point C).

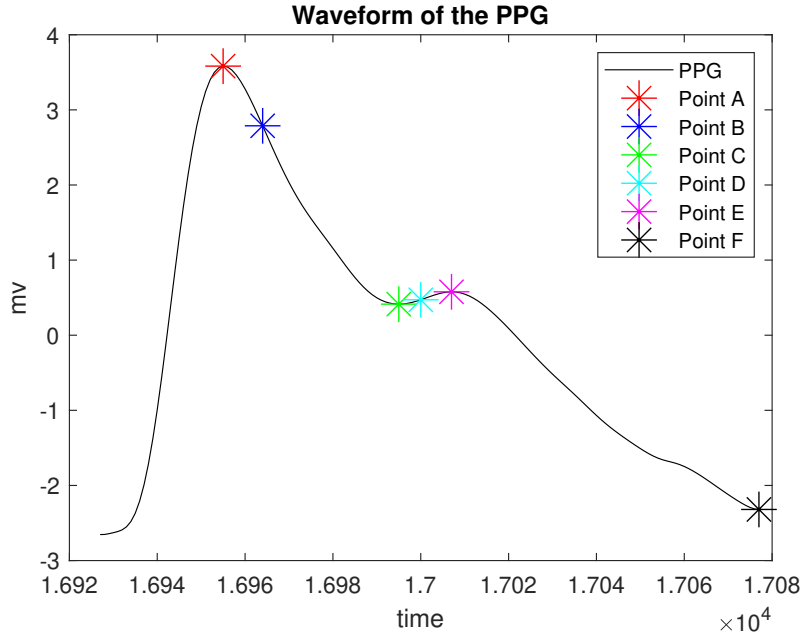
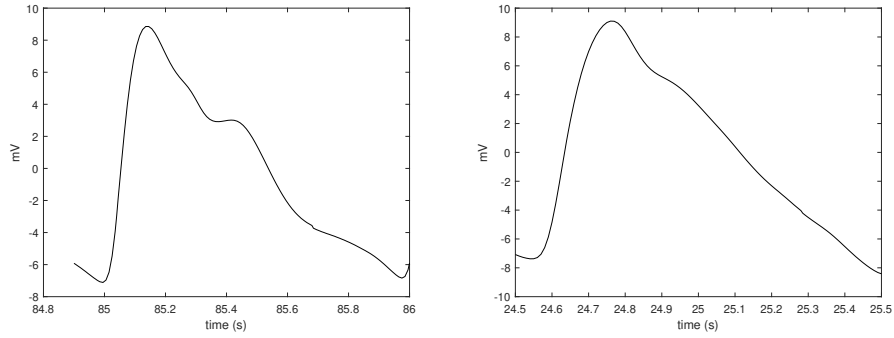


Figura 5.14: *Waveform of the PPG of the patient and its characteristics fiducial points.*



(a) *Young Patient (29 years)* (b) *Old Patient (70 years)*

Figura 5.15: *Example of two different patients, on the left the younger patient where it is possible to define the dicrotic notch and on the right the older patient where the dicrotic notch is impossible to define only by means of morphological characteristics*

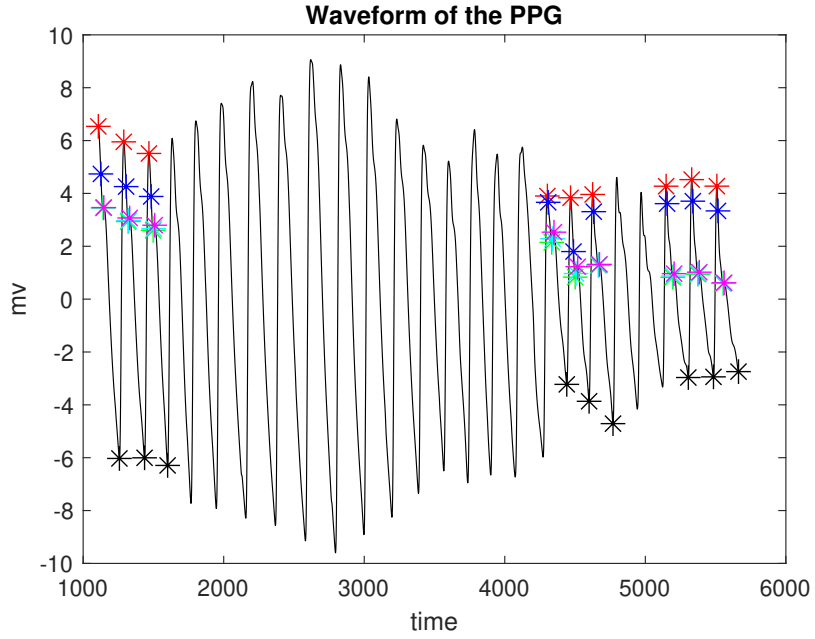
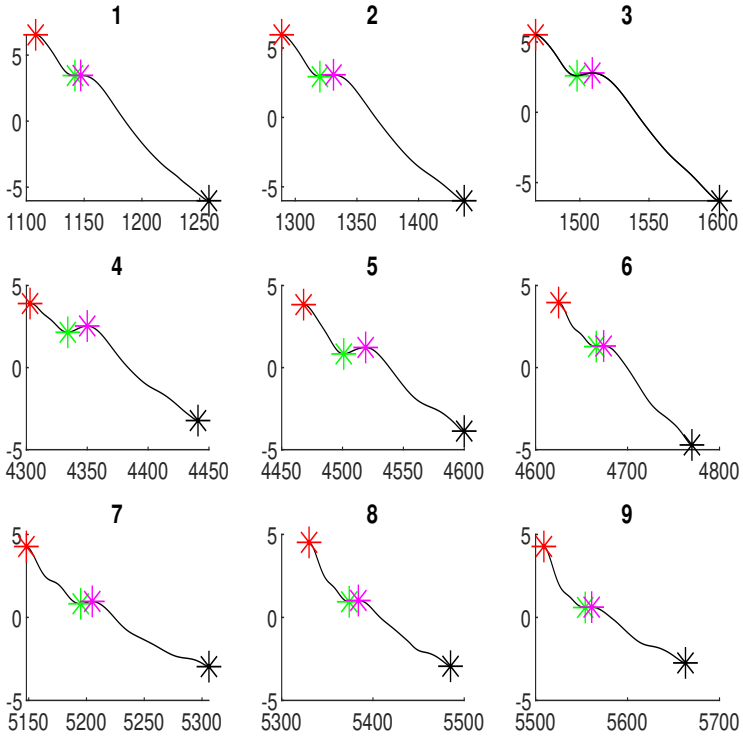


Figura 5.16: *Waveform of the PPG of the patient and its characteristics fiducial points.*

At this point, in the interval between the second and fourth minute (during the pre-occlusion), the algorithm detected randomly ten beats. For each beat, the order of the fiducial points is checked automatically, to exclude all the

beats where are some artefact may change the point position based on some requirement. Therefore, the algorithm automatically excludes the beats, as it is shown in figure 5.16 where the fiducial points were identified in only nine beats with respect to twenty-five beats. (Figure 5.16).

Finally, a manual override was applied. For example, in the patient shown in Figure 5.17, for eighteen beats two beats, number sixteen and the seventeen will be excluded from the analysis because the waveform it is affected by some artefacts.



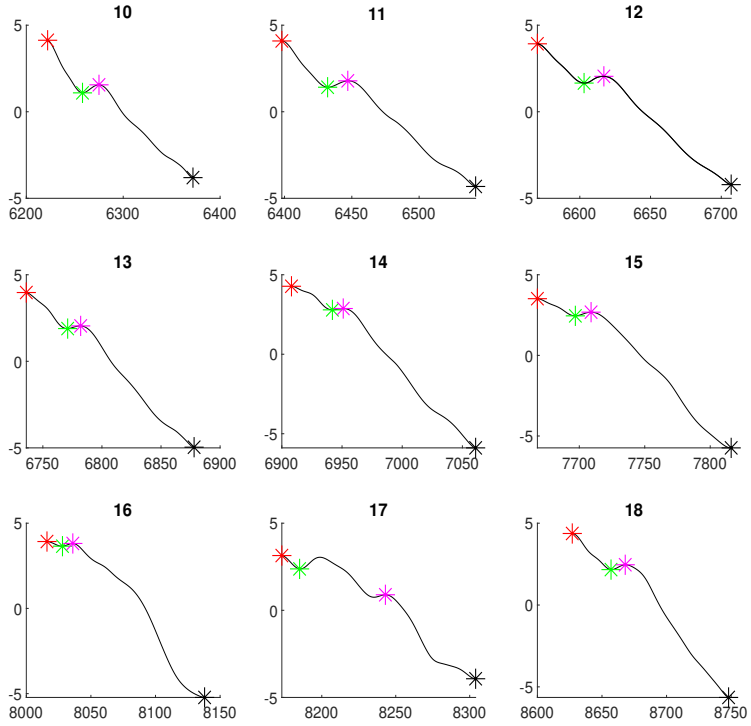


Figura 5.17: *Example of the fiducial points identified in eighteen beats for a patient, in this case, we chose randomly ten beats after excluded the number 16 and 17 where the morphology of the wave or some artefact lead to an error identifications.The points are: sistolic (red), dicrotic notch (green), diastolic (purple)*

.

When for ten beats, the fiducial points had identified correctly, the parameters 5.18 for each patient was calculated automatically following these descriptions[68]:

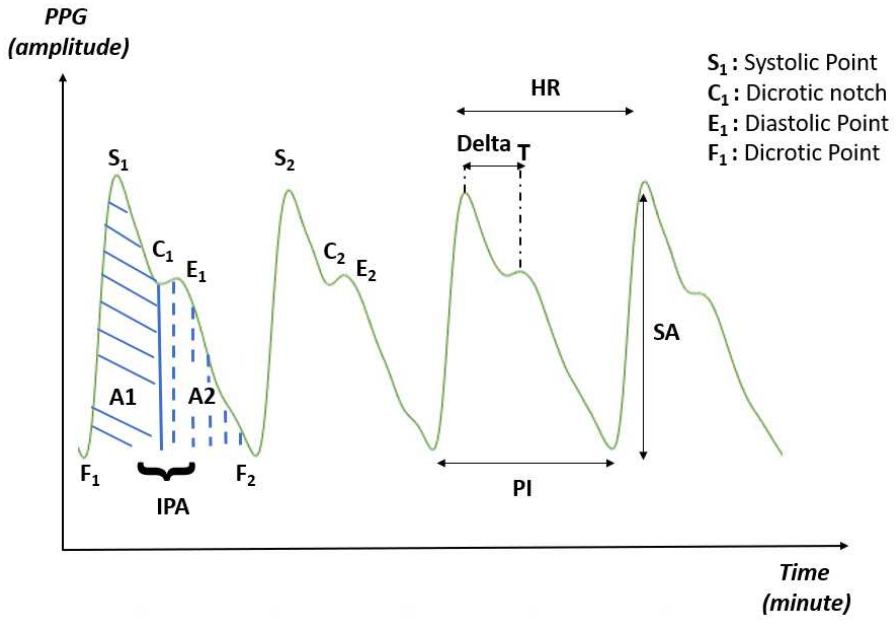


Figura 5.18: *Parameters extracted from the morphological analysis of PPG.*

1. Systolic Amplitude (SA):

$$SA = M_{S_1} - M_{F_1} \tag{5.3}$$

where M_{S_1} and M_{F_1} are the PPG signal amplitude in S_1 (systolic peak) and F_1 (dicrotic point before the systolic peak).

2. Inflection Point Area ratio (IPA):

$$IPA = \frac{A2}{A1} \tag{5.4}$$

where area A1 and area A2 are obtained dividing the pulse area into two areas at the dicrotic notch.

3. Pulse Interval (PI):

$$PI = t_{F2} - t_{F1} \tag{5.5}$$

4. Hearth Rate (HR):
$$HR = \frac{1}{t_{S_2} - t_{S_1}} \tag{5.6}$$
where t_{S_2} is the time at which the second systolic peak occurred.

5. $Delta_T$: is the time between the systolic and diastolic peaks
$$Delta_T = t_{E_1} - t_{S_1} \tag{5.7}$$
where t_{E_1} is the time of diastolic peak.

6. Stiffness Index (SI):
$$SI = \frac{H_P}{(t_{E_1} - t_{S_1})} \tag{5.8}$$
where H_P is the subject's height.

7. Augmentation Index (AI):
$$AI = \frac{(M_{S_2} - M_{F_2}) - (M_{E_2} - M_{F_2})}{Delta_T} \tag{5.9}$$
where M_{S_2} and M_{F_2} are the PPG signal amplitude in S_2 (systolic peak) and F_2 (dicrotic point before the systolic peak), while the M_{E_2} is the PPG signal amplitude in E_2 (diastolic peak).

8. Recovery Time (RT). RT indicates how many seconds, from the maximum value of the PPG during the post-occlusion phase, are required to return to PPG pre-occlusion condition (Figure 5.10)

5.4 Results

The average of FMD and the New_Index were 8,83 % $\pm 2,88\%$ (range 3,6-13,4) and $1,97\pm$ 0,97 (range 1,05-4,38), respectively. Linear regression analysis revealed that FMD and I_RH were significantly correlated in all patients (r=0.73, p<0.01)(Figure 5.19).

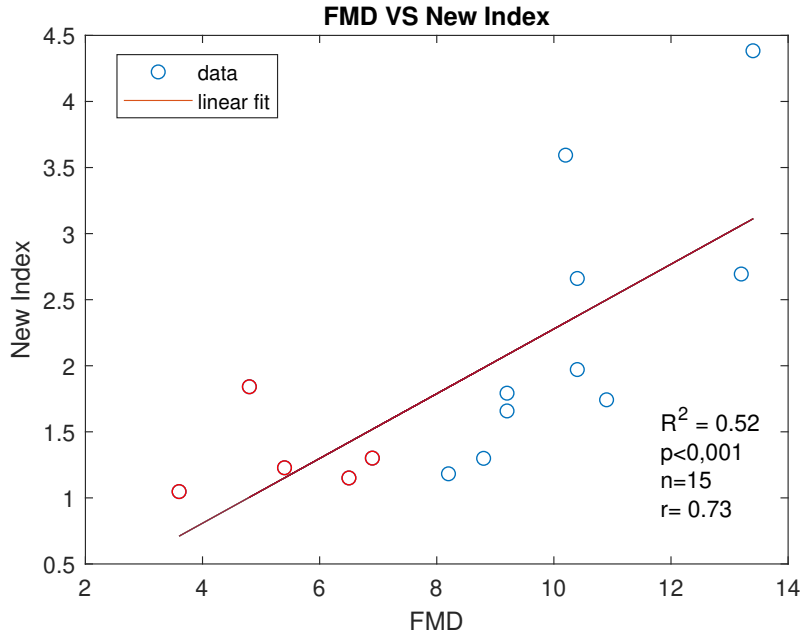


Figura 5.19: *Linear regression evaluation of the relation between I_RH and FMD of the brachial artery in all fifteen patients. In red and in blue the ED and healthy patients respectively (r=0,73, P<0.001)*

Agreement between methods were represented on Bland Altman [70] plots diagram in figure 5.20. All data fall within the interval mean ± 1.96 SD; based on the bias is necessary define a new threshold for the new index, because there is not an agreement between methods with the FMD and with new index calculate by the PPG signal.

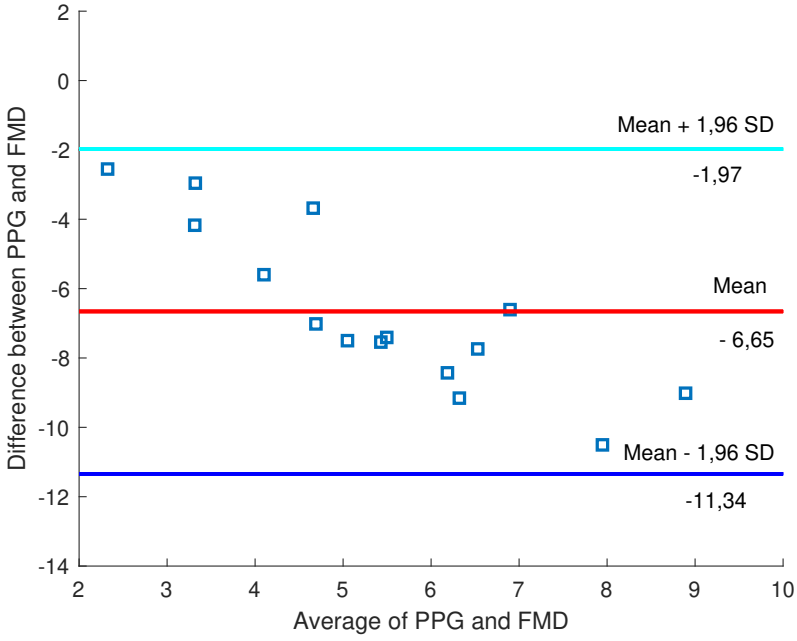


Figura 5.20: *Bland Altman plot of the difference between the method used to calculate the new index I_RH and the gold standard otherwise the FMD. In red the patients with the ED, in blue the healthy patients*

To explain, how the new index reflects the condition of the patient in the qualitative term, the figure 5.21 shown the PPG signal for a healthy patient while the figure 5.22 shown the patient with ED. In the first case, it is clear how in the post-occlusion the amplitude of the PPG increment, the other hand, in the patient with the ED this changes it is not perceptible. Moreover, the FMD and the I_RH were respectively 9,6 and 2,66 for the healthy patient and 4,2 and 1,05 respectively for the patient with ED.

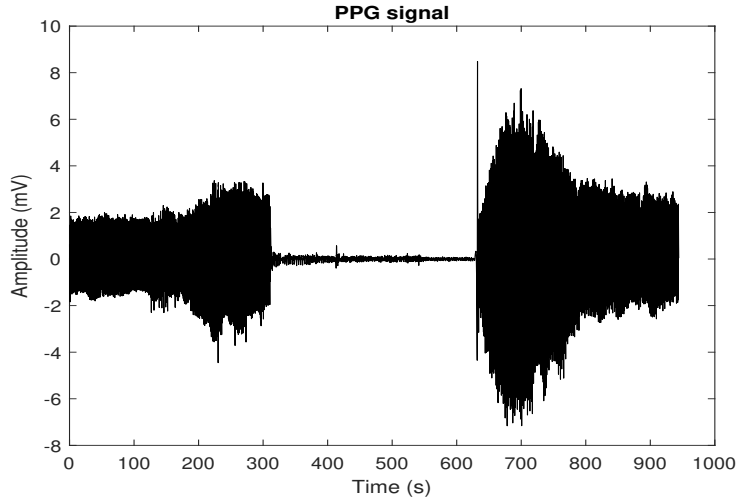


Figura 5.21: *PPG signal in healthy patient*

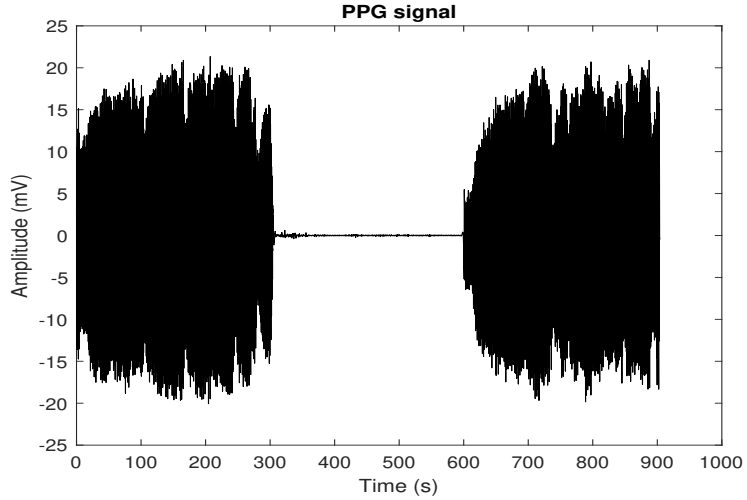


Figura 5.22: *PPG signal in patient with ED*

Table5.3 lists the investigated parameters and their values. The last column represents the number of beats detected from the algorithm for the identification of fiducial points, this value indicates where was impossible identify the dicrotic notch (-), where on the contrary was easier (> 50).

PZ.	Età	Sesso	Weight	Height	BMI (Kg/m2)	Heart rate	Systolic Amplitude	Recovery Time (minute)	IPA	Pulse interval	AI	deltaT	SI	n.beats
1	70	M	80	1,8	24,69	59,71	9,00	3	-	-	-	-	-	11
2	29	F	54	1,64	20,08	77,15	1,68	5	1,01	153,00	1,17	272,00	0,60	108
3	28	F	55	1,68	19,49	86,18	0,90	5	-	-	-	-	-	-
4	23	F	65	1,6	25,39	73,20	6,93	5	0,72	148,70	1,59	252,50	0,63	18
5	62	M	94	1,67	33,71	70,73	2,63	5	0,31	173,20	2,71	507,00	0,33	45
6	27	F	57	1,68	20,20	86,63	3,58	5	0,56	137,80	1,48	220,00	0,76	33
7	34	F	54	1,63	20,32	69,26	1,68	6	0,53	148,40	0,91	233,00	0,70	19
8	21	M	69	1,85	20,16	61,56	2,79	5	0,56	169,40	1,13	256,00	0,72	36
9	39	F	95	1,56	39,04	65,68	0,85	6	-	-	-	-	-	-
10	38	F	50	1,71	17,10	80,19	1,12	5	-	-	-	-	-	86
11	30	M	87	1,77	27,77	54,14	1,72	6	-	-	-	-	-	-
12	42	F	52	1,72	17,58	71,80	1,14	6	0,97	149,00	1,06	260,20	0,66	100
13	25	M	65	1,78	20,52	83,04	4,38	6	0,53	155,40	1,29	242,50	0,73	128
14	29	M	90	1,8	27,78	65,48	2,61	5	0,53	169,78	1,30	270,00	0,67	111
15	41	M	92	1,85	26,88	71,72	7,58	4	0,32	173,20	1,22	198,00	0,93	17
16	44	F	57	1,62	21,72	62,48	2,42	5	0,28	183,00	1,13	166,50	0,97	55
17	30	M	87	1,77	27,77	50,45	3,19	5	0,33	238,00	1,53	280,00	0,63	39
18	41	M	92	1,85	26,88	64,89	8,90	5	-	-	-	-	-	-
19	39	F	80	1,56	32,87	67,87	1,34	4	-	-	-	-	-	-
20	37	M	94	1,85	27,47	51,86	10,90	6	0,39	216,80	1,22	276,00	0,67	70
21	70	M	72	1,7	24,91	88,39	11,60	4	-	-	-	-	-	-
22	54	F	78	1,65	28,65	55,16	11,20	5	-	-	-	-	-	-
23	57	F	62	1,71	21,20	76,82	8,67	5	-	-	-	-	-	-
24	57	M	89	1,78	28,09	70,83	15,39	5	0,96	172,40	1,93	267,00	0,67	24
25	70	M	80	1,8	24,69	57,30	10,57	4	-	-	-	-	-	19
26	29	F	56	1,77	17,87	65,43	1,04	5	0,66	171,80	0,85	264,50	0,67	90
27	37	M	94	1,85	27,47	65,43	1,04	4	0,64	172,40	0,92	265,00	0,70	90
28	55	M	82	1,84	24,22	65,72	13,00	5	-	-	-	-	-	-
29	38	F	50	1,71	17,10	69,12	0,71	5	-	-	-	-	-	-
30	23	F	65	1,6	25,39	58,17	6,04	5	0,57	186,60	1,53	267,00	0,60	22
31	22	M	90	1,92	24,41	70,70	16,07	5	0,71	156,40	1,97	269,50	0,71	109
32	30	M	78	1,76	25,18	73,58	18,37	5	0,60	163,00	1,93	248,50	0,71	111
33	29	F	54	1,64	20,08	75,62	10,98	6	0,56	172,00	1,41	250,56	0,65	76
34	54	M	110	1,85	32,00	67,93	14,42	6	-	-	-	-	-	-
35	53	F	85	1,64	31,00	63,81	14,87	6	-	-	-	-	-	-
36	79	F	73	1,55	30,00	62,57	19,19	6	-	-	-	-	-	-
37	17	F	95	1,73	31,00	80,61	8,39	6	0,52	146,90	1,59	227,00	0,76	59
38	26	M	85	1,9	31,00	78,34	12,81	7	1,46	158,00	2,17	355,63	0,53	130
39	28	M	75	1,83	31,00	64,94	8,25	5	0,52	207,20	1,64	306,00	0,60	97
40	70	M	80	1,8	24,69	52,33	15,51	5	-	-	-	-	-	-
41	22	M	90	1,92	24,41	76,44	14,88	5	0,47	170,00	1,76	280,00	0,69	128
42	53	F	85	1,64	31,00	63,95	11,50	5	-	-	-	-	-	-
43	24	F	61	1,63	22,96	62,21	15,13	4	0,52	192,22	1,54	263,89	0,62	104
44	22	M	63	1,78	19,88	89,79	12,74	5	0,73	140,20	1,53	239,50	0,74	130
45	53	F	61	1,64	22,68	65,37	5,82	4	-	-	-	-	-	-
46	58	M	88	1,78	27,77	56,72	19,84	4	-	-	-	-	-	22
47	17	F	95	1,73	31,00	84,05	13,24	5	0,67	139,00	1,65	246,00	0,70	102
48	22	M	78	1,8	24,07	74,96	15,39	5	0,53	153,00	1,53	223,00	0,81	90
49	42	F	75	1,7	25,95	80,11	7,31	5	0,44	149,80	1,10	196,50	0,87	12
50	39	M	95	1,8	29,32	78,76	10,70	4	-	-	-	-	-	-
51	28	F	61	1,58	24,43	73,95	7,89	5	0,59	164,80	1,49	269,00	0,59	126
52	59	F	92	1,6	35,94	70,00	3,54	5	-	-	-	-	-	-
53	29	F	90	1,71	30,78	61,73	7,85	6	0,29	194,44	1,27	161,11	1,06	115
54	62	M	94	1,67	33,71	84,48	11,35	5	-	-	-	-	-	-
55	36	M	79	1,78	24,93	61,31	2,09	5	0,40	197,60	1,27	249,50	0,71	102
56	22	M	70	1,76	22,60	61,31	2,10	5	0,39	197,20	1,38	247,00	0,71	102
57	40	F	57	1,65	20,94	68,24	0,93	5	-	-	-	-	-	-
58	37	M	68	1,74	22,46	59,64	1,67	5	1,48	176,00	1,14	317,50	0,55	32
59	30	M	75	1,76	24,21	68,28	9,41	5	0,58	177,80	1,25	250,50	0,70	14

Tabella 5.3: *Investigated parameters and their values*

How reported in the table 5.4, for thirty-five patients the parameters were calculated, while for other patients the dicrotic notch was not identified and consequently the parameters were not determined. How reported in the literature [69] and how described in the figure 5.15 in the older patient the identification of the dicrotic notch it is really difficult because the waveform it is less pronounced. Moreover, two patient have congenital mitral valve anomalies that had influenced the PPG morphology and for this reason are excluded from the analysis of the fiducial points.

Tot. PZ		**Age (years)**		
n=59	*dictrotic notch*	*min*	*max*	*mean*
35	yes	17	62	30,7
22	no	28	79	52,04
2	no	30	35	32,5

Tabella 5.4: *The results based on the patient's age. The first row the patients have calculated the parameters, the second-row patients without the dicrotic notch identification and the last one indicate the patient excluded for some morphology anomalies.*

Based on the age, the table 5.4 shown how in the older patients it is more difficult to detect the dicrotic notch. Finally, the table5.5 with all the paramaters calculated by the fiducial points detected by the algorithm.

n=35	**Min**	**Max**	**Mean ± SD**
Age (years)	17	57	29,74 ± 8,65
Weight (Kg)	52,00	95,00	74,18 ± 14,53
Height (cm)	158	192	175 ± 0,09
BMI (Kg/m2)	17,58	31,00	24,56 ± 3,94
Heart rate	50,45	89,79	70,06 ± 9,49
Systolic Amplitude (mV)	1,04	18,37	7,56 ± 5,36
Time (minute)	4,00	7,00	5,18 ± 0,63
IPA	0,28	1,48	0,62 ± 0,28
P_interval	137,80	238,00	170,62 ± 23,18
AI	0,85	2,17	1,41 ± 0,32
Delta T	161,11	355,63	252,67 ± 37,80
SI	0,53	1,06	0,71 ± 0,11

Tabella 5.5: *The mean and the standard deviation for each parameters are reported in this table, with the minimum and maximum value.*

Capitolo 6

CDSS and Machine learning

This chapter presents the Clinical Decision Support Systems (CDSS) based on data collected from the above described device. The CDSS is based on Machine Learning methods and based on a dataset collected during the project. This is one of the main contribution of the theses: the first method for ED clinical evaluation based also on EHR data. The work describe in this chapter it is under review by the journal "MDPI Electronics Journal" .

6.1 Introduction

Cardiovascular Diseases (CVDs) refer to a class of cardiac disorders that, according to the European Heart Network, causes every year 3.9 million deaths in Europe, with estimated costs up to 210 billion euro per year [4]. As reported in the guidelines of the World Health Organization[1] for the assessment and management of cardiovascular risks, several factors (e.g., physical inactivity, tobacco use, obesity) have been shown to influence CVD onset. Moreover, when these factors are present, there is also a high probability of Endothelial Dysfunction (ED), which is actually recognized to be of primary importance to early diagnose CVDs [29, 71, 72]. In physiological conditions, the endothelial tissue regulates many functions, among which the most important is to maintain vascular homeostasis and modulate the vascular tone by balancing the production of vasodilators, including nitric oxide and vasoconstrictors. In presence of ED, the endothelium is liable to anatomical alteration (e.g. smooth muscle cell proliferation and migration, leukocyte adhesion and migration) and its regulation mechanisms are compromised [10], [26].

The current gold standard technique for ED diagnosis is the Flow Mediated Dilatation (FMD), which uses high-resolution UltraSound (US) signals acquired on subject arm. FMD is measured after a 5-minute arm compression followed by relaxation and measured as the percentage increase of the resulted maximum brachial-artery diameter with respect to the baseline diameter [34].

[1] https://www.who.int/cardiovascular_diseases/guidelines/Pocket_GL_information/en/

FMD computation is, however, operator dependent, expensive and requires an expert clinician, thus not being suitable for screening purposes.

To overcome these limitations, studies in the clinical literature highlighted the efficacy of PhotoPlethysmoGraphy (PPG) in assessing ED [3], [45], [47], [50], [7]. PPG is a noninvasive optical technique in which PPG sensors are applied on subject's fingers to measure changes in blood volume a function of time [2], [73]. From the PPG signal, similarly to US-based analysis, the incremental ratio of the PPG signal amplitude (with respect to its baseline) is evaluated by clinicians in a sensitive, threshold-based way (not being compatible with the high variability of the PPG signals).

To successfully tackle data variability, different researchers in similar contexts exploited Machine-Learning (ML) techniques. For example, Weng et al. [74] adopted Random Forest (RF), Logistic Regression (LR), Gradient Boosting Machines (GBM) and Neural Networks (NN) with 30 features extracted from electronic health records (EHRs) (such as blood pressure, Body Mass Index (BMI), gender...) to identify patients at risk of developing CVDs. The overall classification recall was 65.3% (RF), 67.1% (LR), 67.5% (GBM), 67.5% (NN). Similarly, Boursalie et al. [75] used Support Vector Machines (SVMs) to classify features from wearable sensors and EHRs, achieving a classification accuracy of 90.5%. The work that is similar to the one proposed in this paper is [76], in which several ML classifiers (such as SVM and RF) were investigated for the specific task of ED classification, even if focusing on features extracted from FMD data.

Considering the clinical relevance of early-diagnosing ED from PPG data (over the FMD ones), the goal of this research was to test if ML methodologies are suitable for ED classification starting from PPG-signal analysis, by providing a fast and low cost approach to the problem. Specifically, we investigate the following two hypotheses:

- Hypothesis 1 (H1): ML techniques can classify ED by PPG features;
- Hypothesis 2 (H2): Including anthropometric features may improve classification results.

Due to the lack of work in this field of research to test H1 and H2, a new publicly available dataset, the PPG Endothelial Dysfunction Dataset (ppgEDD), was collected[2].

The paper is organized as follows: Sec. 6.2 gives details on the ppgEDD and the features used for endothelial dysfunction classification. Results are presented in Sec. 6.3.

[2] `http://vrai.dii.univpm.it/content/ppgEDD-dataset`

6.2 Methods

This section presents the proposed approach to ED screening from PPG data (Sec. 6.2.1) and the experimental protocol used to investigate H1 and H2 (Sec. 6.2.2).

6.2.1 Endothelial-Dysfunction screening methodology

The proposed method consists of the following steps: (i) data collection (described in the Sec. 5.2.1) (ii) feature extraction (described in Sec. 5.3.3) and (iii) classification (Sec. 6.2.1). The workflow of the approach is shown in Fig. 6.1.

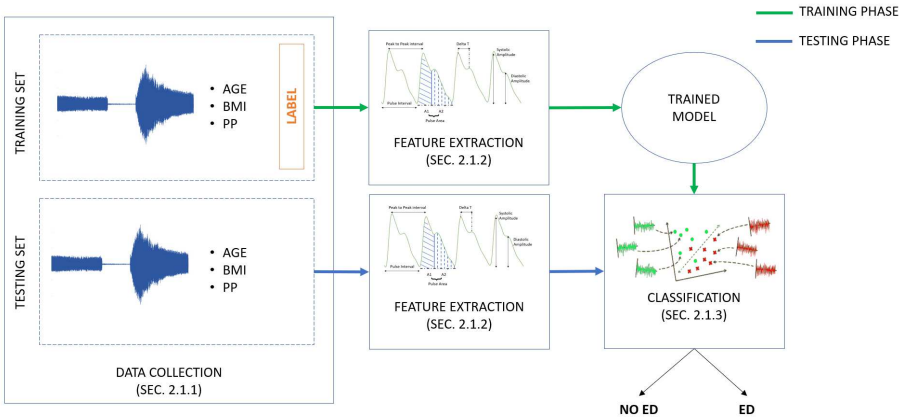
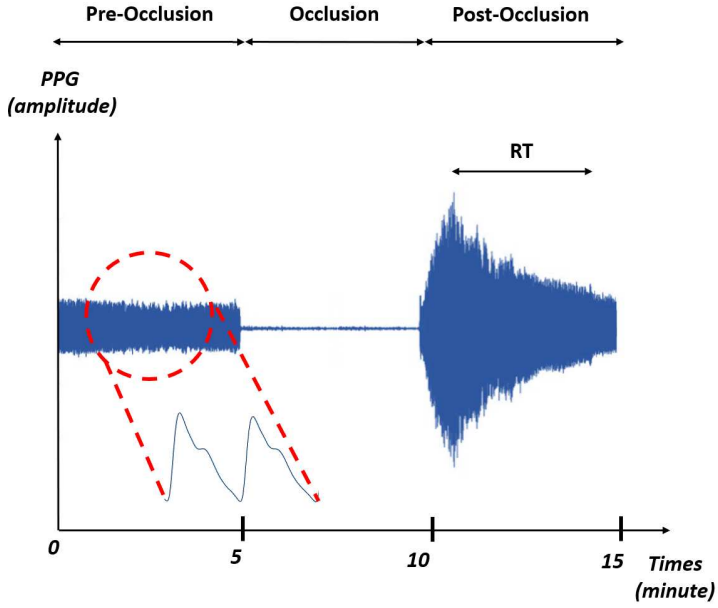


Figura 6.1: *Workflow of the proposed learning-based approach to endothelial dysfunction (ED) screening from photoplethysmographic and anthropometric data.*

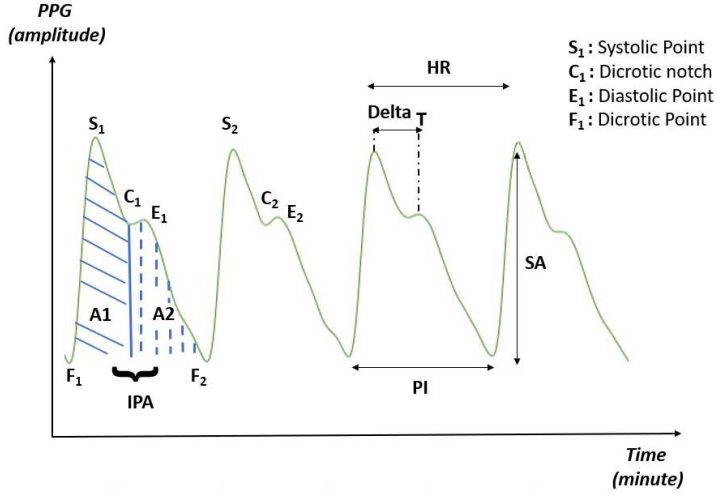
PPG features

Inspired by [68], where a set of PPG features were shown potentially related with cardiovascular variables, in this work we identified eight features (refer to Figure 6.2). The description and extraction of this features from PPG signal is reported in the Sec.5.3.3.

1. Systolic Amplitude (SA)
2. Inflection Point Area ratio (IPA)
3. Pulse Interval (PI)
4. Hearth Rate (HR)
5. $Delta_T$



(a)



(b)

Figura 6.2: *(a) The three phases of the photoplethysmography (PPG) signal acquisition: pre-occlusion (normal blood flow), occlusion (occluded flow), post-occlusion (restored flow). Dotted lines highlights a zoomed signal portion. (b) From the zoomed signal portion, the parameters useful for computing PPG features are highlighted.*

6. Stiffness Index (SI)
7. Augmentation Index (AI)
8. Recovery Time (RT)

For the features extraction of PPG signal, were selected randomly ten beats during the pre-occlusion phase (as introduced in Sec. 5.3.3).

Anthropometric features

Considering our previous experience in this field [76], the following anthropometric features were investigated: age, BMI and pulse pressure (PP), (i.e., the difference between systolic and diastolic blood pressure at rests measured with the sphygmomanometer)[77].

Classification

To perform feature classification, SVMs were implemented [78]. Indeed, SVM decisions are only determined by the support vectors, which makes SVM robust to noise in training data. Here, SVM with the Gaussian kernel (Ψ) are used to prevent parameter proliferation while lowering computational complexity and limiting overfitting. For our binary classification problem, given a training set of N data $\{y_k, \mathbf{x_k}\}_{k=1}^{N}$, where $\mathbf{x_k}$ is the k^{th} input feature vector and y_k is the k^{th} output label, the SVM decision function takes the form of:

$$f(\mathbf{x}) = sign\Big[\sum_{k=1}^{N} a_k^* y_k \Psi(\mathbf{x}, \mathbf{x_k}) + b\Big] \tag{6.1}$$

where:

$$\Psi(\mathbf{x}, \mathbf{x_k}) = exp\{-\gamma||\mathbf{x} - \mathbf{x_k}||_2^2/\sigma^2\}, \qquad \gamma > 0 \tag{6.2}$$

b is a real constant and a_k^* is retrieved as follow:

$$a_k^* = \max\Big\{-\frac{1}{2}\sum_{k,l=1}^{N} y_k y_l \Psi(\mathbf{x_k}, \mathbf{x_l}) a_k a_l + \sum_{k=1}^{N} a_k\Big\} \tag{6.3}$$

with:

$$\sum_{k=1}^{N} a_k y_k = 0, \qquad 0 \le a_k \le C, \qquad k = 1, ..., N \tag{6.4}$$

In this paper, γ and C were retrieved with grid search, as explained more in detail in Sec. 6.2.2.

For the sake of completeness, the performance of other classifiers, i.e. k-nearest neighbors (KNN) [79] and RF [80], were investigated too.

Prior to classification, the feature matrices were normalized within each feature dimension.

6.2.2 Experimental protocol

To investigate the two hypotheses mentioned in Sec. 6.1 different set of features were considered:

- For H1, 8 PPG features were used (Table 6.1)
- For H2, 11 features (3 anthropometric (Table 6.2) + 8 PPG features) were used

Tabella 6.1: *PPG feature mean (± Standard Deviation (SD)) of the PPG endothelial dysfunction dataset (ppgEDD).*

Features	**Mean ± SD**
SA	7.91 ± 5.68
IPA	0.61 ± 0.28
PI	172.92 ± 22.98
HR	69.19 ± 9.67
$Delta_T$	202.48 ± 40.29
SI	0.87 ± 0.18
AI	1.45 ± 0.38
RT	5.05 ± 0.66

Tabella 6.2: *Anthropometric feature mean (± Standard Deviation (SD)) of the PPG endothelial dysfunction dataset (ppgEDD)*

Features	**Mean ± SD**
Age [years]	39.0 ± 16.0
BMI [Kg/m^2]	25.7 ± 4.9
PP [mmHg]	44.15 ± 12.1

Considering the limited size of ppgEDD, Leave-One-Out (LOO) cross validation (CV) was implemented for testing purposes as suggested in the ML literature (e.g. [81]). LOO-CV implies that, each time, 58 patients were used for training and the remaining one for testing purpose.

During the training phase, classifier-hyperparameter tuning was implemented using a grid-search and LOO-CV approach. For SVMs, the grid-search space for γ and C was set to [1,0.1,0.001,0.0001] and [1, 10,100,1000], respectively. The grid-search space for KNN number of neighbors was [1,3,5,7,9] and that for the number of trees for RF was [5,10,15,20,30,40].

The performance of each classifiers was evaluated in terms of accuracy (Acc), recall (Rec) and precision ($Prec$):

$$Acc = \frac{TP + TN}{TP + TN + FP + FN} \tag{6.5}$$

$$Rec = \frac{TP}{TP + FN} \tag{6.6}$$

$$Prec = \frac{TP}{TP + FP} \tag{6.7}$$

where TP and FN refer to subjects with ED that were and were not classified correctly, respectively and TN and FP refer to subjects without ED that were and were not classified correctly, respectively

All the experiments were implemented using scikit-learn Python libraries[3].

6.3 Results

We tested our approach on ppgEDD dataset, in order to compare the endothelial function differences between patient with ED (N=28) and patient without the disease (N=31) based on the PPG signal. A full leave-one-out cross-validation is performed in our experiments procedure described in Section 6.2.2. In Table 6.3 and Table 6.4 the performance of each classifier are shown for H1 and H2, respectively. For H1, the best performance in terms of accuracy (Acc = 71%) was obtained with SVM, with a recall of 59% and a precision of 73%. The confusion matrices for KNN, RF and SVM are shown in Fig. 6.3a, b, c.

When investigating H2, as shown in Table 6.4, the SVM classification results were still the best, with a further improvement to 67% (Rec) and 69% ($Prec$). The normalized confusion matrix for KNN, RF and SVM are shown in Fig. 6.3d.

There results suggest that SVM was higher accuracy than that of KNN and RF based classifiers. The classification results and the values of statistical parameters indicated that the SVM had considerable success in the PPG signals classification by comparing with other classification methods. The conclusion drawn in the applications demonstrated that the features extracted from the PPG signal are possible correlated with the ED, which represent well the PPG signals, and by the usage of these features a good distinction between classes can be obtained. Therefore, the classification of ED by PPG signal should be a good method.

[3]http://scikit-learn.org/stable/ index.html

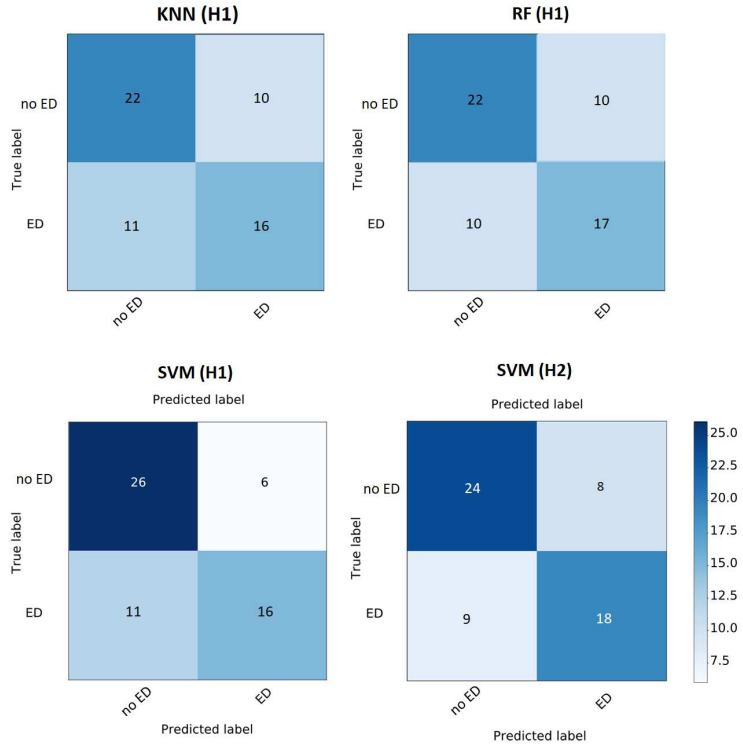


Figura 6.3: *Confusion matrices (CMs) obtained when classifying photoplethysmography features (H1) with (a) K-Nearest Neighbor (KNN), (b) Random Forest (RF) and (c) Support Vector Machine (SVM) classifier. (d) CM for SVM obtained when testing H2 (both photoplethysmography and anthropometric features).*

Tabella 6.3: *Investigation of H1: Classification performance obtained when classifying PPG features with K-Nearest Neighbor (KNN), Random Forest (RF) and Support Vector Machine (SVM) classifiers. Classification accuracy (Acc), recall (Rec) and precision (Prec) are reported.*

Classifier	*Acc*	*Rec*	*Prec*
KNN	0.64	0.59	0.62
RF	0.66	0.63	0.63
SVM	**0.71**	**0.59**	**0.73**

Tabella 6.4: *Investigation of H2: Classification performance obtained when classifying photoplethysmography and anthropometric features with KNN, Random Forest (RF) and SVM classifiers. Classification accuracy (Acc), recall (Rec) and precision (Prec) are reported.*

Classifier	*Acc*	*Rec*	*Prec*
KNN	0.64	0.52	0.64
RF	0.49	0.44	0.44
SVM	**0.71**	**0.67**	**0.69**

Capitolo 7

Discussion and conclusions

In conclusion, this research work presents a novel device that satisfy all the requirements of an ideal screening device to detect the ED based on a fully automated data processing and Clinical Decision Support Systems for assisted ED diagnosis.

The device contributes to the early detection of ED, preventing cardiovascular complications and lowering the number of premature deaths, using also a novel data processing method inside a Clinical Decision Support System for assisted diagnosis. Moreover, an innovative application is the use of the new device on cancer patients to monitor the effect of chemotherapeutic drugs. This aspect has been addressed in the context of a regional project called Intelligent Oncology Telecare (IOT), where the device in question plays a central role in the cancer patient monitoring system.

The scientific and technical contributions of this thesis were presented by: explaining the endothelium and reviews the state-of-the-art techniques for assessing ED and their limitations; introducing how ED early detection can be applied inside the IOT project; describing the phases to develop the device (conceptual design, analysis and design of software and hardware, including the investigation of the ergonomic design of the device and the assembly of all components); introducing the machine learning approaches to analyse and improve the diagnosis of ED; describing the development of the new index to discriminate the presence of the ED and the new algorithm to define the fiducial points useful for the parameters calculation from the PPG. All the proposed hardware and software devices and solutions were extensively tested using an advanced prototype on real patients and evaluating preliminary clinical trials.

The main contributions of this Thesis can be summarised as follows:

- Design and development of a new medical device for ED screening;
- Design and development of data-driven approaches for the analysis of signals acquired with the new device;
- Testing of the new device and of the Clinical Decision Support System in the actual clinical practice.

The device design and development has been a complex process rife with regulations, specifications, application requirements, and end user needs and all of which are balanced and adhered to for a successful product.

Results prove the correctness of the design intuition trough the real device implementation, the effectiveness of the biomedical data processing technique and of the Clinical Decision Support System applied to a real dataset and real patients, using the proposed device. The application to Oncology Telecare is suitable and the use of the overall approach on real clinical trials will apply the proposed device and methodology to the oncological care follow-up.

This work shows that the proposed technique to identify a new index, based only on the timing of discrete components of the PPG is capable of detecting the ED in a similar manner of FMD (gold standard). Clearly, fifteen people constitute a preliminary dataset, but they are a good starting point to identify the way forward. On the other hand, this approach is definitely less expensive than the FMD, and we think that more quantitative investigation may include the study of the reproducibility and repeatability to establish the method may be useful.

Moreover, it is important to remember that the assessment of ED with the gold standard it is not highly reproducible because the ultrasound methods are highly operator dependent.

Results from the present work highlight the detection accuracy of the fiducial points from the detection algorithm. It is appeared robust and shows a good performance to calculate the parameters. Failed detection depends on the impossibility to detect the dicrotic notch because for some patient was less pronounced. In this case, the study of the first derivative it is not sufficient. A possible solution to overcome this problem it is to work with a different approach as the wavelet transform a powerful time frequency analysis.

We think that a combination of these techniques may be a useful tool to detect these fiducial points in an automatic way in the PPG signal and for the consequent determination of the parameters.

About the parameters, we chose these: Systolic Amplitude (SA), IPA, Pulse Interval, Large Artery Stiffness Index (SI), and the Augmentation Index because we think that they may have a correlation with the vascular tone on of the function regulate from the endothelium. For this reason, we study these parameters, for the future, testing the prototype and with a big dataset will possible verify this correlation.

Furthermore, the calculation of the recovery time, qualitative we can suppose that it is an important factor to discriminate the healthy patient from the ED patient. In fact, after the occlusion of the brachial artery, the endothelium produce automatically the NO to dilate the artery, if the endothelium

works correctly the vasodilation and vasoconstriction change very quickly and therefore the recovery time is shorter.

All this study it a starting point to investigate these features, but in the future, by the clinical trial, will be possible to increment the dataset and compare the results with the gold standard.

Moreover, in the future will be useful, to try the new approach to detect the fiducial points will be based on the classification of the waveform with the machine learning techniques.

Finally, future works will cover a complete edge, fog, cloud device to better optimize the Internet of Thing architecture behind the data hierarchy design.

The solution will strength the ability to follow up on clinical therapy of different cancer, allowing a better quality of life and personalized therapy design.

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Appendices

A.1 Clinical Trial Protocol procedure

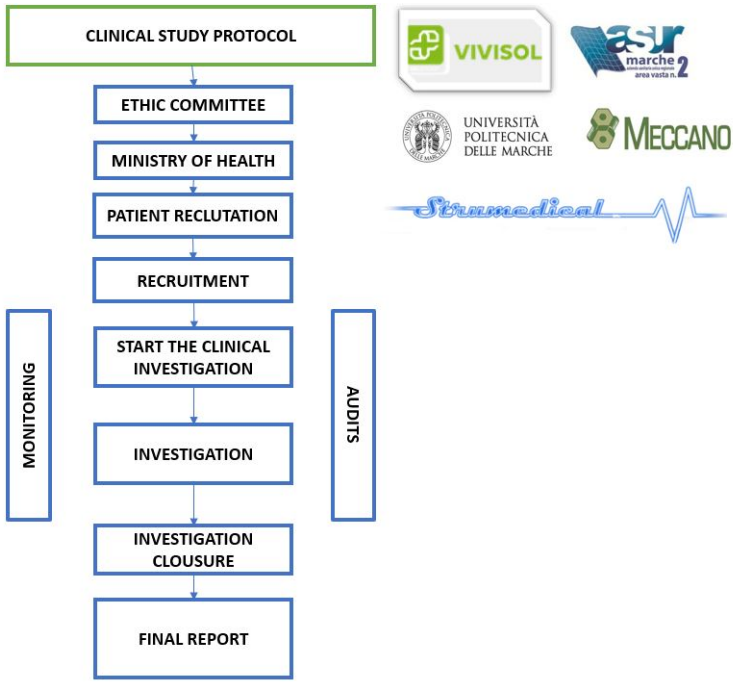


Figura 1: *Clinical Study Protocol procedure, for this part had collaborated the Vivisol, Meccano, Strumedical companies and the local health authority "Azienda Sanitaria Unica Regionale Marche"*

A.2 Function Analysis System Technique

Figura 2: *Function Analysis System Technique and Abstraction in Conceptual Design Process*

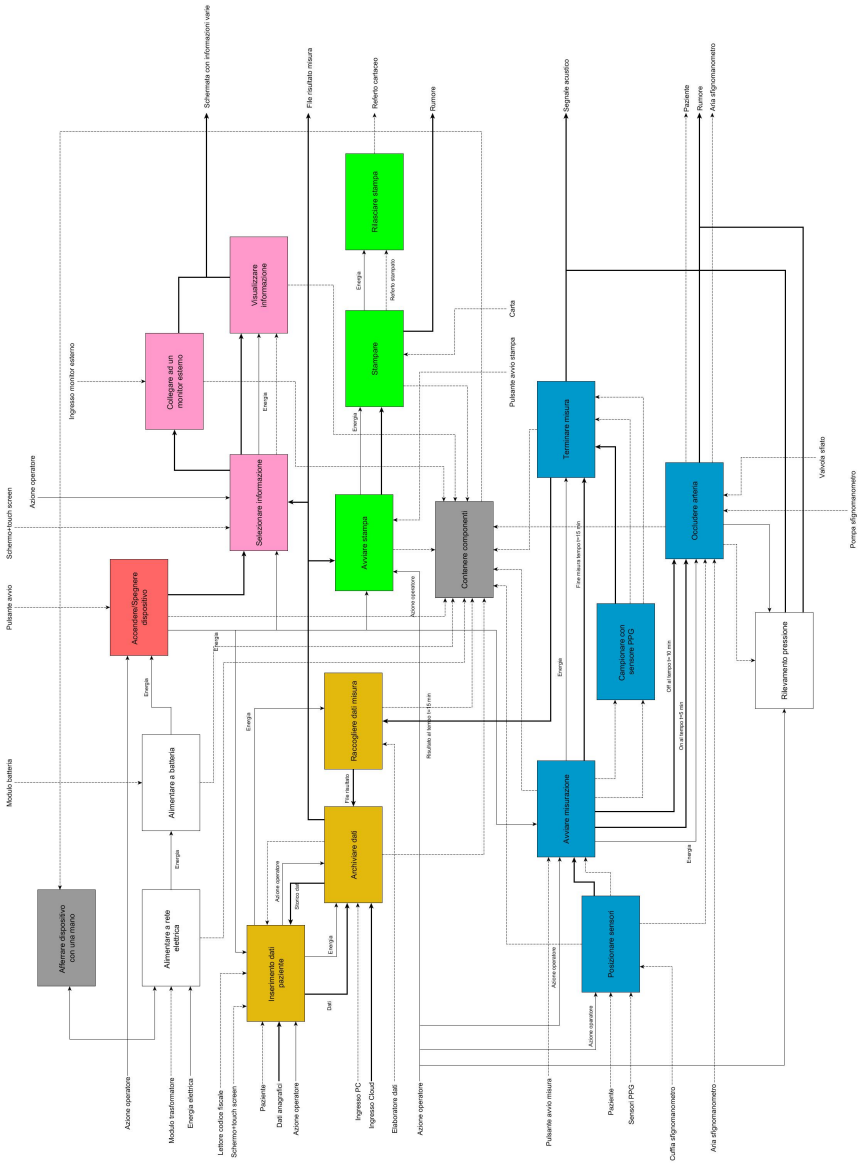


Figura 3: *Abstraction process second level*

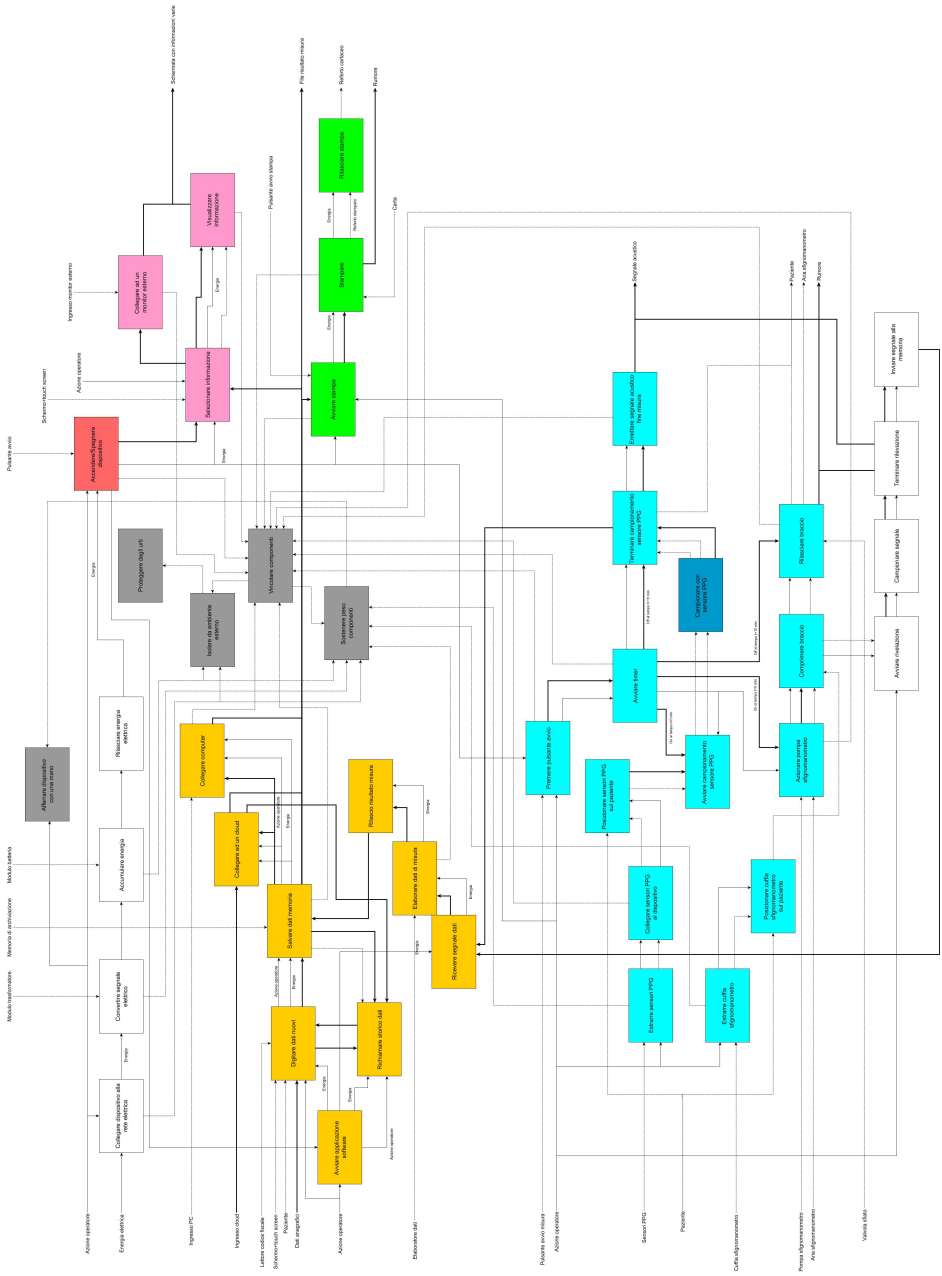


Figura 4: *Abstraction process third level*

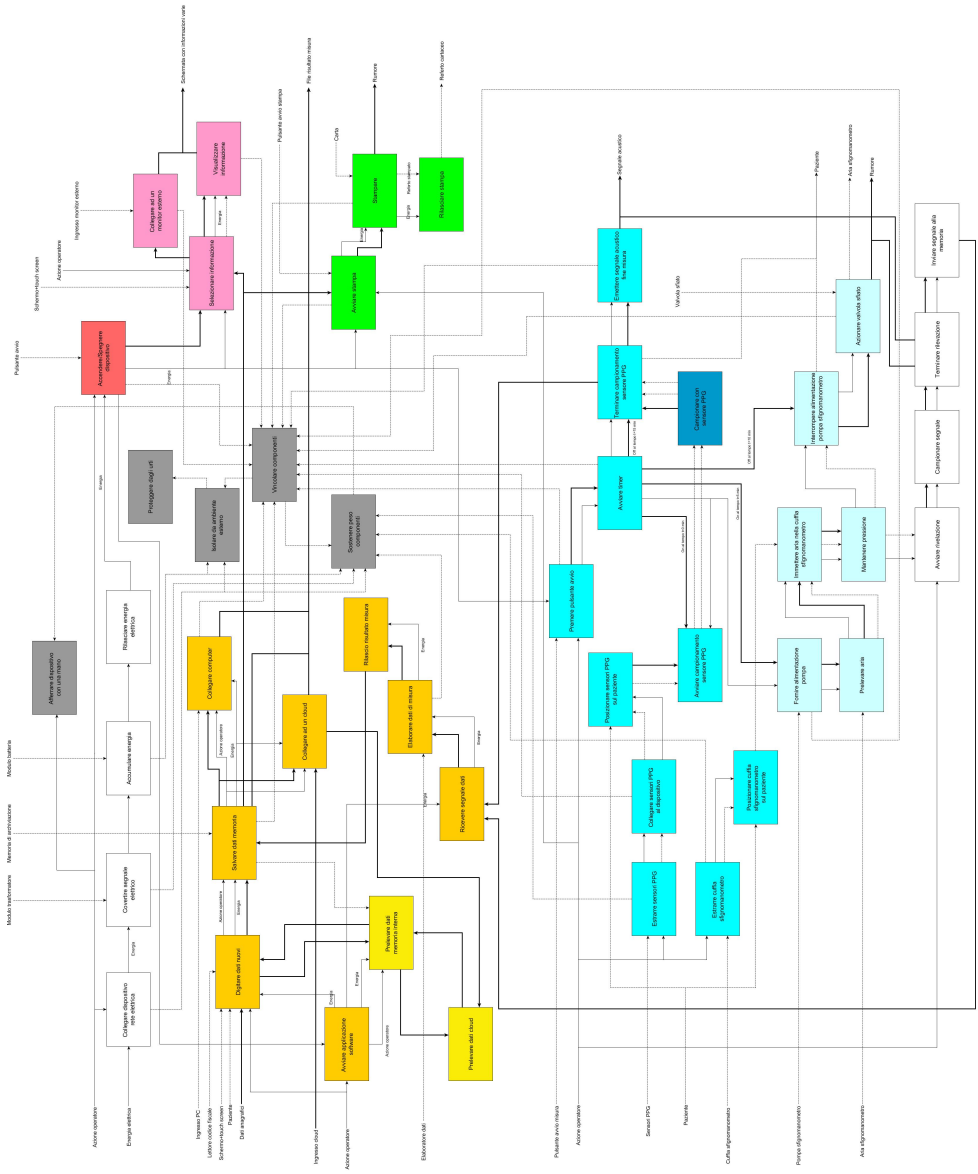
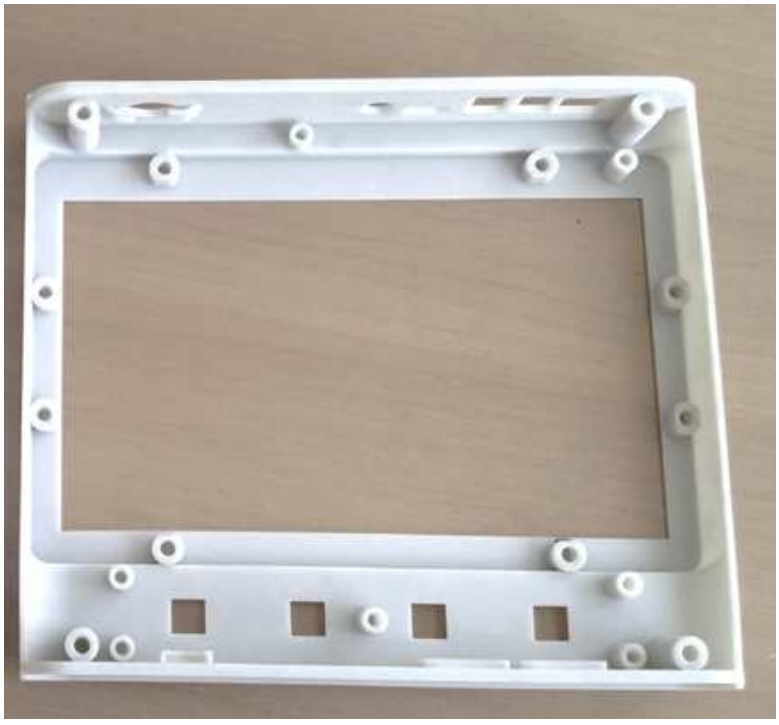


Figura 5: *Abstraction process fourth level*

A.3 3D printed chassis

(a)



(b)

Figura 6: *3D printed chassis, view from above (a) and below (b)*