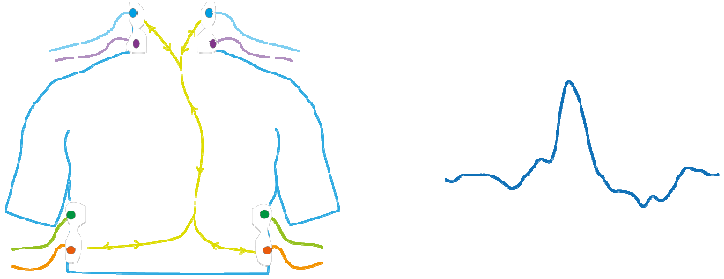
Universitat de Girona



The use of Impedance Cardiography to better characterize Resistant Hypertensive patients and therapeutic optimization versus 25 mg Spironolactone: A randomized controlled trial

Final Degree Project – Study protocol
January 2015

Author: Joana Filipa Correia Oliveira

Tutor: Dr. Fernando Pinto
Tutor UdG: Dr. Pedro Torguet

Faculty of Medicine
University of Girona

CONTENTS

ABBREVIATIONS

ABPM	Ambulatory Blood Pressure Monitoring
ACE	Angiotensin Converting Enzyme
BP	Blood Pressure
CHEDV	Centro Hospitalar Entre o Douro e Vouga
CO	Cardiac output
CV	Cardiovascular
DBP	Diastolic Blood Pressure
eGFR	Estimated Glomerular Filtration Rate
HBPM	Measurement Home Blood Pressure Measurement
HT	Hypertension
ICG	Impedance Cardiography
MAP	Mean Arterial Pressure
OBPM	Office Blood Pressure Measurement
PAD	Peripheral Artery Disease
PHCs	Primary Health Care Centres
PP	Pulse Pressure
RAS	Renina Angiotensin System
RHT	Resistant Hypertension
SBP	Systolic Blood Pressure
SV	Stroke Volume
SVR	Systemic Vascular Resistance
TEB	Thoracic Electrical Bioimpedance

1. SUMMARY

Resistant hypertension is an important public health issue, affecting 10 % of treated hypertensive patients. These patients are the most affected by target organ damage and high cardiovascular event rates, presenting higher levels of morbidity and costs for the national health system.

The treatment of resistant hypertension presents a challenging task for the clinicians despite the greater awareness to the issue and the improvements at the level of the treatment of these patients. Indeed, it is unclear whether the administration of 25 mg of spironolactone is the most appropriate therapeutic strategy for these patients. The range of alternative treatments is large and the most recent guidelines are not prescriptive about the best choice of treatment.

The aim of this study is to conduct a randomized controlled triple-blind trial to compare two different approaches for resistant hypertensive patients: routine treatment with 25 mg spironolactone or treatment according to the hemodynamic study- Impedance Cardiography in the improvement of blood pressure control. This study will be conducted in Hospital Entre o Douro e Vouga E.P.E. (CHEDV), Santa Maria da Feira, Portugal. CHEDV is responsible for supporting 25 Primary Health Care Centers, from where the sample of 982 true resistant hypertensive patients will be taken. We will collect systolic/diastolic blood pressure, mean arterial pressure, pulse pressure, nocturnal hypertension and circadian classification variables with the ABPM at the baseline and 3-months follow up. The higher blood pressure or potassium safety criteria will be collected during the follow-up.

Keywords: *Resistant Hypertension, Thoracic Electrical Bioimpedance, Impedance Cardiography, Hemodynamic Parameters anti-Hypertensive therapy, 25 mg Spironolactone*

2. INTRODUCTION

Hypertension (HT) is a major public health problem. It has been considered one of the most frequent diseases and the leading global risk for mortality, which represents a large burden on society(1). According to the World Health Organization (WHO) it is not only responsible for 12.8% of total deaths (equivalent to 7.1 million) worldwide but also for 3.8% of years of life lost from premature death and unhealthy life due to illness or disability (2).

Hypertension is a major modifiable risk factor responsible for 62% of cerebrovascular disease and 49% of ischemic heart disease (2). The prevalence of HT is of 30% to 45% in Europe, numbers that tends to increase with age (3).

High blood pressure has a wide range of complications, including cardiovascular (CV) events (e.g. stroke, myocardial infarction, sudden death, heart failure, peripheral artery disease (PAD) or renal failure). A patient is considered hypertensive when systolic blood pressure (SBP) is higher than 140 mmHg and/or the diastolic blood pressure (DBP) is greater than 90 mmHg (3).

In spite of the varied pharmacological and non-pharmacological treatments, a small group of these patients have a form of HT known as *resistant hypertension* (RHT). Resistant hypertensive patients tend to be at a much higher risk of target organ damage(such as ventricular hypertrophy, hypertensive retinopathy and renal disease – microalbumin, haematuria, or renal impairment) and cardiovascular events (4,5) when compared to controlled hypertensive patients. Therefore, these require more intensive diagnosis and specific interventions.

RH is defined as the failure to achieve target blood pressure levels (<140/90 mmHg for the overall population) after a regular administration of 3 antihypertensive drugs including one diuretic in optimal or best tolerated doses (3).The difficult control of the hypertension may arise from several causes, patient or doctor- related, or associated with the condition or the medication, as presented in Figure 1.

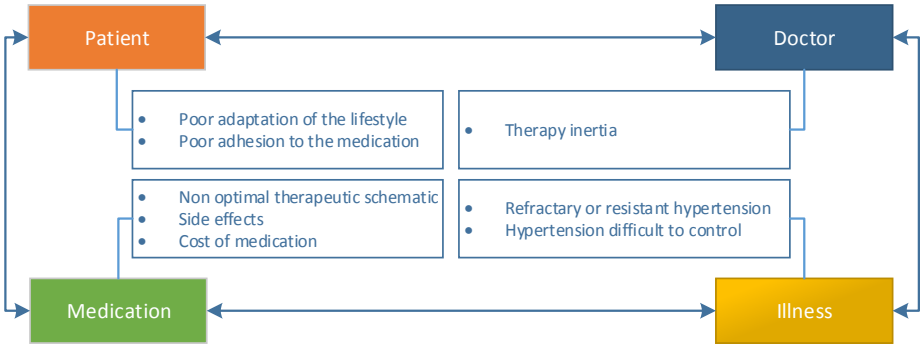


Figure 1 – Factors associated with hypertension of difficult control [adapted from(6)]

The true prevalence of RHT is a matter of debate, due to inadequate sample size in published, erroneous definition of the condition, or inadequate diagnostic approach. Data from the BP-CARE study has shown that these values can range between 5 and 30% of the hypertensive population (7) .

Amongst the hypertensive treated patients recruited on the Spanish Ambulatory Blood Pressure Monitoring Registry, 12.2% had resistant hypertension(8). According to the study PHYSA(9), the prevalence of RHT in Portugal is estimated at 8% of treated hypertensive patients. In order to meet the diagnosis of RHT several conditions of apparent or pseudo-resistant hypertension have to be excluded, such as:

- → Improper office blood pressure measurements;
- → White-coat effect;
- → Heavily calcified or arteriosclerotic arteries that are difficult to compress (elderly patients), where the only way to accurately measure blood pressure is intra-arterially;
- → Poor patient response to treatment: may be caused by medication side effects, difficult dosing schedules, costs of medication, memory or psychiatric issues or poor doctor-patient interaction;
- → Inadequate medication doses or combinations

The diagnosis of a resistant hypertensive patient is based on the confirmation of its resistance towards the treatment and on the identification of the causes of such condition. Attention should be given to secondary causes of hypertension such as primary aldosteronism, that may be more frequent than thought in the past, or renal artery stenosis due to atherosclerosis, very common in the elderly (3).

A complete diagnosis should gather detailed information about the patient history and lifestyle, a meticulous physical examination and laboratory tests to investigate related risk factors, organ damage or glucose alterations(3).

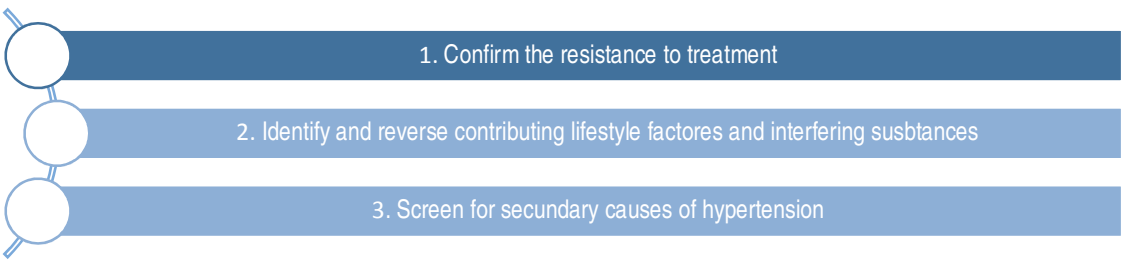


Figure 2 – Resistant hypertension diagnosis adapted from(3) *Mancia G.*

There are several methods to measure blood pressure (BP), both in the office and out-of-office. The latter allows a more frequent assessment of blood pressure and once it is done away from the medical environment, it is more reliable than the first, because some confusing factors are removed (3). In the following Table 1 there is a more clear evaluation of the reliance of each method, comparing the Office Blood Pressure Measurement (OBPM), Home Blood Pressure Measurement (HBPM) and Ambulatory Blood Pressure Measurement (ABPM).

Table 1 – Comparative table of the different forms of blood pressure measurements (adapter from (Torguet, P))

	OBPM	HBPM	ABPM
REAL BP VALUES	Questionable	Yes	Yes
"DIPPER" STATUS	No	No	Yes
MORNING INCREASE	No	Questionable	Yes
BP VARIABILITY	No	Questionable	Yes
DURATION OF THE PHARMACOLOGICAL EFFECT	No	Yes	Yes

As pointed out in Table 1, it can be concluded that the ABPM is the most reliable method to evaluate BP.

Even though the definition of RHT relies on clinical BP, the use of ABPM leads to a better diagnosis and characterization of resistant patients, excluding those affected by white coat effect and removes observer bias and measurement error(8,10). White-coat resistant hypertension is frequent with a prevalence in the range of 35 to 40% (10). Furthermore, the evaluation of the patient BP along his circadian cycle improves the definition of the pathophysiologic profile, thus promoting a more accurate and reproducible analysis of the effects from the treatment[1] and of the adequacy of the administration times. It has shown better results when compared to clinical measurements in reflecting target organ damage, its modifications induced by medication, in predicting its development and progression, allowing the classification of the circadian pattern of BP as dipping or non-dipping – in hypertension, non-dipping status has been associated with high-cardiovascular risks(11).

ABPM has received increasing attention at three levels: during **diagnostic**, **treatment** and identification of **target organ damage** or **cardiovascular events.** Furthermore, ABPM should be performed regularly, to exclude false resistance, to better quantify the BP elevation and the effect of the variations on medication(11).

[1] As proven by the SIMPLICITY HTN-3 study, the BP reduction after the use of renal denervation measured by the ABPM was 30–40% inferior to the ones measured by office BP (47).

RHT is a multifactorial condition and a complex hemodynamic disorder mostly caused by the inadequate and suboptimal pharmacological treatment in actively treated patients(12).

According to the most recent guidelines, the treatment of HT is based on two pillars: non-pharmacological and pharmacological (3).

The non-pharmacological treatment requires a good doctor-patient relation and the involvement of a multidisciplinary team to lead to a better adhesion of the patient to the therapy while improving his life quality. This kind of interventions should endorse the education and motivation of the patient in order to a successfully achieve (3,13,14).

- → Weight loss in overweight and obese patients (less 5.1kg of weight reduces BP by 4.4/3.6 mmHg (DBP/SBP) in average;
- → Regular physical exercise (aerobic activity can be beneficial for prevention and treatment);
- → Diet changes – more fibres and fruits, less fats, calories and salt (1.4g reduction in dietary sodium is related with a reduction of BP of 2.7/5.0 mmHg and 1.0/2.0 in hypertensive and non-hypertensive individuals, respectively (14))
- → Moderated intake of alcohol (80/140g per week for women/men) and caffeine;
- → Abolition of exogenous substances.

The pharmacological treatment focuses on the blockage of all the possible mechanisms of BP elevation (15). Patients classified as resistant hypertensive will already have been medicated with at least three antihypertensive drugs, an angiotensin converting enzyme (ACE) inhibitor or angiotensin receptor blocker, a calcium channel blocker and a thiazide-type diuretic, which is a synergic combination of BP elevation mechanism blockers (3).

Despite the possibility of reducing the BP of RHT by further increasing medication doses, most patients need the administration of more than three drugs. The 2013 ESH/ESC Guidelines (3) suggest that all drug classes with

mechanisms of action with differences from the three present drugs are able to lower BP in at least some of these patients. According to this (after maximum tolerated doses of the previous referred three drugs) a good response can be obtained with a 4th agent which can be (3):

- → Mineralocorticoid receptor antagonists – spironolactone, at low dosages (25-50 mg/day) or eplerenone, unless it is contraindicated;
- → Alpha-1-blocker doxazosin;
- → Further increase in diuresis with loop diuretic replacing thiazides or chlorthalidone if renal function is impaired;
- → Amiloride, in the case of elevated blood volume, that may add its effect of a previously given thiazide diuretic. However, it may also favour hyperkalaemia, thus not being indicated in patients with reduction of estimated glomerular filtration rate eGFR.

Although the guidelines suggest different antihypertensive treatment options, many studies show that spironolactone in a low-dosage is highly effective when added to previous treatment (16,17) even when primary aldosteronism is absent (18).

The BP response to spironolactone may be accounted for the elevated plasma aldosterone levels frequently accompanying RHT, either because aldosterone secretion escapes the early reduction associated with renina angiotensin system(RAS) blockade or due to undetected primary aldosteronism (3).

There are more published studies with spironolactone used in the treatment of resistant hypertension than with any other antihypertensive already mentioned. In addition, a recent study implies that when comparing the response to BP spironolactone is roughly double that of other classes of antihypertensive medications in resistant hypertensive patients. (19) To support this, comparative studies were carried out with amiloride, doxazosin and spirolactone and in both a more significant improvement in pressure values was observed when spironolactone was used (20,21).

Blood pressure control without an increase in medication has been the focus of some studies(3), culminating in the development and evaluation of two alternatives: carotid baroreceptor stimulation and sympathetic denervation of renal arteries. Despite showing promising results the device requires technical improvements to prevent some complications and local side effects observed. This therapy needs further testing to assure its efficiency and applicability (3).

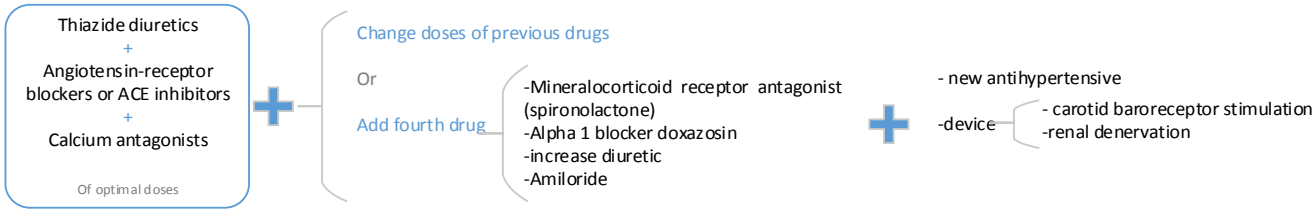


Figure 3 –Treatment according guidelines adapted to(3) *Mancia G.*

Despite the advances made to improve the level of treatment of resistant hypertension patients, the control of BP values continues to be challenging. The management of HT has to be focused in the need to improve long-term CV outcomes, in order to increase the proportion of patients achieving target BP, according to recommended guidelines (6) because small decreases in blood pressure values cause major improvements to the level of the patient's prognosis (22).

In recent years, the weight of evidence indicates that RHT treatment may benefit from being considered a global hemodynamic disorder. So, investing in a hemodynamic approach and further processing in accordance with the amended pathophysiological mechanism, has gained more clinical relevance over time (23–25).

Hemodynamics: *hemo – blood, dynamics – the science of the forces involved in the movement*(26) including cardiac function and peripheral vascular physiological characteristics (27).

BP is certainly the most used parameter for the evaluation of cardiovascular function. However, it is an incomplete indicator if used alone. BP and more specifically mean arterial pressure (MAP) is the result of two hemodynamic

parameters: Cardiac Output (CO) determined by the stroke volume and the heart rate and Systemic Vascular Resistance (SVR)(23), therefore, intravascular volume, cardiac inotropy and systemic vascular resistance are the hemodynamic component of BP physiology (23).

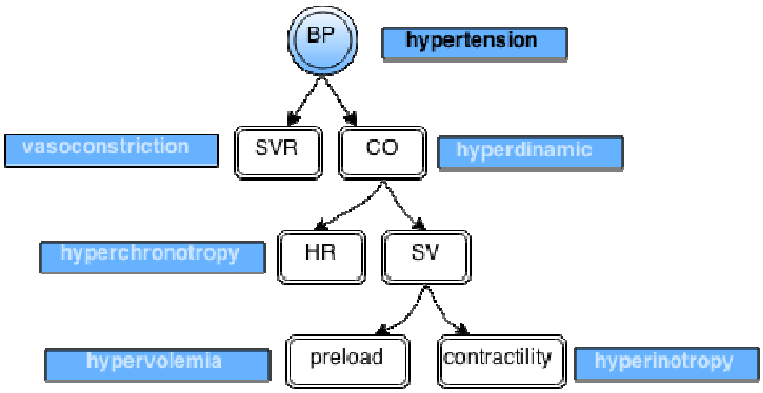


Figure 4 – The different hemodynamic components of hypertension(24) *Viigima M.*

Nevertheless, hemodynamic disorders of elevated CO, SVR or both are the phenotypic characteristics of increased blood pressure. CO, SVR or both are fundamental parameters to understand the pathophysiology of hypertension and to guide diagnostic, prognostic and therapeutic management decisions (24).

Hypervolemia, hyperinotropy or vasoconstriction, the hemodynamic causes of HT cannot be evaluated by physicians regularly. This is why, nowadays, the BP problem is treated not as a disease, but as a symptom. The current treatment selection is chosen independently of the hemodynamic status of the patient, since the hemodynamic causes of the BP elevation are not evaluated (24).

Historically, most hemodynamic information (CO and SVR) used in research is acquired using invasive methods, such as arterial cannulation and placement of pulmonary artery catheter. However, these procedures are not appropriate for routine care. Echocardiography provides an early non-invasive measurement of CO, however it is costly and highly operator dependent (23).

Advances in non-invasive hemodynamic monitoring using Impedance cardiography (ICG) also known as Thoracic Electrical Bioimpedance (TEB) have been successfully developed, making it a unique, affordable, non-invasive and valuable tool, being as rigorous as invasive methods in the assessment of hemodynamic status(23). In multiple studies have been found that when compared with invasive techniques, the ICG technology demonstrate high correlation and accuracy in the hemodynamic measurement. These studies were only applied in populations in situations that justify the risks associated with the invasive techniques and with significant underlying cardiovascular conditions because of the inherent risks of these techniques (28–32).

Therefore we can consider ICG as a method used to obtain hemodynamic parameters, beyond that ICG device have received CE clearance (Annex 1).

ICG is a diagnostic method based on the measurement of the electrical properties of the tissues/resistance of body tissue. The impedance, a measurement of the opposition presented to the passage of current, depends on the tissue, its contents and modifications and is measured by applying an oscillating electric current on electrodes and quantifying the voltage changes detected on the receiving electrodes, all placed on the patient's thorax.(33)

Variations in the thoracic bioimpedance can then be converted into changes in blood and pulmonary volume. Filtering the last component, the device can retrieve volume and velocity of blood in the aorta, as illustrated by Figure 5(34).

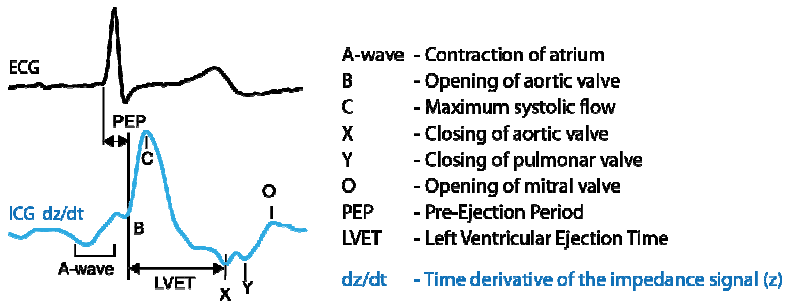


Figure 5 – Interpretation of the changes in impedance (adapted from niccomo™ brochure)(34)

During diastole, the erythrocytes assume a random orientation, causing more resistance to the electrical current (decreasing conductivity). During systole, the erythrocytes align with the blood flow, easing the passage of current,

decreasing electrical resistance. These changes in conductivity allow the calculation of peak aortic acceleration of blood and the left ventricular ejection time, used then to derive blood flow velocity and stroke volume (23,33)

To summarize, the changes in cardiac cycle and in the volume of blood in the aorta, result in changes in the electrical conductivity, which will be represented in changes in the thoracic impedance. The changes in the cardiac cycle are used to calculate the hemodynamic parameters(33).

Insight on the hemodynamic status may bring improvements to the diagnostic, treatment and prognostic of a hypertensive patient. There are several Hemodynamic parameters obtained by the ICG, as presented in the ICG report (0) to target hypertensive treatment, there will be considered the ones described in the Table 2(33).

Table 2 – Impedance Cardiography Parameters(24,35)

	Parameter		Description	Unit
Impedance Cardiography Parameters	CO	Cardiac Output	Amount of blood put out by the heart in a given space of time	L/min
	SV	Stroke Volume	Amount of blood put out by the heart in a beat CO/HR × 1000	mL
	SVRI	Systemic Vascular Resistance Index	SVR/BSA	$dyn \cdot s \cdot cm^{-5}/m^2$
	TFC	Thoracic Fluid Content	Total fluid conductivity in the chest, including extravascular and intravascular fluid	$kOhm^{-1}$

In order to reduce BP, selected antihypertensive drugs are used in order to target underlying hemodynamic abnormalities hence its therapy shall reside on a correct identification and correction of the factors that contribute to the HT and which are present on the individual patient.

The treatment based on the hemodynamic status follows the algorithm presented in the therapeutic strategy of the protocol (Figure 6). The ability of ICG-guided therapy to improve hypertension control rates have been demonstrated and also considered important for the future treatment of hypertension (36–39).

This technology is considered cost-effective, allows a better control of the BP and leads to economic benefits in the costs of hypertension and associated cardiovascular disease expenses (23).

ICG allows finding the cause of increased blood pressure and shows the patient cardiovascular state. It leads to a decrease of therapeutic inertia and suboptimal doses because through the ICG data doctors are able to predict

therapeutic responses and/or toxicities to pharmacological or other interventions. This allows the physician to combine therapies that without this information would not combine. As previously said the major cause of resistance to treatment is an inadequate drug and doses prescription.

3. JUSTIFICATION

Until the present date, there were found 2 published studies Taler *et al.* 2002 *and* Smith *et al.* 2006 (36,37) which compare the treatment according to the data of ICG with any prescribed anti-hypertensive drug, according to the clinic experience of the physician.

None of these investigations define the study population according to the strict definition of resistant hypertension described in hypertension guidelines. Beyond that, in these studies, the diagnosis of hypertension is based in the Mercury shygomanometer (registered by the nurse) (36) and oscillometric technique (37) and not with ABPM leading to an inaccurate definition of true resistant hypertensive patients. As described above, these studies considered a group treated according to the results of ICG and another group treated according to the clinic experience of the physician.

Therefore, and in view of the evidence described above in the great utility of therapeutic approach, we propose to conduct studies comparing this therapeutic strategy with the most common clinic practice (25mg spironolactone), in order to confirm or refute the benefit of this therapeutic approach, individualized and directed.

Thus, this study will be the first with these characteristics. It has great importance for this group of patients, becoming novel and appealing to all the medical community as a possibility to update hypertensive guidelines. In fact, there is not a unanimous neither a "perfect" therapeutic strategy in this group of patients, which is the one with the most target organ damage with consecutively increased risk of mortality.

4. HYPOTHESIS

H1: A strategy based on the interpretation of hemodynamic parameters obtained with bioimpedance for targeting treatment of resistant hypertensive patients is more effective in reducing **24h, day and nightsystolic and diastolic blood pressure** compared with a strategy based on the routine use of 25 mg spironolactone.

H2: A strategy based on the use of hemodynamic parameters obtained by bioimpedance orientation for treating resistant hypertensive patients improves the **24h, day and night pulse pressure, the 24h, day and night mean arterial pressure, the classification of circadian pattern BP and nocturnal hypertension** when compared to a strategy based on the use of systematic of 25 mg spironolactone.

H3: A strategy based on the use of hemodynamic parameters obtained by bioimpedance orientation for treating resistant hypertensive patients has less patients with levels of **OBPM higher or equal than 180 and/or 110 mmHg and/or potassium equal or more than 5.5 mEq/L** during the follow up when compared to a strategy based on the systematic use of 25 mg spironolactone.

5. OBJECTIVES

5.1 Primary objective

Check if a strategy based on the interpretation of hemodynamic parameters obtained with bioimpedance for targeting treatment of resistant hypertensive patients is more effective in reducing **24h, day and night systolic and diastolic blood pressure** compared with a strategy based on the routine use of 25 mg spironolactone.

5.2 Secondary objectives

Compare the effectiveness of the treatment based on the interpretation of the parameters obtained by the bioimpedance above the routine use of spironolactone 25 mg improving **24h, day and night pulse pressure, 24h, day and night mean arterial pressure, the classification of circadian pattern BP and nocturnal hypertension** in resistant hypertensive patients

Compare which of the therapeutic strategies – treatment based on the interpretation of the parameters obtained by the bioimpedance or the routine use of 25 mg spironolactone –has less patients with **levels of OBPM higher or equal than 180 and/or 110 mmHg and/or potassium equal or more than 5.5 mEq/L** during the follow up.

6. METHODS

6.1 Study design

This project proposes prospective, triple blind, randomized controlled trial with parallel groups.

6.2 Description of the study

Primary Health Care centres (PHCs) will send a group of resistant hypertension patients according to a pre-selection form (Annex 3) to the Hospital Entre o Douro e Vouga (CHEDV). These participants will be submitted to a blood and urine analysis and others explorations (electrocardiogram, Doppler ultrasound of renal arteries).These explorations form part of the clinical practice of a resistant hypertensive patient allowing the exclusion of the causes for secondary hypertension. After that, they will be submitted to an ambulatory blood pressure monitoring (ABPM) that will confirm if the hypertension is a truly resistant hypertension. If this result is positive, an Impedance Cardiography test (ICG) will be performed. These participants will be randomly divided in two groups, each treated with a different approach, either using the routine treatment with spironolactone or hemodynamically based. The effectiveness of the different treatments will be evaluated with ABPM prior and 3 months after the beginning of therapy, checking the reduction in BP and the improving of the characterization of other parameters given by ABPM, as represented in Figure 6.

6.3 Study flow chart

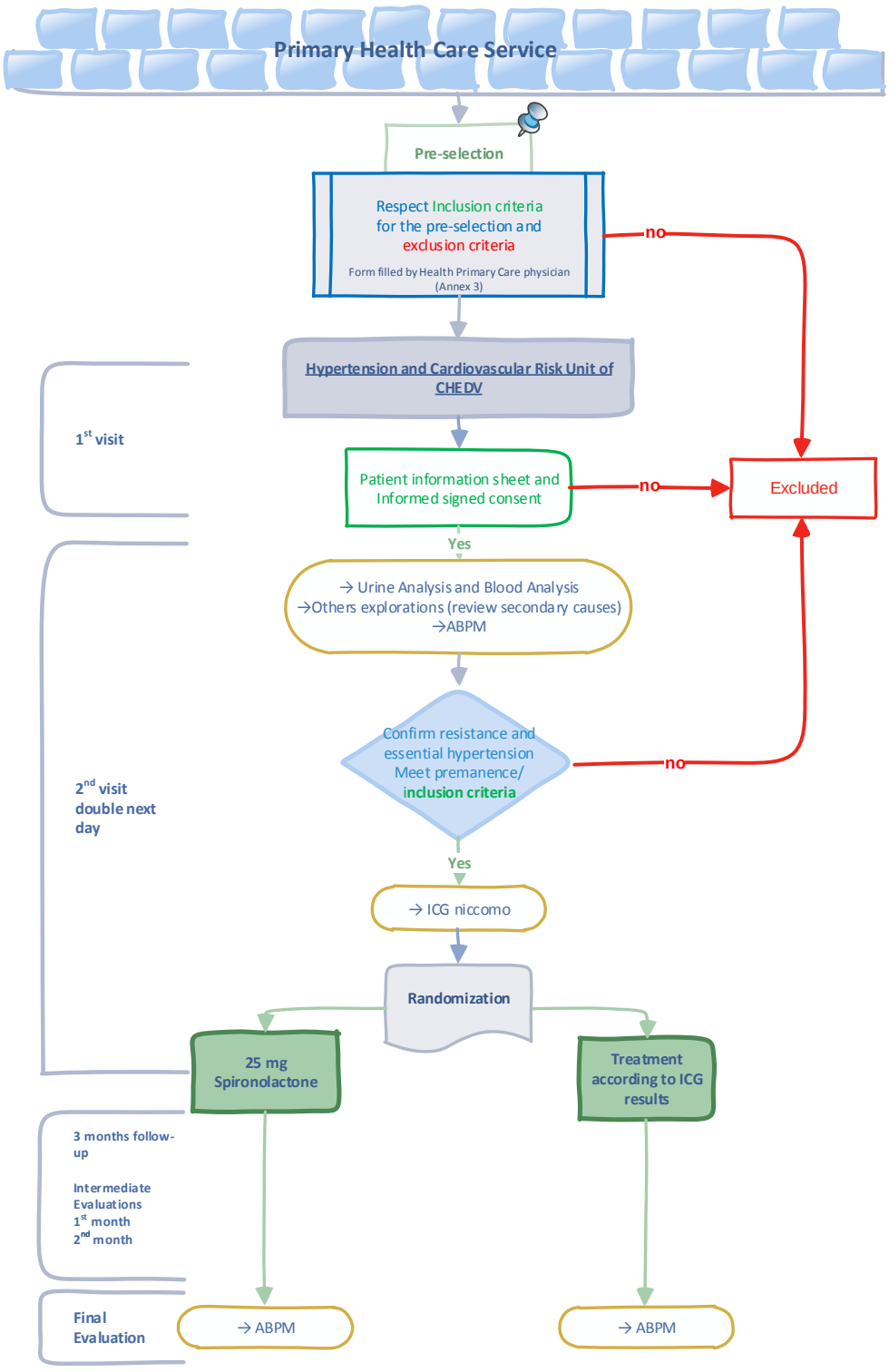


Figure 6 – Study flow chart

6.2 Participants

The study will be performed in resistant hypertensive patients from PHCs belonging to Santa Maria da Feira/Arouca. The patients will be initially screened by the general practitioner (GP) who filled the pre- selection form (Annex 3) and if he meets the inclusion and exclusion criteria, will be referred to Hypertension and Cardiovascular Risk Unit in the Cardiology service of Centro Hospitalar entre Douro e Vouga, E.P.E. (CHEDV) in Santa Maria da Feira, Portugal where the study will be held, during 3 years.

6.2.1 Inclusion and exclusion criteria

The patients selected to the described study follow the criteria presented in Table 3.

Table 3 – Inclusion and Exclusion criteria

Inclusion criteria	Exclusion criteria
Inclusion criteria for the *pre selection* (Primary Health Care Criteria) ▪ Office Blood pressure higher than 140/90 mmHg after the administration of 3 or more antihypertensive agents of different classes including one diuretic in optimal dosage ▪ More than 18 years old **Inclusion criteria *for the permanence*** in the trial (CHEDV criteria) ▪ All patients have an ABPM confirming the inadequacy of control of BP- **True resistant hypertension** is defined by **one or more** of the following changed parameters: 135/ 85 mmHg for daytime, >120/70mmHg for night-time, and >130/80 mmHg for 24 hours ▪ Essential resistant hypertension	– Not available for 3 months follow-up; – Non-compliance with medication as the cause of treatment resistance stated at the beginning of the study. – History of intolerance / allergy to any of antihypertensive possible – Already treated with spironolactone – Patient who has a clear indication to one of the drugs different from the ones under study – Drug interferences (Annex 4Annex 4) – Secondary causes of hypertension detected by analytical, clinical or complementary evidence *(Annex 4)* – Hiperkaliemia (>5.5mEq/L) – Severe cardiovascular disease or cardiovascular event **Severe cardiovascular disease**: → Congestive Heart Failure (CHF) → Uncontrolled ischemic cardiopathy → Chronic Kidney Insufficiency (CKI)Estimated Glomerular Filtration Rate < 30 according to CDK- EPI equation **Cardiovascular events** → Acute myocardial infarction or anginal episode Road stroke / transient ischemic attack → Amputations by vascular problems – Hepatopathy; Neoplasms; – Pregnant women – ICG without any abnormality in hemodynamic parameters – Possibility of **biased hemodynamic studies** (example: large liquid quantities in the thorax as it may affect the tissue conductivity) *(Annex 4)* – hypersensitivity to sensor gel or adhesive skin lesion interfering with sensor placement

6.3 Sample selection

A consecutive non-probability sampling will be taken from resistant hypertensive patients who are diagnosed in different Primary Health Care Centres. CHEDV will support all these inputs between January 2015 and December 2016, two years of sample recruitment. Patients, who meet the required criteria, will be recruited through the promotion of the study. Participants will be given an information sheet (Annex 5) describing the study and if the patients agree to be part of the study an informed consent will be signed at CHEDV.(Annex 6)

6.4 Sample size

We used GRANMO to calculate the sample size. We have assumed an alpha risk of 0.05 and a beta risk of 0.2 of a two-sided test. The common standard deviation is assumed to be 10 for the ABPM measures. It has been anticipated a drop-out rate of 0.20.

The minimum expected difference between the two groups is 2 mmHg, because according to meta-analysis conducted on more than 1 million hypertensive subjects there was decrease of 10 % on stroke mortality and about 7% of mortality from IHD or other vascular causes just with a 2 mmHg reduction in SBP(22). Thus, 2 mmHg was clinically meaningful in the reduction of BP because it implicates the patient's prognosis. Given these parameters, the required sample size was 491 subjects in the spironolactone group and 491 in the group treated according to ICG (982 patients in total).

We propose a single centre trial, but because we need a large sample size which cannot be achieved by a single PHC, we propose recruiting individuals from various PHCs across the municipality. Therefore, we have the possibility to achieve a much more representative sample of the population.

The clustering effects (patients may be more similar within each health primary centre) among the different health primary centres do not need to be taken into account because all patients are random and this is a single centre study and for that there is no risk of contamination. For the required sample size, we expect that all PHCs recruit hypertensive patients according to the prevalence of this disease of each centre.

Centro Hospitalar de Entre o Douro e Vouga, E.P.E., where the research will take place, is responsible for providing health care to a population of around 340,000 inhabitants, resident in the municipalities of Santa Maria da Feira, Arouca, São João da Madeira, Oliveira de Azeméis, Vale de Cambra, Ovar and Castelo de Paiva .
According to National Health System, the CHEDV is responsible for support of inputs of all Primary Health Care Centres related areas mentioned above corresponding to 25 primary care facilities.

According to PHYSA study, 42.2 % of the Portuguese population is hypertensive and about 8 % are resistant hypertensive. If CHEDV is responsible for 340,000 inhabitants, 142,800 are hypertensive and 11,424 of those are resistant hypertensive, so it is possible to reach the wanted number for the study sample.

So, it is imperative to ensure that these PHCs meet certain requirements to be able to collaborate in this trial:

- → Must belong to the area covered by CHEDV (to avoid increase the losses because of distance)
- → Must have a weekly rate of inclusion on the study of 15 patients in two years of study, the direct contact between the CHEDV and different PHCs allows to adapt the flow of patients according to the required sample.

6.5 Interventions

6.5.1Randomization and blinding

The patients will be divided in two groups according to a simple randomization with a 1:1 ratio. The randomization is made using a random numbers generator. Assignment of treated according the hemodynamic parameters or with 25 mg of spironolactone will be kept in sequentially number opaque envelopes.

While patients in the spironolactone group will not be treated according to hemodynamic parameters, they will undertake bioimpedance to ensure participants are blind to the treatment received.

The envelopes will be opened by the doctor who analyses the results of bioimpedance.

The randomization sequence will be computer-generated using the SPSS instrument and will be performed by the statistician who will analyse the data concerning the study. Both groups received education about the importance of medication compliance, which was supported by the doctor at beginning of the treatment and in the follow up.

6.5.2 Degree of blinding

This will be a triple blind trial since its participants, the doctor (who gave the treatment and follow the patient) and the statistical consultant (data analyst) will remain unaware of those being treated using clinical practices and those treated according to the hemodynamic study.

The doctor administering the treatment must be different from the one analysing the result of bioimpedance (this last task must always be done by the same doctor).

The physiscian who analyse the bioimpedance results, will write to the first doctor the correspondent drugs which will be identified with a set of digit, this will prevent the doctor who administrates the drugs from knowing what active principle is the patient taking.

All drugs have a specific code. They all have the same shape and size and the same number of drugs will be administered to both groups of patients.

The doctor responsible for indicating the treatment prescribes drugs writing down the code given by the doctor who examined the bioimpedance parameters.

These drugs will be dispensed by a third element which is the Hospital Pharmacy who knows the drugs by their respective codes.

6.5.3Description therapeutic strategy

→ One group treated with 25 mg spironolactone daily single intake

→ One group treated according to the results of ICG

The treatment based on the hemodynamic status follows the algorithm presented in Figure 7(23,39).

The antihypertensive medicine is also chosen according to the ICG results held in supine position. In addition, elegy be altered according to the drug hemodynamic variable, when there is more than one variable abnormal choice of antihypertensive drug will be taken according with predominantly hemodynamic variable changed. Therefore, peripheral vasodilator agents would be added in patients with elevated vascular resistance index (SVRI); Beta blockers would be added or dosage would be increased in subjects with a high CI; Diuretics would be used when thoracic fluid content (TFC) is increased.

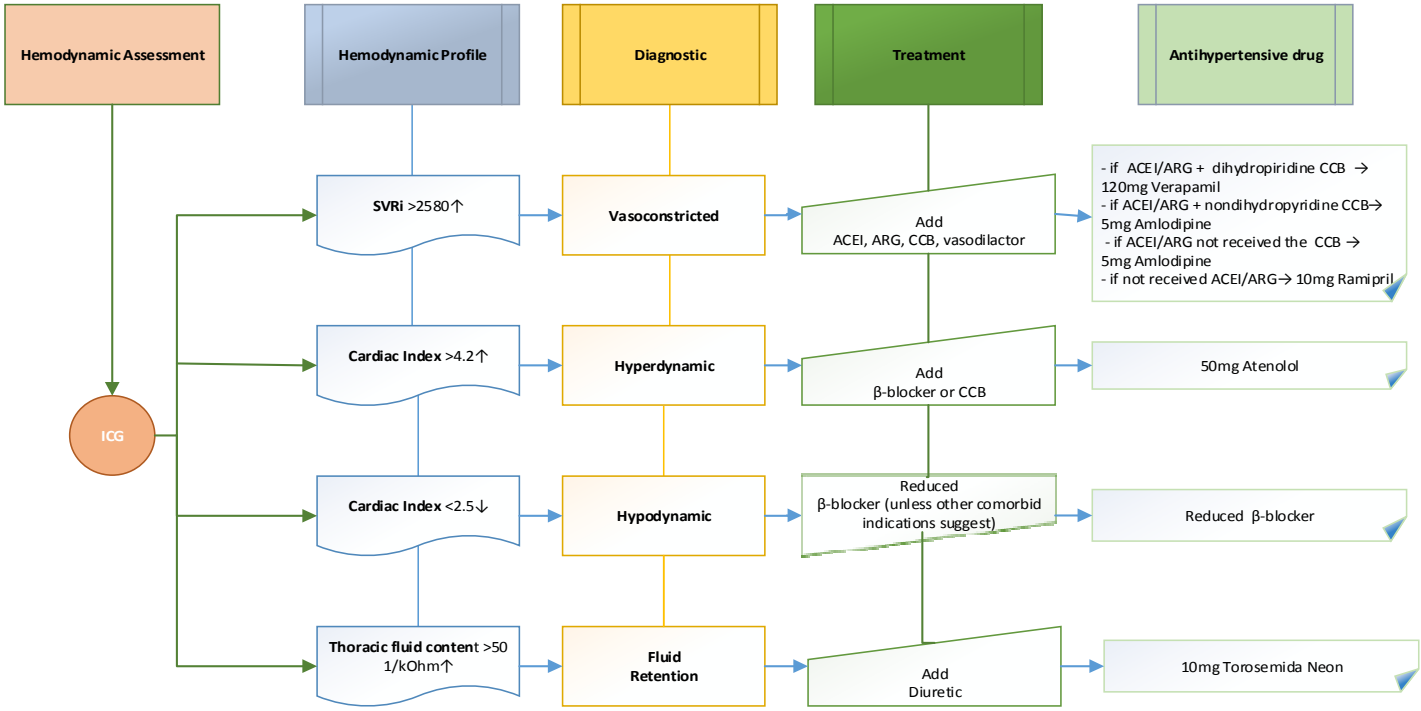


Figure 7 – Anti-hypertensive therapy with hemodynamics [adapted from(23,39)] (SVRI- Systemic Vascular Resistance Index ACEI – Angiotensin converting enzyme inhibitor, ARB – Angiotensin II Receptor Blockers, CCB – Calcium channel blocker)

6.5.4 Follow up

After starting treatment, both groups will be followed by two medical visits during these three months.

The first one will be performed at first month and the second one in the second month after the treatment. The patient will be asked for any side effects of antihypertensive drugs, office blood pressure measure and a blood analysis.

The main objective with this visit is to certify the safety of the study. If there are security issues in our study, these will be taken into account as follows:

- If office blood pressure (OBPM) is higher or equal than 180/110 mmHg
- If the potassium is equal or higher than 5.5mEq/L

In both cases, if there are any safety issues the patients will stop the intake the assigned drug and will follow treatment at the researcher's discretion. They will be taking into account in the starting group but will not follow the expected treatment according to the trial protocol (intention-to-treat analysis). A blood analysis can be ordered if the researcher considers it appropriate

6.7 Outcomes and baseline covariates

Primary outcome variable

Systolic and diastolic blood pressure 24h, day and night are continuous quantitative variables. They will be measured by ABPM and are represented in millimetres of mercury (mmHg). These variables will be measured before treatment and at final of the 3 months of follow up

Secondary outcome variables

The **pulse pressure (PP):** is the difference between systolic and diastolic blood pressure (PP= SBP-DBP) and is measured in millimetres of mercury (mmHg).This pressure is a good indicator of the state of the stiffness of the arteries, especially the aorta. Several studies, have identified a link between high PP and increased cardiovascular mortality (40,41). REGARDS Study (42) is a recently study that show that PP was an independent risk factor for acute CHD. PP more than 55 mmHg is considered a risk factor for cardiovascular disease. PP is continuous quantitative variables will be measured by ABPM, accessed before the treatment and at final of the 3 months of follow up.

The **Mean arterial pressure (MAP)**: 24h, day and night – is the average arterial pressure during a single cardiac cycle, also measured millimetres of mercury (mmHg). It relates flow, pressure and resistance using the following expression: MAP = (CO × SVR) + CVP, using the cardiac output (CO), systemic vascular resistance (SVR), and central venous pressure (CVP). MAP is a continuous quantitative variable that will be measured by ABPM, accessed before the treatment and at final of the 3 months of follow up.

The **Circadian classification** is given according to the percentage of night descent of blood pressure compared to the average daytime blood pressure as described in

Table 4. When we performed the statistical analysis, we grouped into two groups (dipping pattern or non-dipping pattern), taking into account the clinical practice. This variable will be measured by ABPM, accessed before the treatment and at final of the 3 months of follow up.

Table 4 – Circadian Classification

Dip value	Classification	
$< 0\%$	Riser	$\text{Dip} = \left(1 - \frac{SBP_{\text{sleeping}}}{SBP_{\text{walking}}}\right) \times 100\%$
$\mathbf{0 - 10\%}$	Non-dipper	
$\mathbf{10 - 20\%}$	Dipper	
$\mathbf{20\%}$	Extreme dipper	

→

Dipping pattern	**Dipper pattern** **Extreme dipper**
Non dipping pattern	Riser Non-dipper

The **Nocturnal hypertension** defines a pattern of BP where BP measured during sleep is higher than that measured when the patient is awake. This is a continuous quantitative variable, but for the statistical analyses, it will be converted in a dichotomous variable: The participant will be classified as presence or absence of nocturnal hypertension. Nocturnal hypertension will be measured by ABPM, accessed before the treatment and at final of the 3 months of follow up.

The **High blood pressure or potassium safety criteria:** is defined when BP is equal or higher than 180 and/ or 110 mmHg and/ or K^+ is equal or higher than 5.5 mEq/L. This is a composite variable. BP and K^+ are continuous quantitative variables but will be converted in a dichotomous variable for the statistical analyses taking into account the safety criteria. The participant will be classified as presence or absence of these safety criteria. This variable will be accessed during the follow-up, at first and second month, using the OBPM and by analysis of a sample of blood.

Input variable: being allocated in the group of patient treated according to impedance cardiography or the group of patients treated systematically with 25 mg of spironolactone.

Baseline covariates

→ *Age* (years)

→ *Gender* (male or female)

→ *Body mass index* (measure in kilos/meter^2)

→ *Ethnicity*

- White non Hispanic; White Hispanic; Black; Asian

→ *Diabetic (yes/no):* consider diabetic when baseline glycemia is higher than 126mg/dL; HbA1c ≥6.5% in two measures or treated with antidiabetic drugs

→ *Hyperlipidemia (yes/no):* consider dyslipidemia when HDL cholesterol <40 mg/dL male or <50 mg/dL Women; LDL >130mg/dL; total cholesterol > 200 mg/dL; triglycerides > 200 mg/ dL or dyslipemia treatment

→ *Sodium in urine 24h* (normal/ abnormal): normal < 250 mEq/L / abnormal > 250mEq/L

→ *Number of antihypertensive drugs* (number)

→ *Pill count* (compliant/ non-compliant): compliant >80%-120% non-compliant <80% according to the equation explained on measurement instruments

→ *Estimate glomerular filtration rate (*eGFR.*): (*normal/ abnormal) normal >60 mL/min abnormal 30-59 mL/min

6.8 Measurement instruments

The measurement instruments required for this study are Blood and Urine analysis, OMROM M6 automatic sphygmomanometers (Omron Healthcare, The Netherlands), pre-selection form, the ABPM device (Spacelabs Redmond, USA 90207 monitor), the Impedance Cardiography device niccomo™ (Medis, Ilmenau, Germany) and pill counts.

6.8.1 Instruments to measure some covariates, study security and exclusion criteria

Blood and urine analysis

A nurse will collect blood and urine analysis at the beginning of the study. These analyses are part of usual clinical practice of a resistant hypertensive patient, that allow to quantify some covariates (diabetic condition, hyperlipidemia, estimate glomerular filtration rate and 24 hour sodium in urine) and discharge some causes of secondary RTH.

The **blood analysis** contains hemogram, plasm renin, urea/ creatinine, serum creatinine, glomerular filtration rate, ionogram (Na^+/K^+, Ca^{2+}, P) glycemia, HbA1c, uric acid, total cholesterol, HDL/LDL, TAG, total bilirubin, GOT/GPT, LDH, TSH the **urine analysis** contains urine sediment, the albumin/creatinine coefficient and 24 hour urinary (sodium, microalbumin and catecholamines).

Additional blood analysis will be performed by a nurse, at the first and second months of follow up, to evaluate the safety of the study taking into account possible side effects of the antihypertensive drugs. This blood analysis contains estimate glomerular filtration rate, ionogram (Na^+/K^+, Ca^{2+}, P).

All the analysis will be made in the Clinical Biochemical Department of the Hospital that it is duly authorized and qualified by the responsible authority.

Pill counts

Pill counts measure compliance of patient in each of the intermediate visits as well as in the final evaluation. When percentage of compliance is higher than 80–120%, the patient is considered a compliant patient.

The compliance will be calculated according to the following equation:

Equation 1 Pill counts

$$\%\, adherence = \frac{quantaty\ dispensed - quantaty\ remaining}{prescribed\ number * number\ days\ between\ dispensing\ data\ and\ the\ visit} \times 100$$

Office blood pressure measurement - OMROM M6 (HEM-7001-E)

Blood pressure was measured by the physician with OMROM M6 automatic sphygmomanometers (Omron Healthcare, The Netherlands) using appropriate cuffs according to individual-sized arms. This machine that is validated for the measurement of blood pressure (43) is used in the first and second following visits working as an evaluation of the safety of the study.

The first measure of OBPM is done simultaneously in both arms to establish the control arm (the one that presents higher levels of BP) and the following measures will be only performed in that arm.

It must be done two different measures with at least one minute of break time. If the difference between both determinations is higher than 5 mmHg, a third measurement must be made and then a final average of all results.

All measures of all blood pressures must follow recommendations of the most recent European hypertension guidelines(3).

Pre-selection form

This is a form that is completed by the GP. He is the responsible for analysing the presence of the preselection criteria for inclusion in study as well as the presence of any exclusion criteria. In this way, only plausible patients are send to participate in the sample, presented in (Annex 3).

6.8.2 Instruments to measure outcomes

ABPM (Ambulatory Blood Pressure Monitoring): Spacelab 90207 monitor

Ambulatory Blood Pressure Monitoring (ABPM) is an out-of-office BP automated measuring method that, during a 24-hour period, takes the brachial BP at fixed time intervals(11).

A non-invasive ambulatory BP will carry out with Spacelab 90207 monitor (Spacelabs Healthcare ABP system) which record BP 24hours, day and night, PP 24h, day and night, MAP 24h, day and night and circadian classification. It is usually performed on the non-dominant arm of the patient. The accuracy of this device was previously validated(44).

As it follows the patient during his daily activities and night sleep, the overall hemodynamic load and BP variability estimation is more accurate. The patient should take note of the time of medication, meals and sleep.

The ABPM registries are considered invalid if 25% of the measurements are invalid, with periods of more than an hour without any evaluation or sleep disturbances of more than an hour. The patient must keep the usual medication and the BP should be measured every 20 minutes during the day and every 30 min during nocturnal period, defined according to the routine of each individual patient.

6.8.3 Instrument to measure hemodynamic parameters to target treatment

ICG System description:Niccomo™ (Non Invasive Continuous Cardiac Output Monitor)

Niccomo™ is a non-invasive, portable device that measures hemodynamic parameters using impedance cardiography (ICG) and impedance plethysmography (IPG), with the size of a small monitor and presented in Figure 8 flexible and easy to use. This equipment conforms to the European Directives (CE norms) as verified by the declaration of conformity in (Annex 1) and is certified by the IECEE, also presented in (Annex 7), being developed and commercialized by a certified entity – Medis. This is validated for the measurement of hemodynamic variables (30).

It allows a non-invasive hemodynamic diagnostic and monitoring technology, which uses an algorithm to analyse thoracic electrical bioimpedance, providing major haemodynamic parameters in real-time (45). It uses four dual sensors, placed on the patient's neck and thorax. The most upper and lower pads apply a constant, high frequency, low intensity, and alternating current not perceived by the patients while the remaining measure the modified signal (changes in electrical impedance as a result of modification in thoracic cavity). ICG signals are detect as well for the sensors, as the voltage of the electrical current that crosses the thorax, is proportional to the thoracic impedance.

The cardiac index (CI) and SVR index (SVRI) are obtained by the cardiac output (CO) and the systemic vascular resistance (SVR) which is settle for body and size by indexing to each patient's body surface area. The inverse of baseline chest impedance is known as thoracic fluid content (TFC), and it is directly proportional to total fluid, intravascular and extravascular fluids, and any change in one of these values will produce a response in the other. The measurable valuables will also be modified with posture change from supine to standing positions, which were used as markers of cardiopulmonary volume. Using the measured impedance and the blood pressure provided by a deviated arm puff, the device interprets the several hemodynamic parameters based on the concepts described previously.

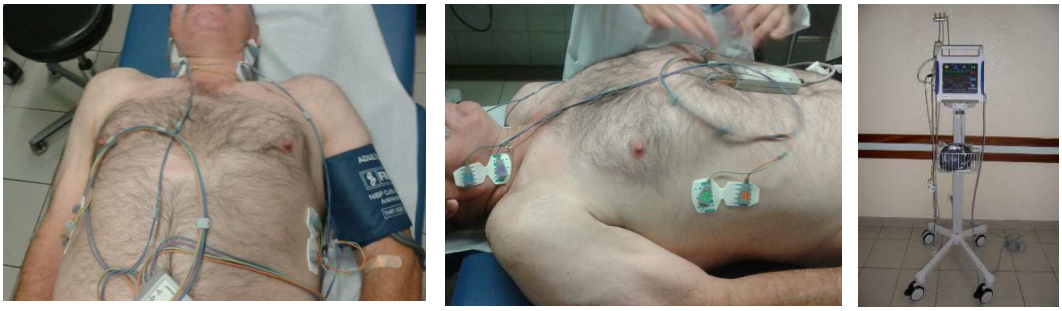


Figure 8 – Pictures of the niccomo™ at Centro Hospitalar Entre o Douro e Vouga (CHEDV)

In order to operate the device, it should be safely placed near the patient and connected with the main supply. To obtain the correct parameters and indexes, the patient data must be entered prior to the proceeding (age, height, weight, gender and identification). Afterwards, the cuff should be placed on the non-dominant arm to acquire the blood pressure. The electrodes can now be placed on the patient, two on each side of the neck and two on each side of the thorax, according to the colour coding specified on the device, as exemplified in figure 7.The application of the electrodes, entering the required patient information, and obtaining a complete hemodynamic profile in an ICG status report takes approximately ten minutes to perform.

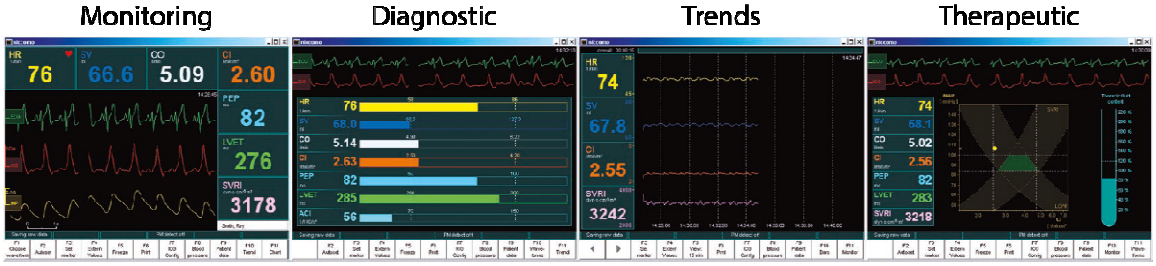


Figure 9 – Results obtained with niccomo™ (GmbH Medizinische Messtechnik , 2013)(34)

As exemplified in Figure 9, the measured data can be showed in different ways: monitoring – for time evolution of the parameters; diagnostic – showing the value for the different parameters and ideal ranges calculated based on the patient data introduced before; trends – for results obtained during large periods; therapeutic – showing a

graphic display of interaction between SI, MAP, SVRI and LSWI, the current and the ideal status of the patients. Considering the altered variables and the hemodynamic objective established by the device for the individual patient, a therapeutic re-evaluation of the patient can be made, changing the different therapeutic components.

6.9 Methods of data collection

The data will be collected from the pre-selection form and from the clinical medical records of each participating patient, being afterwards reflected on the study data base.

7. STATISTICAL ANALYSIS

Continuous outcomes will be initially described as means and standard deviation and interquartile range for each randomized group, and categorical outcomes will be reported as counts N (%) with 95% of confidence interval in each group.

All baseline covariates will be compared according to the same criteria that will be described to follow. A comparison will be made between the covariates of both groups to ensure that the randomization was verified and both groups are homogeneous.

For the base-case, unadjusted differences between randomized arms in both primary and secondary outcomes will be reported. Hypothesis tests will be conducted to detect statistically significant differences: normally-distributed outcomes will be compared using Student's t-tests, non- normal distributed outcomes will be contrasted with Mann–Whitney *U* test. For categorical nominal outcomes the Fisher test and Chi-square test will be used.

An intention to treat (ITT) analysis will be performed throughout in order to avoid misleading artefacts that can arise in intervention research such as the occurrence of noncompliance that can happen if patients end up taking other medicines than those prescribed. ITT is also performed when patients present levels of blood pressure equal or higher than 180/110 mmHg and/or potassium equal or higher than 5.5 mEq/L for safety reasons because these must be excluded from the treatment according to the protocol of the previous group.

Data will be recorded on computer database using the software Microsoft Excel. All statistical analyses will be carried out using the Statistical Package for the Social Science (SPSS), version 22.0, and all tests will be considered statistically significant at a p value ≤0.05.

8. ADVERSE EVENTS COMMUNICATION

The presence of adverse events should be reported by the investigator. An independent member of the investigation and collaborators team, will be responsible to analyse these adverse and unexpected events.

A communication circuit will be made according to the Adverse Event Severity Scale described in Table 5.

Table 5 – Adverse Event Severity grading scale

Severity	Description
Mild	Discomfort noticed, but no disruption of normal daily activity
Moderate	Discomfort sufficient to reduce or affect normal daily activity
Severe	Incapacitating with inability to work or to perform normal daily activity

a) If the adverse event is mild, the report will be made by mail.
b) If the adverse event is moderate, the report will be made by an e-mail.
c) If the adverse event is severe, the report will be made by phone or e-mail.

All this information will be recorded in the patient's medical record and will be also included in a report at the end of the clinical trial.

9. ETHICAL ASPECTS

Prior to the beginning of the investigation, the participants will be informed about the study to the fullest extent using simple and understandable language in order to allow a fully knowledgeable decision. Simultaneously, they will receive a patient information sheet, containing information on the study and sign a written informed consent (Annex 5) and (Annex 6).

In order to guarantee medical confidentiality, a secure digital database will be used and the patients' names will be replaced by a number to ensure anonymity. These measures are used to comply with the regulations established in Portuguese Law nº 67/98 from 26 of October 1998 **Law of personal data protection**. This clinical trial guarantees to take the responsibility towards its members if any adverse event is suffered because of our study/intervention.
It will be performed an insurance for the possible damages during the trial. In case of the steering committee observe any severe side effect the study must be stopped. According to the international Conference on

Harmonisation guideline for Good Clinical Practice (GCP) the criteria to consider serious adverse events can be found in (Annex 8).

The current study was already approved by **the ethical committee** of clinic research of the Centro Hospitalar entre o Douro e Vouga, where all research will be carried out. We also asked permission to the direction of our centre and the direction of each primary care that collaborates in our study.

We asked the advice and consent of the CEIC (National Ethics Committee for Clinical Research) and also asked for authorization to the **INFARMED – Autoridade Nacional do Medicamento e Produtos de Saúde, I.P.**
This study will be performed according to Portuguese laws related to clinical trial: The conducting of clinical trials on medicines for human use is governed by Law n.21/2014 of 16 April that implements Directive 2001/20/EC of the European Parliament and of the Council of 4 April in Portuguese legislation.

The study also respects the WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects of June 1964, revised on October 2013.

As it is now recommended, the trial has also been registered at a national registry of clinical studies (RNEC) and registered with an International Standard Randomized Controlled Trial Number (http://www.controlled-trials.com) and has been submitted to ClinicalTrials.gov (http://clinicaltrials.gov). The investigators have shown no conflicts of interest in any of the aspects of this study.

10. STUDY LIMITATIONS AND BIASES

Being a randomized prospective design of the trial, the risk of bias regarding background factors is lowered. However, some limitations can be priory identified, such as:

- → The need to commute to the hospital and complementary exams;
- → The possibility of losing patients due to unpredicted situations (such as death, address change)
- → Difficult to know how many patients will be lost for not complying permanence criteria in the study

11. WORK PLAN

Personnel:

- → Investigators: Joana Oliveira, Dr. Fernando Pinto and Dr. Pedro Torguet
- → Collaborators: General Practitioner from the PHCs Nursery staff and Cardio-pneumology technicians
- → Coordinator of the research group for each centre participating in the study.
- → Trial Steering Committee (TSC)
- → Data manager
- → Statistical consultant

This investigation has been designed in four stages as it is explained below:

STAGE 1 – Coordination Phase (2 months):

In this phase, the contact with Primary Health Care Centres will be done by the investigators of the research team. We aim to be able to explain the entire project and be sure that the PHCs fulfilled the requirements to be a part of the study and have the capacity to complete the sample in order to ask to collaborate on research, remitting the resistant hypertensive patients to CHEDV for 2 years.

To assure a good communication between the coordinator of the research of multiple PHCs, TSC and the investigators, once a month meetings are established gathering the main investigator and coordinators.

The Trial Steering Committee (TSC) is responsible to provide the overall supervision of the trial that is in charge of evaluating safety dates of all participants. A member in charge of patient flow analysis evaluates the recruitment time in order to prove that the rate of inclusion of patients is being fulfilled.

In this stage all the members of the research team will be together in an organizational and informative meeting. In the first meeting we will establish the objectives of the study and concrete all the procedures that must be performed during the field work of this project. The main tasks will be distributed and planned during the timeline of the study in order to be executed properly and also take place the training of cardio-pneumology technicians in order to perform the ICG exam.

In this phase we will discuss and elaborate the definitive protocol and also ask for administrative authorization and ethical approval.

In order to guarantee the quality of the members/staff, they will be chosen according to qualifications and skills related to the tasks that need to develop.

STAGE 2 – Field research (27 months):

To recruit 982 patients to be part of the study will be necessary 24 months, because the CHEDV's flow of patients related to the study is 15 a week. According to the establish timeline, the target number could be achieved in a year and a half. Given that 37.5% of the patients diagnosed by the primary care centres as resistant are not real resistant hypertensive patients and 5%-10 % are not essential resistant hypertensive patients they will be excluded. We will add another half year (making a 24months) to be able to make a 458 patients margin to cover this possible losses(8,10,46).

Once the patients are candidates:

If the patients are candidates to be part of our study sample, the form (Annex 5) will be given, and the goals of our research will be explained. After the informed consent (Annex 6) is signed, the patients will proceed in the study. These pre-selected patients will be submitted to:

I. **ABPM** to confirm that the hypertension is really resistant and others examination to exclude secondary causes
II. The nursing staff will extract a blood sample to the **blood analysis** and also will be performed a **urine analysis**
III. There will be an **impedance analysis** performed by cardio-pneumology technicians;
IV. The treatment begins given the group to which the patient belongs, if it is part of the group whose treatment meets with the results of bioimpedance or forms part of the group treated with regularly spironolactone;
V. The patient have a follow-up of 3 months where there will be 2 intermediate visits
VI. In the last visit the ABPM will be repeated

The data of each patient will be collected at the beginning and the end of the study, and will be entered in the database concurrently with the trial development by a data manager

STAGE 3 – Data analysis and interpretation of the results (2 months):

During the study, each 6 months and at the end of the study, the statistical consult analyse the results. The collected information will be analysed using the appointed statistical data analysis and will be performed an interpretation of the outcomes.

STAGE 4 – Publication and dissemination of research findings (5 months):

The corresponding article will be written and the research finding will be widely disseminated.

The timeline of the project is provided in (Annex 9)

12. DISSEMINATION PLAN

The findings of this research should be widely disseminated through training sessions, meetings, conference presentations, as the national meetings of Portuguese Hypertension Society and in Spanish Hypertension Society and also in Journals like Revista Portuguesa Hipertensão e Risco Cardiovascular, Revista Clinica Española, Circulation, Hypertension, Journal of Hypertension, New England, Lancet and BMJ. In the case of obtaining conclusive results and therefore a significant benefit of a therapeutic strategy, we would also ask for the consideration of the modification of the present guidelines.

13. STUDY REQUIREMENTS TO CARRY OUT THE PROJECT

The project will take place at CHEDV which is considered a national reference centre in the hypertension field. The unit for hypertension cardiovascular risk has all the need requirements to embrace the realization of this study.

→ **Equipment** to develop this research project such as informatics equipment suitable to process databases, a room with impedance cardiography, as well as a significant number of ABPM equipment, ECG equipment and OMROM M6 automatic sphygmomanometers are available.

→ **Healthcare professionals**:

- Physicians from the Cardiology service of CHEDV: responsible for the analysis of ICG, antihypertensive drugs prescription and follow up of these patients.
- General Practitioner from the Primary Care service: allocated to the pre-selection of resistant hypertensive patients.
- Cardio-pneumology technicians: qualified to perform bioimpedance tests, placement and removal of ABPM.
- Nursery staff: responsible for the blood and urine collection and measurement of weight and height.

→ **Building**: laboratory service: to analyse blood and urine; hospital pharmacy: offers prescription drugs, which are encoded; department of imaging (realization of kidney Doppler ultrasound).

Some of the required services for this research is already present and can be used without increasing the cost of the project. The required equipment not used in the usual clinical practice applied to a hypertensive resistant patient will be supported by this study research. Furthermore, the project will require the allocation of some research related services, such as a steering committee, statistical consultant, a data manager, physicians of CHEDV to interpret the ICG test, cardio-pneumology technicians to perform the ICG and the final ABPM tests.

14. BUDGET

	Category	Quantity	Time	Price	Cost
Personnel Costs	1) Physicians of CHEDV ICG Interpretation	1	5h/week (96 weeks)	40€/h	19.200 €
	2) Cardio-pneumology technicians	2	5h/week (96 weeks)	20€/h	19.200 €
	4) Statistical consulting	1	160h	35€/h	5.600 €
	5) Data Manager	1	100h	20€/h	2.000 €
	6) Steering committee	3	28h	50 €/h	4.200 €

	Category	Quantity	Description	Price	Cost
Services and disposable items costs	ABPM (final)	982	Batteries	1,50 €	
			Cleaning cuffs	0,50 €	
			Execution	5,20 €	
			Overall-ABPM test	7.20 €	7.070,40 €
	ICG	982	Electrodes (4)	2,50 €	
			Periodic revisions ICG	1,20 €	
			Execution	6,30 €	
			Overall-ICG test	10,00 €	9.820 €
	Print forms	982+458[2]	Pre-selection forms	0,10 €	340,4€
		982	Information sheet	0,15 €	
			Informed consent	0,05 €	
	Liability insurance				7.000€

	Activity	Price	Cost
Coordination meetings and Dissemination of the results	Coordination meetings with Primary Health Care Services		1.425 €
	Article publication (3 articles) - Translation service: 3 X 600 - Open access 1500		3.300 €
	Investigation meetings - ***Portuguese Society of Hypertension and Spanish Society of Hypertension***		1600 €
	o Inscription	500€ x 2	
	o Travel	100€ x2	
	o Accommodation	200€ x2	
Total amount of aid claimed			**80.755,8 €**

[22]Margin to cover possible losses

15. IMPACT OF THE PROJECT ON THE INTERNATIONAL HEALTH SYSTEM

Given that resistant hypertension is the largest unsolved health problem in Europe, improving the clinical practice in these patients will have a clear impact on their health care, especially in the public health system.

Thus it may be possible to specify a single therapeutic strategy in resistant hypertension which may lead to some changes in the hypertension treatment guidelines, which will allow a more unanimous action by the medical community decreasing the clinical variability on medical attention of resistant hypertension patients.

This research can lead to develop new hypothesis to future studies with the objective to determine more precisely different pathophysiology that explain the resistant hypertension.

16. BIBLIOGRAPHY

1. Stevens G. Global health risks: Mortality and burden of disease atributable to selected major risks. Bull World Health Organ [Internet]. 2009;87:646. Available from: http://www.who.int/healthinfo/global_burden_disease/GlobalHealthRisks_report_full.pdf

2. Rodgers A, Vaughan P, Thomson P, Edejer T, Evans D, Lowe J. Reducing Risk Promoting Heathy Life. The World Health Report [Internet]. Geneva: World Health Organization; 2002. Available from: http://www.who.int/whr/2002/en/whr02_en.pdf?ua=1

3. Mancia G, Fagard R, Narkiewicz K, Redon J, Zanchetti A, Böhm M, et al. 2013 ESH/ESC guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). Eur Heart J [Internet]. 2013 Jul [cited 2014 Jul 10];34(28):2159–219. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23771844

4. Sim JJ, Bhandari SK, Shi J, Liu IL, Calhoun D, McGlynn E, et al. Characteristics of resistant hypertension in a large, ethnically diverse hypertension population of an integrated health system. Mayo Clin Proc [Internet]. 2013 Oct [cited 2014 Dec 16];88(10):1099–107. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3909733/?tool=pmcentrez

5. Armario P, Oliveras A, Hernández Del Rey R, Ruilope LM, De La Sierra A. Prevalence of target organ damage and metabolic abnormalities in resistant hypertension. Med Clin (Barc) [Internet]. 2011 Oct 15 [cited 2014 Dec 16];137(10):435–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21719041

6. Armario P, Oliveras A, de la Sierra A. Hipertensión arterial resistente. Hipertens y Riesgo Vasc [Internet]. 2014 Apr [cited 2014 Dec 16];31(2):58–65. Available from: http://linkinghub.elsevier.com/retrieve/pii/S1889183713001128

7. Brambilla G, Bombelli M, Seravalle G, Cifkova R, Laurent S, Narkiewicz K, et al. Prevalence and clinical characteristics of patients with true resistant hypertension in central and Eastern Europe: data from the BP-CARE study. J Hypertens [Internet]. 2013 Oct [cited 2014 Dec 16];31(10):2018–24. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23838657

8. De la Sierra A, Segura J, Banegas JR, Gorostidi M, de la Cruz JJ, Armario P, et al. Clinical features of 8295 patients with resistant hypertension classified on the basis of ambulatory blood pressure monitoring. Hypertension [Internet]. 2011 May [cited 2015 Jan 16];57(5):898–902. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21444835

9. Polonia J, Martins L, Pinto F, Nazare J. Prevalence, awareness, treatment and control of hypertension and salt intake in Portugal: changes over a decade. The PHYSA study. J Hypertens [Internet]. 2014 Jun [cited 2014 Dec 22];32(6):1211–21. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24675681

10. Persu A, O'Brien E, Verdecchia P. Use of ambulatory blood pressure measurement in the definition of resistant hypertension: a review of the evidence. Hypertens Res. 2014;37:967–72.

11. Syrseloudis D, Andrikou I, Andrikou E, Dimitriadis K, Stefanadis C. Ambulatory blood pressure monitoring in resistant hypertension. Int J Hypertens [Internet]. 2011 Jan [cited 2014 Dec 16];2011:285612. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3095903/?tool=pmcentrez

12. Marko Yakovlevitch M, Henry R. Black M. Resistant Hypertension in a Tertiary Care Clinic. Arch Intern Med. 1991;151:1786–92.

13. Myat A, Redwood SR, Qureshi AC, Spertus J a, Williams B. Resistant hypertension. BMJ [Internet]. 2012 Jan [cited 2014 Dec 16];345(November):e7473. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23169802

14. He FJ, MacGregor G a. Effect of modest salt reduction on blood pressure: a meta-analysis of randomized trials. Implications for public health. J Hum Hypertens [Internet]. 2002 Nov [cited 2014 Dec 16];16(11):761–70. Available from: http://www.ncbi.nlm.nih.gov/pubmed/12444537

15. Calhoun D, Jones D, Textor S, Goff DC, Murphy TP, Toto RD, et al. Resistant hypertension: diagnosis, evaluation, and treatment: a scientific statement from the American Heart Association Professional Education Committee of the Council for High Blood Pressure Research. Circulation [Internet]. 2008 Jun 24 [cited 2014 Nov 20];117(25):e510–26. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18574054

16. Václavík J, Sedlák R, Plachy M, Navrátil K, Plásek J, Jarkovsky J, et al. Addition of spironolactone in patients with resistant arterial hypertension (ASPIRANT): a randomized, double-blind, placebo-controlled trial. Hypertension [Internet]. 2011 Jun [cited 2014 Dec 12];57(6):1069–75. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21536989

17. Engbaek M, Hjerrild M, Hallas J, Jacobsen I. The effect of low-dose spironolactone on resistant hypertension. J Am Soc Hypertens [Internet]. 2010 [cited 2014 Dec 16];4(6):290–4. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21130975

18. Nishizaka M, Zaman M, Calhoun D. Efficacy of low-dose spironolactone in subjects with resistant hypertension. Am J Hypertens [Internet]. 2003 Nov [cited 2014 Dec 16];16(11):925–30. Available from: http://ajh.oxfordjournals.org/cgi/doi/10.1016/S0895-7061(03)01032-X

19. Egan BM, Li J. Role of aldosterone blockade in resistant hypertension. Semin Nephrol [Internet]. 2014 May [cited 2014 Dec 17];34(3):273–84. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25016399

20. Rodilla E, Costa J, Pérez-Lahiguera F, Baldó E, González C, Pascual JM. Spironolactone and Doxazosin Treatment in Patients With Resistant Hypertension. Rev Española Cardiol (English Ed [Internet]. 2009 Feb [cited 2014 Dec 17];62(2):158–66. Available from: http://linkinghub.elsevier.com/retrieve/pii/S1885585709715348

21. Lane D, Beevers D. Amiloride 10 mg is less effective than spironolactone 25 mg in patients with hypertension resistant to a multidrug regime including an angiotensin-blocking agent. J Hypertens. 2007;25(12):2515–6.

22. Vavricka S, Himmelmann A, Schaffner A. Age-specific relevance of usual blood pressure to vascular mortality : a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet. 2002;360:1903–13.

23. Ventura HO, Taler SJ, Strobeck JE. Hypertension as a hemodynamic disease: the role of impedance cardiography in diagnostic, prognostic, and therapeutic decision making. Am J Hypertens [Internet]. 2005 Feb [cited 2014 Nov 22];18(2 Pt 2):26S–43S. Available from: http://www.ncbi.nlm.nih.gov/pubmed/15752931

24. Viigimaa M, Talvik A, Wojciechowska W, Kawecka-Jaszcz K, Toft I, Stergiou GS, et al. Identification of the hemodynamic modulators and hemodynamic status in uncontrolled hypertensive patients. Blood Press [Internet]. 2013 Dec [cited 2014 Nov 8];22(6):362–70. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23607284

25. Ferrario CM. New approaches to hypertension management: Always reasonable but now necessary. Am J Hypertens. 2005;18:23–91.

26. Hornby AS, Turnnbull J, Lea D, Parkinson D, Philips P, Francis B, Webb S et al. Oxford Advanced Learner´s Dictionary. 8th ed. Oxford: Oxford University Press; 2010.

27. Mosby´s Medical Dictionary. 8th ed. London: Elsevier; 2009.

28. Sageman WS, Riffenburgh RH, Spiess BD. Equivalence of bioimpedance and thermodilution in measuring cardiac index after cardiac surgery. J Cardiothorac Vasc Anesth [Internet]. 2002 Feb [cited 2014 Dec 17];16(1):8–14. Available from: http://linkinghub.elsevier.com/retrieve/pii/S1053077002166390

29. Dvanced A, Hronic DEC, Ailure HEF, Albert BNM, Hail MD, Li J, et al. Equivalence of the bioimpedance and thermodilution methods in measuring cardiac output in hospitalized patients with advanced, decompensated chronic heart failure. Am J Crit care. 2004;13(6):469–80.

30. Lorne E, Mahjoub Y, Diouf M, Sleghem J, Buchalet C, Guinot P-G, et al. Accuracy of impedance cardiography for evaluating trends in cardiac output: a comparison with oesophageal Doppler. Br J Anaesth [Internet]. 2014 Oct [cited 2014 Dec 12];113(4):596–602. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24871872

31. Faini A, Omboni S, Tifrea M, Bubenek S, Lazar O, Parati G. Cardiac index assessment: validation of a new non-invasive very low current thoracic bioimpedance device by thermodilution. Blood Press [Internet]. 2014 Apr [cited 2014 Dec 16];23(2):102–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23926884

32. Raaijmakers E, Faes J, Scholten R, Goovaerts H, Heethaar R. A Meta-analysis of published studies concerning the validity of Thoracic impedance Cardiography. Ann New York Acad Sci. 1999;873:121–7.

33. Cybulski G. Ambulatory Impedance Cardiography. Heidelberg: Springer; 2011.

34. Niccomo Impedance cardiography. Ilmenau: medis;

35. Mehra M, Ventura H. Improvement in Blood Pressure Control With Impedance Cardiography-Guided Pharmaologic Decision Making. lejacq. 2004;54–8.

36. Taler SJ, Textor SC, Augustine JE. Resistant Hypertension: Comparing Hemodynamic Management to Specialist Care. Hypertension [Internet]. 2002 May 1 [cited 2014 Dec 6];39(5):982–8. Available from: http://hyper.ahajournals.org/cgi/doi/10.1161/01.HYP.0000016176.16042.2F

37. Smith RD, Levy P, Ferrario CM. Value of noninvasive hemodynamics to achieve blood pressure control in hypertensive subjects. Hypertension [Internet]. 2006 Apr [cited 2014 Nov 16];47(4):771–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16520405

38. Flack JM. Noninvasive hemodynamic measurements: an important advance in individualizing drug therapies for hypertensive patients. Hypertension [Internet]. 2006 Apr [cited 2014 Nov 22];47(4):646–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16520406

39. Ferrario CM, Flack JM, Strobeck JE, Smits G, Peters C. Individualizing hypertension treatment with impedance cardiography: a meta-analysis of published trials. Ther Adv Cardiovasc Dis [Internet]. 2010 Feb [cited 2014 Nov 16];4(1):5–16. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20042450

40. Brown DW, Giles WH, Greenlund KJ. Blood pressure parameters and risk of fatal stroke, NHANES II mortality study. Am J Hypertens [Internet]. 2007 Mar [cited 2015 Jan 4];20(3):338–41. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17324749

41. Benetos A, Rudnichi A, Safar M, Guize L. Pulse Pressure and Cardiovascular Mortality in Normotensive and Hypertensive Subjects. Hypertension. 1998;32(3):560–5.

42. Glasser SP, Halberg DL, Sands C, Gamboa CM, Muntner P, Safford M. Is pulse pressure an independent risk factor for incident acute coronary heart disease events? The REGARDS study. Am J Hypertens. 2014 Apr;27(4):555–63.

43. Altunkan E, Kayatu N. Validation of the Omron M6 (HEM-7001-E) upper-arm blood pressure measuring device according to the International Protocol in adults and obese adults. Blood Press Monit. 2007;4:219–25.

44. Brien EO, Mee F, Atkins N, Malley KO. Accuracy of the SpaceLabs 90207 determined by the British Hypertension Society Protocol. J Hypertens. 1991;9(6):573–4.

45. Davey C, Wilsonh S. Market Review: Haemodynamic monitoring systems. London: Centre for Evidence-based Purchasing; 2010.

46. Viera AJ, Neutze DM. Diagnosis of Secondary Hypertension: An Age-Based Approach. Fam Physician. 2010;82(12):1471–8.

47. Bakris GL, Townsend RR, Liu M, Cohen S a, D'Agostino R, Flack JM, et al. Impact of Renal Denervation on 24-hour Ambulatory Blood Pressure: Results from SYMPLICITY HTN-3. J Am Coll Cardiol [Internet]. Elsevier Ltd; 2014; Available from: http://www.ncbi.nlm.nih.gov/pubmed/24858423

17. ANNEXES

Annex 1. Declaration of conformity CE niccomo™

MEDIZINISCHE MESSTECHNIK GmbH

KONFORMITÄTSERKLÄRUNG / DECLARATION DE CONFORMITE
DECLARATION OF CONFORMITY / DICHIARAZIONE DI CONFORMITA /
DECLARATION DE COFORMIDAD

CE 0197

Name und Adresse der Firma Nom et adresse de l´entreprise Nome e indirizzo della ditta Name and address of the firm Nombre y dirección de la empresa	medis. Medizinische Messtechnik GmbH Werner-von-Siemens-Str. 8 D - 98693 Ilmenau Germany
Wir erklären in alleiniger Verantwortung, dass das Medizinprodukt Nous déclarons sous notre propre responsabilité que le dispositif médical Dichiariamo sotto nostra responsabilità che il dispositivo medico We declare under our sole responsibility that the medical device Declaramos bajo nuestra propia responsabilidad que el producto médico	**Niccomo** – Cardiac Output Monitor
der Klasse de la classe / della classe / of class / de la classe	II a
allen Anforderungen der Medizinprodukte-Richtline 93/42/EWG entspricht, die anwendbar sind remplit toutes les exigences de la directive sur les dispositifs médicaux 93/42/EWG qui le concernent soddisfa tutte le disposizioni della direttiva 93/42/EWG che lo riguardano meets all the provisions of the EC directive 93/42/EEC which apply to it reune todas las exigencias según la directiva 93/42 CEE relativa a los productos médicos que le son aplicables	
Angewandte Richtlinie / Applied directive Zertifikatsnummer / Certificate Nummer Erstellt durch / Issued by	93 / 42 / EEC, Annex V DD 60040098 0001 TÜV Rheinland LGA Products GmbH
Datum der Anbringung des CE-Zeichens Date de la fixation du CE - signe Date of the mounting of the CE indication Data del montaggio del CE - indicazione Fecha del montaje del CE - indicación	10.10.2006
Ort, Datum Lieu, date / Luogo, data / Place, date / Lugar, fecha	Ilmenau, den 20.11.2014
Name und Funktion Nom et fonction /Nome e funzione / Name and function / Nombre y cargo	Dr. Olaf Solbrig / Geschäftsführer medis. Medizinische Meßtechnik GmbH Werner-von-Siemens-Str. 8 D-98693 Ilmenau ☎ 0 36 77 / 46 29 - 0

medis.
Medizinische Messtechnik GmbH
Werner-von-Siemens-Str. 8
D - 98693 Ilmenau
Germany

Meiningen HRB 1139
USt.-Id.-Nr. DE 150 933 290
Steuer-Nr. 156 / 114 / 00557
Geschäftsführer / Director:
Dr. Olaf Solbrig

Fon + 49-(0)3677-46 29-0
Fax + 49-(0)3677-46 29-29
email info@medis-de.com
http://www.medis-de.com

HypoVereinsbank Coburg
Konto-Nr. 46 20 223
BLZ 783 200 76
IBAN DE05 7832 0076 0004 8202 23
S.W.I.F.T. HYVEDEMM480

Annex 2. Impedance Cardiography status report

Impedância cardiográfica

nome: DESPACHO

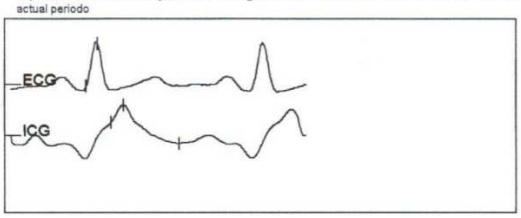
Último Nome, Primeiro Nome:

Identif do doente: 97836

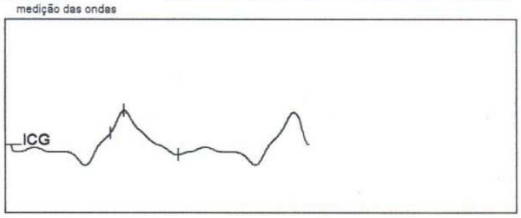
Data de nascimento	Altura	Peso	Género
16.11.1947	160 cm	63 kg	Homem

FC	Frequência cardíacaca	88	1/min	58 – 86
HPD	Ciclo cardíaco	679	ms	698 – 1034
SBP	Pressão Arterial Sistémica	139	mmHg	100 – 140
DBP	Pressão Arterial Diatólica	88	mmHg	60 – 90
PAM	Pressão arterial média	104 (139/88)	mmHg	70 – 105
VE	Volume de ejecção	52	ml	58 – 108
IEjecI	Índice de ejecção	31	ml/m²	35 – 65
DC	Débito cardíaco	4.6	l/min	4.1 – 7.8
IC	Índice Cardíaco	2.8	l/min/m²	2.5 – 4.7
DO_2I	Índice de distribuição de oxigénio	523	ml/min/m²	520 – 985
SVR	Resistência ventricular esquerda	1718	dyn·s·cm^{-5}	1014 – 1558
SVRI	Íncice da resistência vascular sistémica	2845	dyn·s·cm^{-5} m²	1680 – 2580
LCW	Trabalho ventricular esquerdo	6.2	kg*m	5.0 – 9.1
LCWI	Índice do trabalho do ventrículo esquerdo	3.8	kg*m/m²	3.0 – 5.5
IV	Índice de velocidade	52	1/1000/s	33 – 65
ACI	Índice de aceleração	80	1/100/s²	70 – 150
Heather	Heather index	14.1	Ohm/s²	7.0 – 20.0
PPEjec	Período de pré-ejecção	101	ms	50 – 100
LVET	Tempo de ejecção ventricular esquerda	261	ms	200 – 300
STR	Razão tempo sístole	0.39 (101/261)		0.30 – 0.50
ETR	Razão tempo ejecção	38	%	20 – 40
Z_0	Impedância base	28.3	Ohm	20.0 – 33.3
TFC	Fluidos torácicos acumulados	35.3	1/kOhm	30.0 – 50.0
SpO_2	Saturação de Oxigénio	98	%	90 – 95

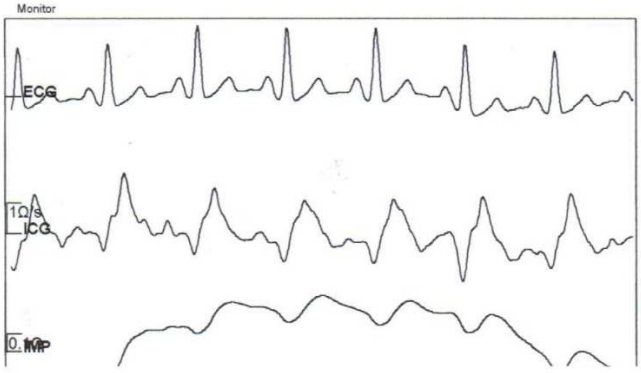
actual periodo



medição das ondas



Monitor



Notas:

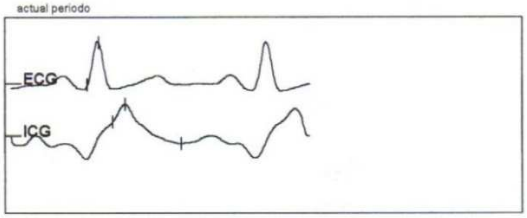
Impedância cardiográfica

Último Nome, Primeiro Nome			Identif do doente
			97836
Data de nascimento	**Altura**	**Peso**	**Género**
16.11.1947	160 cm	63 kg	Homem

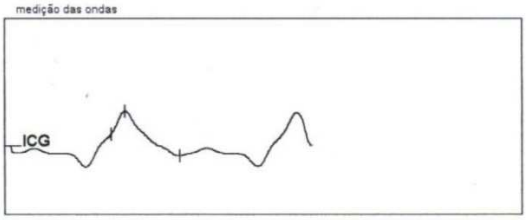
nome

FC.....88 1/min	IC.....2.8 l/min/m²	Heather.....14.1 Ohm/s²
HPD.....679 ms	DO_2I.....523 ml/min/m²	PPEjec.....101 ms
SBP.....139 mmHg	SVR.....1718 dyn·s·cm^{-5}	LVET.....261 ms
DBP.....88 mmHg	SVRI.....2845 dyn·s·cm^{-5} m²	STR.....0.39
PAM.....104 mmHg	LCW.....6.2 kg*m	ETR.....38 %
VE.....52 ml	LCWI.....3.8 kg*m/m²	Z_0.....28.3 Ohm
IEjecI.....31 ml/m²	IV.....52 1/1000/s	TFC.....35.3 1/kOhm
DC.....4.6 l/min	ACI.....80 1/100/s²	SpO_2.....98 %

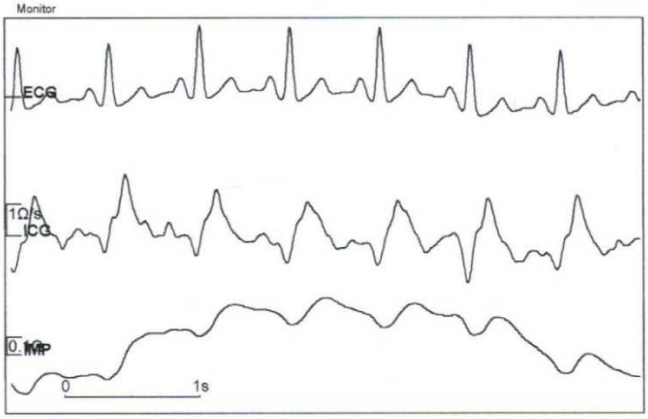
actual periodo



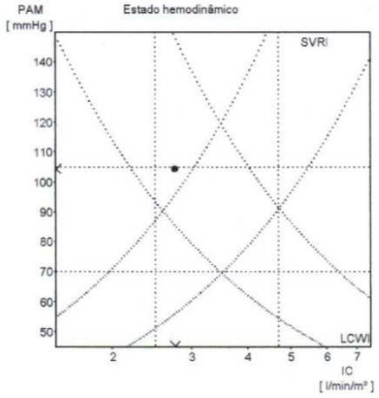
medição das ondas



Monitor

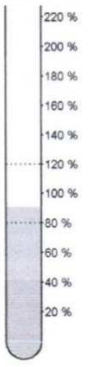


Estado hemodinâmico



FC.....88 1/min	58	86
PAM....104 (139/88) mmHg	70	105
VE.....52 ml	58	108
IC.....2.8 l/min/m²	2.5	4.7
SVR.....1718 dyn·s·cm^{-5}	1014	1558
TFC.....35.3 1/kOhm	30.0	50.0
ACI.....80 1/100/s²	70	150

Fluidos torácicos acumulados



Notas:

Impedância cardiográfica

nome: DE PÉ

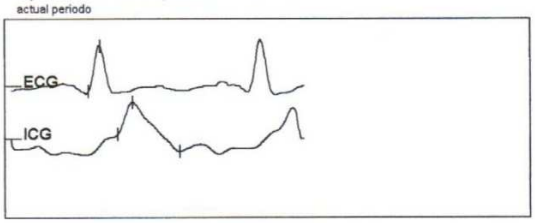
Último Nome, Primeiro Nome

Identif do doente: 97836

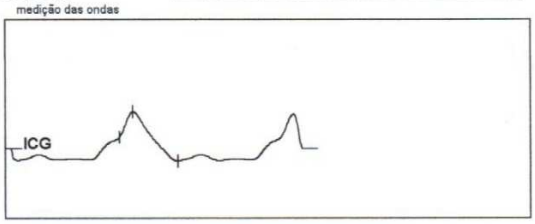
Data de nascimento	Altura	Peso	Género
16.11.1947	160 cm	63 kg	Homem

FC	Frequência cardíacaca	96	1/min	58 – 86
HPD	Ciclo cardíaco	626	ms	698 – 1034
SBP	Pressão Arterial Sistémica	114	mmHg	100 – 140
DBP	Pressão Arterial Diatólica	77	mmHg	60 – 90
PAM	Pressão arterial média	89 (114/77)	mmHg	70 – 105
VE	Volume de ejecção	44	ml	58 – 108
IEjecI	Índice de ejecção	27	ml/m²	35 – 65
DC	Débito cardíaco	4.2	l/min	4.1 – 7.8
IC	Índice Cardíaco	2.6	l/min/m²	2.5 – 4.7
DO_2I	Índice de distribuição de oxigénio	485	ml/min/m²	520 – 985
SVR	Resistência ventricular esquerda	1573	dyn·s·cm^{-5}	1014 – 1558
SVRI	Índice da resistência vascular sistémica	2605	dyn·s·cm^{-5} m²	1680 – 2580
LCW	Trabalho ventricular esquerdo	4.8	kg*m	5.0 – 9.1
LCWI	Índice do trabalho do ventrículo esquerdo	2.9	kg*m/m²	3.0 – 5.5
IV	Índice de velocidade	52	1/1000/s	33 – 65
ACI	Índice de aceleração	87	1/100/s²	70 – 150
Heather	Heather index	12.2	Ohm/s²	7.0 – 20.0
PPEjec	Período de pré-ejecção	119	ms	50 – 100
LVET	Tempo de ejecção ventricular esquerda	222	ms	200 – 300
STR	Razão tempo sístole	0.54 (119/222)		0.30 – 0.50
ETR	Razão tempo ejecção	35	%	20 – 40
Z_0	Impedância base	29.7	Ohm	20.0 – 33.3
TFC	Fluidos torácicos acumulados	33.6	1/kOhm	30.0 – 50.0
SpO_2	Saturação de Oxigénio	98	%	90 – 95

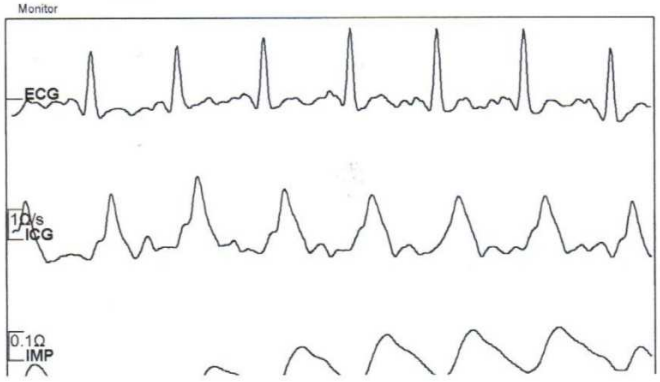
actual periodo



medição das ondas



Monitor



Notas:

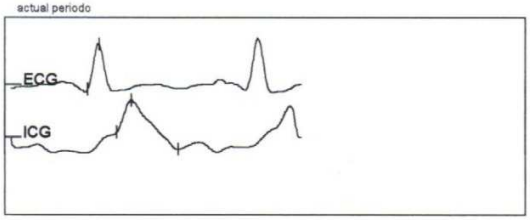
Impedância cardiográfica

Último Nome, Primeiro Nome	Identif do doente	nome
	97836	DE PÉ

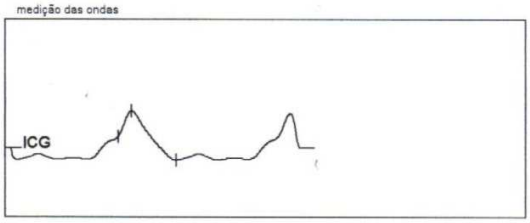
Data de nascimento	Altura	Peso	Género
16.11.1947	160 cm	63 kg	Homem

FC.....96 1/min	IC.....2.6 l/min/m²	Heather.....12.2 Ohm/s²
HPD.....626 ms	DO_2I.....485 ml/min/m²	PPEjec.....119 ms
SBP.....114 mmHg	SVR.....1573 dyn·s·cm^{-5}	LVET.....222 ms
DBP.....77 mmHg	SVRI.....2605 dyn·s·cm^{-5} m²	STR.....0.54
PAM.....89 mmHg	LCW.....4.8 kg*m	ETR.....35 %
VE.....44 ml	LCWI.....2.9 kg*m/m²	Z_0.....29.7 Ohm
IEjecI.....27 ml/m²	IV.....52 1/1000/s	TFC.....33.6 1/kOhm
DC.....4.2 l/min	ACI.....87 1/100/s²	SpO_2.....98 %

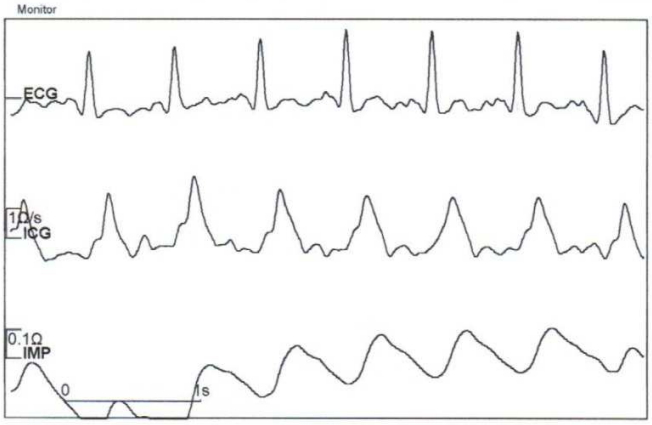
actual periodo

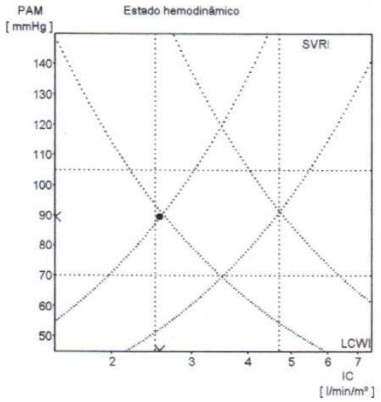


medição das ondas



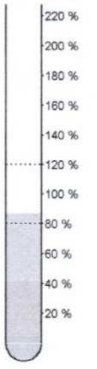
Monitor





FC.....96 1/min	58	86
PAM....89 (114/77) mmHg	70	105
VE.....44 ml	58	108
IC.....2.6 l/min/m²	2.5	4.7
SVR.....1573 dyn·s·cm^{-5}	1014	1558
TFC.....33.6 1/kOhm	30.0	50.0
ACI.....87 1/100/s²	70	150

Fluidos torácicos acumulados



Notas:

Annex 3. Annex Pre-selection form

Centro Hospitalar de Entre o Douro e Vouga, E.P.E.

SOCIEDADE PORTUGUESA DE HIPERTENSÃO
Portuguese Society of Hypertension

"The use of bioimpedance to better characterize resistant hypertensive patients and therapeutic optimization versus 25 mg spironolactone- A randomized trial"

Main Investigators: Joana Oliveira, Dr. Fernando Pinto and Dr. Pedro Torguet

Identification of Primary Health Care service:_____

Responsible General practitioner:_____

Identification number of the patient:_____

For this patient to participate as a study element in this research, it was necessary to establish a close communication with the patient and to have an access to his clinical history as well as measuring his blood Pressure.

Patient meets all preset inclusion criteria:

- More than 18 years ☐Yes ☐No
- Office Blood pressure higher than 140/90 mmHg after the administration of 3 or more antihypertensive agents of different classes including one diuretic in optimal dosage ☐Yes ☐No

These inclusion criteria plus the absence of any of the exclusion criteria makes this patient a candidate to be part of this study.

Exclusion criterias are the following:

- Not available for 3 months follow-up; ☐Yes ☐No
- Non the compliance with medication as the cause of treatment resistance ☐Yes ☐No
- History of intolerance / allergy to any of antihypertensive possible ☐Yes ☐No
- Already treated with spironolactone ☐Yes ☐No
- Drug interferences ☐Yes ☐No
    - (Nonsteroidal anti-inflammatory drugs, Sympathomimetics, Cocaine, amphetamines, other illicit drugs Oral contraceptive hormones Adrenal steroid hormones Erythropoietin Cyclosporine and tacrolimus, Licorice, Over-the-counter dietary and herbal supplements)

- Secondary causes of hypertension ☐Yes ☐No
  - Renal parenchymal disease, Renovascular disease, Primary aldosteronism, Obstructive sleep apnoea (OSA), Pheochromocytoma, Cushing's syndrome, Thyroid diseases, Aortic coarctation, Intracranial tumours
- Hiperkaliemia (>5.5) ☐Yes ☐No
- Severe cardiovascular disease or cardiovascular event in the last 6 months ☐Yes ☐No
  - Severe cardiovascular disease (Congestive Heart Failure (CHF), Uncontrolled ischemic cardiopathy, Chronic Kidney Insufficiency (CKI)(Fg<60 ALB/CREAT >30
  - Cardiovascular events (Acute myocardial infarction or anginal episode Road stroke / transient ischemic attack Amputations by vascular problems)
- Hepatopathy; ☐Yes ☐No
- Neoplasms; ☐Yes ☐No
- Pregnant women ☐Yes ☐No
- Possibility of **biased hemodynamic studies** ☐Yes ☐No

  (Septic shock, Pleural effusion, Significant pulmonary oedema, Hemothorax, acute lung injury, Severe mitral or aortic regurgitation dilatation of aorta, Pacemakers with minute ventilator sensors, Patient less than 30 kg or greater than 155 kg, Below 120 cm or above 230 cm, chronic anaemic patients
- hypersensitivity to sensor gel or adhesive skin lesion interfering with sensor placement ☐Yes ☐No

For respecting all criterias of inclusion and exclusion this patient is a candidate for being part of the study, so he is referred to Hypertension and Cardiovascular Risk Unit in the Cardiology service of Centro Hospitalar entre Douro e Vouga, E.P.E. (CHEDV) in Santa Maria da Feira

DOCTOR'S NAME DATE SIGNATURE

_____ ___ / ___ / 20__ _____

Annex 4. Description of some exclusion criteria

Secondary causes of hypertension and drug interference

Drug Induced	
→ Nonsteroidal anti-inflammatory drugs (including cyclo-oxigenase-2 inhibitors) → Sympathomimetics (decongestants, anorectics) → Cocaine, amphetamines, other illicit drugs → Oral contraceptive hormones → Adrenal steroid hormones → Erythropoietin → Cyclosporine and tacrolimus → Licorice (included in some chewing tobacco) → Over-the-counter dietary and herbal supplements (e.g. ginseng, yohimbine, ma huang, bitter orange)	
Identifiable causes of hypertension (secondary hypertension):	
→ Renal parenchymal disease → Renovascular disease – the most common reason → Primary aldosteronism → Obstructive sleep apnoea (OSA)	→ Pheochromocytoma → Cushing's syndrome → Thyroid diseases → Aortic coarctation → Intracranial tumours

Biased hemodynamic studies

Biased Hemodynamic Studies
→ Septic shock → Pleural effusion → Significant pulmonary oedema → Hemothorax, acute lung injury → Severe mitral or aortic regurgitation dilatation of aorta → Pacemakers with minute ventilator sensors → Patient less than 30 kg or greater than 155 kg → Below 120 cm or above 230 cm, chronic anaemic patients

Annex 5. Patient information sheet

Centro Hospitalar de Entre o Douro e Vouga, E.P.E.

SOCIEDADE PORTUGUESA DE HIPERTENSÃO
Portuguese Society of Hypertension

Participant Information Sheet

"The use of bioimpedance to better characterize resistant hypertensive patients and therapeutic optimization"

Dear Patient,

You are being requested to participate in a research study. Participation in this study is voluntary. Before you decide if you wish to participate in this study, it is important that you read this information sheet and ask the study responsible doctor to explain you any question you may have, as well as why the research is being done and what it will involve. Please take your time to read the following information attentively. This study has been reviewed and approved by an ethics committee - the Hospital's Clinical Research Ethics Committee and by National Ethics Committee for Clinical Research (CEIC). This project has been authorized by INFARMED - Autoridade Nacional do Medicamento e Produtos de Saúde, I.P.

Please do not hesitate in contact us if there is anything that is not clear or if you want to know more information.

Investigators: Joana Oliveira, Dr. Fernando Pinto and Dr. Pedro Torguet

Collaborators: Physicians from the Cardiology of CHEDV; General Practitioner from the Primary Care service; Nursery staff, Cardiopneumology technicians, Data manager and a Statistical consultant

Location: in the Hypertension and Cardiovascular Risk Unit of Cardiology service in Centro Hospital Entre o Douro e Vouga, E.P.E..

PURPOSE

Hypertension has been considered one of the most frequent diseases. Our study aims are to compare the efficacy of two different approaches in the treatment of resistant hypertension, in the decrease of blood pressure values. Despite of the clear benefits of numerous classes of antihypertensive therapies, many times control rates are suboptimal and do not reach national goals, remaining a major unsolved problem in Europe. This lack of control in resistant hypertensive patients has a significant cost in public health, producing clinical, and economic consequences for the health care system and consequently to our society.

Additionally, it has been proven that resistant hypertensive patients experiment an immensely high cardiovascular event rates, chronic kidney disease and coronary heart disease.

Improvements in the treatment way for these patients may contribute to a decrease in the risk of ischemic heart disease and fatal stroke. This being said, improving the rate of blood pressure reduces the mortality and long term adverse cardiovascular events as well as short and long term cost both clinically and economically.

TREATMENT GROUPS

This is a randomized controlled research project in which there will be two groups in the study receiving different treatments. The aim is to compare the results of each treatment group in order to find which treatment may be more useful in patient care. To ensure that the treatment groups will be similar, at baseline it will assign a random group, which means that neither you nor the study doctor can choose their treatment group. You will have the same probability of being in each of two treatment groups. The results will be compared to see if one of the treatments is better than the other.

CONFIDENTIALITY

Your medical information and any other information collected for this research project will be kept confidential in conformity with Portuguese Law nº 67/98 from 26 of October 1998 (Law of personal data protection). The data will also be used solely for the purposes of this project. Any information collected will be replaced by a number, which will identify the patient in all the stages of this project.

DISSEMINATION PLAN

The results of this study will be presented at the national meetings of the Spanish and Portuguese Hypertension Society, apart from that we would like to publish this study in Journals like Revista Portuguesa Hipertensão e Risco Cardiovascular, Revista clinica Española, Circulation, Hypertension, Journal of Hypertension, New England, Lancet and BMJ. In the case of obtaining conclusive results and therefore a significant benefit of a therapeutic strategy, we would also ask for the consideration of the modification of the present guidelines.

IF I DECID TO BE A PART OF THIS STUDY

1. **What do I have to do?**

Before the beginning of the treatment you will be submitted a blood and urine analysis an Ambulatory Blood Pressure Measurement (ABPM- for assessment of blood pressure, during 24 hours) and others explorations (electrocardiogram (ECG) and doppler ultrasound of renal arteries). You will return to the hospital in the following day, and if the obtained values obtained meet the criteria for permanence of our study, it will be performed a bioimpedance analysis (ICG) and start an antihypertensive treatment. A three months follow up will be held, and during this period it will be taken place two intermediate visit, being requested a blood analysis. At the end of the study the ABPM will be repeated.

Annex 6. Consent form

Centro Hospitalar de Entre o Douro e Vouga, E.P.E.

SOCIEDADE PORTUGUESA DE HIPERTENSÃO
Portuguese Society of Hypertension

Consent Form

"The use of bioimpedance to better characterize resistant hypertensive patients and therapeutic optimization"

Main Investigators: Joana Oliveira, Dr. Fernando Pinto, Dr. Luís Martins and Dr. Pedro Torguet
Collaborators: Physicians from the Cardiology of CHEDV; General Practitioner from the Primary Care service; Nursery staff, Cardiopneumology technicians and Statistical consultant
Location: in the Hypertension and Cardiovascular Risk Unit of Cardiology service in Centro Hospital Entre o Douro e Vouga, E.P.E..

Patient Identification Number for this trial:

Please initial all boxes

- ☐ I have had the opportunity to consider the information
- ☐ I have received enough and clear information about the study and I understand
- ☐ I have been informed about the purpose and implications of this study
- ☐ Ask questions and have had these answered satisfactorily
- ☐ I understand that my participation is voluntary
- ☐ I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected.
- ☐ I give permission for the doctors and the colaborators access to my records
- ☐ I understand that my data this data will be used exclusively for the purposes of this project.

I agree to take part in the above study. ☐

PATIENT'S NAME	DATE	SIGNATURE
_____	___ / ___ / 20__	_____
DOCTOR'S NAME	DATE	SIGNATURE
_____	___ / ___ / 20__	_____

Annex 7. ICEE

IEC IECEE CB SCHEME

Ref. Certif. No.

DE 2-014571

IEC SYSTEM FOR MUTUAL RECOGNITION OF TEST CERTIFICATES FOR ELECTRICAL EQUIPMENT (IECEE) CB SCHEME

SYSTEME CEI D'ACCEPTATION MUTUELLE DE CERTIFICATS D'ESSAIS DES EQUIPEMENTS ELECTRIQUES (IECEE) METHODE OC

CB TEST CERTIFICATE
CERTIFICAT D'ESSAI OC

Product Produit	Non-ivasive haemodynamic monitor
Name and address of the applicant Nom et adresse du demandeur	medis. Medizinische Messtechnik GmbH Werner-von-Siemens-Str. 8 98693 Ilmenau, Deutschland
Name and address of the manufacturer Nom et adresse du fabricant	medis. Medizinische Messtechnik GmbH Werner-von-Siemens-Str. 8 98693 Ilmenau, Deutschland
Name and address of the factory Nom et adresse de l'usine Note: When more than one factory, please report on page 2 Note: Lorsque il y plus d'une usine, veuillez utiliser la 2ème page	medis. Medizinische Messtechnik GmbH Werner-von-Siemens-Str. 8 98693 Ilmenau, Deutschland
Ratings and principal characteristics Valeurs nominales et caractéristiques principales	AC 100-240V; 0.5-0.2A; 50/60Hz
Trade mark (if any) Marque de fabrique (si elle existe)	none
Model/type Ref. Ref. de type	niccomo
Additional information (if necessary may also be reported on page 2) Les Information complémentaire (si nécessaire, peuvent être indiqués sur la 2ème page)	
A sample of the product was tested and found to be in conformity with Un échantillon de ce produit a été essayé et a été considéré conforme à la	**PUBLICATION** **EDITION** IEC 60601-1:1988+A1+A2 IEC 60601-2-30:1999 IEC 60601-2-49:2001
As shown in the Test Report Ref. No. which forms part of this Certificate Comme indiqué dans le Rapport d'essais numéro de référence qui constitue une partie de ce Certificat	21151233 001

This CB Test Certificate is issued by the National Certification Body
Ce Certificat d'essai OC est établi par l'Organisme National de Certification

TÜVRheinland®

TÜV Rheinland LGA Products GmbH
Tillystraße 2 · 90431 Nürnberg, Germany
Phone + 49 221 806-1371
Fax + 49 221 806-3935
Mail: cert-validity@de.tuv.com
Web: www.tuv.com

TÜV Rheinland LGA Products GmbH TÜVRheinland Zertifizierungsstelle

Date: 27.09.2010

Signature: Dipl.-Ing. F. Möcking

10.061 12.09

Annex 8. Serious Adverse Events

A serious adverse event is any adverse event that meets any of the following criteria:

- Fatal (i.e., the adverse event actually causes or leads to death)
- Life Threatening (i.e., the adverse event, in the view of the investigator, places the patient at immediate risk of death)

  This does not include any adverse event that had it occurred in a more severe form or was allowed to continue might have caused death.
- Requires or prolongs inpatient hospitalization
- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- Significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

Annex 9. Workplan

	ACTIVITY	PERSONNEL	Ano 2014			Ano 2015		Ano 2016		Ano 2017						
			Oct	Nov	Dec	Jan - Jun	July-Dec	Jan - Jun	July-Dec	Jan	Feb	Mar	Apr	May	June	July-Dec
STAGE 0 Pre-Coordination phase	Literature Review	Investigators														
	Provisional study protocol elaborated															
STAGE 1 Coordination Phase	Presentation the protocol to the Primary Care Centers	Investigators and GP														
	Identify the Health Care Centers interested and able to collaborate in the study															
	Elaboration, presentation and discussion of the definitive protocol															
	Ask Approval of ethics comittee and administrative authorization	Investigators														
	Meeting with the team	All the team														
	Creation of a database	Data manager														
	Training of cardio-pneumology	Cardio-pneumology														
	Periodic contact between coordinators and main investigators	PHCs coordinators Investigators and TSC				**Once a month**										
STAGE 2 Field Research	Sample selection (Recruitment)	GP and investigators														
	Follow up	All the team														
	Safety evaluation and overall supervision	TSC														
	Processing database	Data manager				**Every 3 months**										
STAGE 3 Data analysis and Interpretation of results	Data analysis	Statistical consultant					**Every 6 months**									
	Interpretation of the results	Investigators														
STAGE 4 Publication and dissemination of the research findings	Article writting	Main investigators														
	Publication & Dissemination															

Annex 10. Image and video capture consent

Centro Hospitalar de Entre o Douro e Vouga, E.P.E.

SOCIEDADE PORTUGUESA DE HIPERTENSÃO
Portuguese Society of Hypertension

Autorização para filmagem e fotografias

Título do projeto: *"The use of bioimpedance to better characterize resistant hypertensive patients and therapeutic optimization"*

Principais Investigadores: Joana Oliveira, Dr. Fernando Pinto e Dr. Pedro Torguet

Para a realização do protocolo de investigação gostaria de tirar algumas fotografias e proceder a filmagens do exame de bioimpedância.

Estas imagens serão somente utilizadas para fins de elaboração e exposição do protocolo de investigação. Todas as imagens que permitam a sua identificação não serão publicadas, e aquelas que sejam expressamente necessárias se procederão a uma desfocagem da face.

Após a obtenção desta informação autoriza a filmagem de todo o procedimento, bem como a realização das fotografias?

☒ Sim autorizo

☐ Não autorizo

Nome do paciente: Abel Sousa Marques

Assinatura: Abel Marques

Hospital Entre Douro e Vouga, 6 de Novembro de 2014

Centro Hospitalar de Entre o Douro e Vouga, E.P.E.

SOCIEDADE PORTUGUESA DE HIPERTENSÃO
Portuguese Society of Hypertension

Autorização para filmagem e fotografias

Título do projeto: *"The use of bioimpedance to better characterize resistant hypertensive patients and therapeutic optimization"*

Principais Investigadores: Joana Oliveira, Dr. Fernando Pinto e Dr. Pedro Torguet

Para a realização do protocolo de investigação gostaria de tirar algumas fotografias e proceder a filmagens do exame de bioimpedância.

Estas imagens serão somente utilizadas para fins de elaboração e exposição do protocolo de investigação. Todas as imagens que permitam a sua identificação não serão publicadas, e aquelas que sejam expressamente necessárias se procederão a uma desfocagem da face.

Após a obtenção desta informação autoriza a filmagem de todo o procedimento, bem como a realização das fotografias?

☒ Sim autorizo

☐ Não autorizo

Nome do paciente: Francisco da Silva Santos

Assinatura: _____

Hospital Entre Douro e Vouga, 11 de Dezembro de 20_