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Christophe Smeets

DOCTORAL DISSERTATION

Remote monitoring in heart failure with a focus on thoracic bioimpedance: challenges and opportunities

Promoter: Prof. Dr Pieter Vandervoort | UHasselt
Co-promoters: Prof. Dr Lars Grieten | UHasselt
Prof. Dr Chris Van Hoof | KU Leuven

Promoter: Prof. Dr. Pieter Vandervoort

Co-promoters: Prof. dr. Chris van Hoof | KULeuven
Prof. dr. Lars Grieten | Hasselt University

Jury members: Prof. dr. Marcel Ameloot (Chair) | Hasselt University

Prof. dr. Annick Timmermans | Hasselt University

Prof. dr. ir. Ronald Thoelen | Hasselt University

Prof. dr. Tiny Jaarsma | Linköping University

Prof. Dr. Emeline Van Craenenbroeck | University of Antwerp

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Voor mijn liefste broer, Laurent.

Mijn zon, mijn ster…

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LIST OF ABBREVIATIONS

AC	alternating current
ACE-I	angiotensin converting enzyme inhibitors
AF	atrial fibrillation
AMS	automated mode switch
ATP	antitachycardia pacing
BioZ	bioimpedance
BIV	biventricular
BMI	body mass index
BNP	brain natriuretic peptide
Bpm	beats per minute
BW	blood withdrawal
CHF	congestive heart failure
CI	confidence interval
CRT	cardiac resynchronization therapy
CRT-D	CRT with defibrillator
CRT-P	CRT without defibrillator
CWT	continuous wavelet transform
DC	direct current
DSP	digital signal processing
eGFR	estimated glomerular filtration rate
ER	emergency room
ESC	European Society of Cardiology
FFC	fast fluid challenge
GE	General Electric Company
GHD	gestation-induced hypertensive disorders
GP	general practitioner
HF	heart failure
HR	heart rate
ICD	implantable cardioverter-defibrillator
CIED	cardiovascular implantable electronic device
CIED^{-}	CIED without an available bioimpedance algorithm
CIED^{+}	CIED equipped with a bioimpedance algorithm
IQR	interquartile range

LOA	limits of agreement
NYHA	New York Heart Association
PMT	pacemaker mediated tachycardia
PVC	premature ventricular complexes
PYFU	patient-years of follow-up
SD	standard deviation
SFC	slow fluid challenge
SVT	supraventricular tachycardia
VF	ventricular fibrillation
VT	ventricular tachycardia

Holy grail

/ˈhəʊli/ /greɪl/

1. *Also called: Grail, Sangraal*

2. *(in medieval legend) the bowl used by Jesus at the Last Supper. It was allegedly brought to Britain by Joseph of Arimathea, where it became the quest of many knights*

3. *(in modern spirituality) a symbol of the spiritual wholeness that leads a person to union with the divine*

4. *Informal: any desired ambition or goal*

From: Collins English Dictionary - Complete & Unabridged 2012 Digital Edition

GENERAL INTRODUCTION

'In the middle of difficulty lies opportunity' - Albert Einstein

(DECOMPENSATED) HEART FAILURE

"Heart failure (HF) is a clinical syndrome characterized by typical symptoms (e.g. breathlessness, ankle swelling and fatigue) that may be accompanied by signs (e.g. elevated jugular venous pressure, pulmonary crackles and peripheral edema) caused by a structural and/or functional cardiac abnormality, resulting in a reduced cardiac output and/or elevated intracardiac pressures at rest or during stress" according to recently published guidelines of the European Society of Cardiology [1]. In layman's terms, HF is a chronic, progressive condition in which the heart muscle is unable to pump enough blood through the body to meet the body's demand for blood and oxygen. In general, the heart can't keep up with its workload. Heart failure is a major health problem affecting more than 10% in the elderly over 70 years of age and is associated with a high morbidity and mortality [1-5]. All cause survival rates are low, with only 50% of patients still alive within five years after first diagnosis. Hospitalization rates are even higher with one-year hospitalization rates of approximately 40% and readmission rates of 30-45% within six months after initial admission [6-9]. The major reason for HF (re)hospitalizations are related to congestion or fluid overload (i.e. congestive HF). These high (re)admission rates put a large burden on the current healthcare system, since HF accounts for 1-2% of all healthcare expenditures [10-13]. However, improvements in treatment strategies and their implementation have improved survival rates and reduced (re)hospitalization rates.

Heart failure treatment is focused on improving clinical status, functional capacity and quality of life, prevent hospital (re)admission and reduce mortality. Current guidelines prescribe initial drug treatment with angiotensin-converting enzyme inhibitors, followed by beta blocker and mineralocorticoid receptor antagonist treatment with uptitration to the maximum tolerated evidence-based dose. In addition, diuretics are recommended to relieve the signs and symptoms of congestion. Symptomatic patients receiving optimal drug dose who are still experiencing a reduced ejection fraction (≤35%), a left bundle branch block or a very wide QRS complex (≥150 ms), qualify for cardiovascular implantable electronic device (CIED) implantation [1]. These patients are at high risk of dying due to disease progression or ventricular tachyarrhythmias. Device-based therapies including implantable cardioverter defibrillators (ICD) and cardiac resynchronization therapy (CRT) both favorably affect mortality. ICDs are useful in preventing sudden cardiac death in patients with known,

sustained ventricular tachycardia or fibrillation by constantly monitoring the patient's heart rate. In case of an abnormal heart rhythm, the device delivers an electric shock to restore a normal heartbeat. CRT devices restore ventricular synchrony to improve the heart's pump efficiency and increase blood flow, thereby alleviating some HF-related symptoms, such as shortness of breath. Clinical studies also suggest a decrease in hospitalization and morbidity, as well as an improvement in quality of life [1, 14-16].

CIED'S AND REMOTE MONITORING

Patients with HF benefit from regular follow-up and monitoring of biomedical parameters to optimize treatment strategies and detect the development of complications or disease progression that may require a change in disease management. Cardiovascular implantable electronic devices enable remote monitoring of device and disease-related parameters in a continuous way [17]. In fact, remote monitoring can be seen as a care cycle. Remote monitoring data from a patient with a CIED is sent via a communication gateway to the clinical call center, where the data can be reviewed by a remote monitoring nurse or cardiologist. Subsequently, feedback can be coupled to the patient (Figure 1). Remote follow-up of HF patients may offer distinct advantages to patients, healthcare workers, and society as well. It incorporates device monitoring (i.e. surveillance for technical device problems and device programming) and disease monitoring (i.e. early detection of rhythm disorders and in some devices changes in thoracic impedance) [18-23]. Implementation of a remote monitoring program may substitute some of the scheduled outpatient device checks and therefore reduce the workload in outpatient device clinics [24-26]. Although some studies have shown a reduction in the number and duration of HF hospitalizations [27] and an improvement in survival [28], other studies [29, 30] have shown conflicting results on a possible clinical benefit of remote monitoring. A shortcoming in current studies is the lack of standardization and information concerning actions taken based on remote monitoring data. Hence, it is very difficult to assess which components of a remote monitoring program contribute to perceived outcome benefits [19]. A better insight and standardization in remote monitoring strategies is therefore urgently needed.

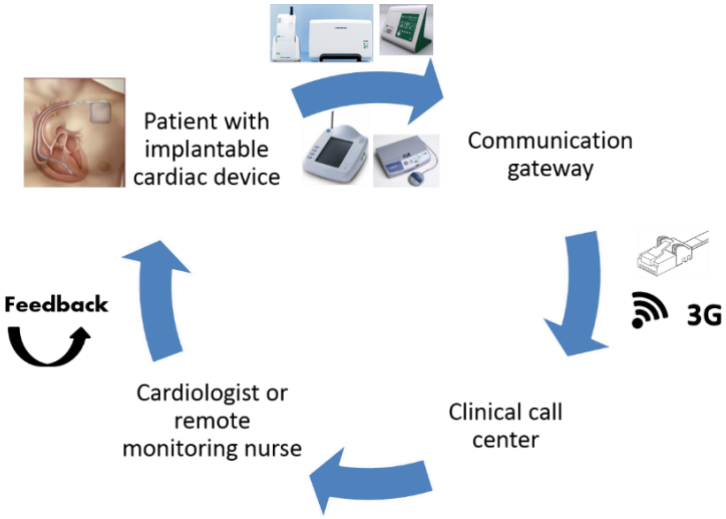

Figure 1: Schematic overview of the remote monitoring care cycle.

INVASIVE BIOIMPEDANCE MONITORING BY CIEDS

Over the last decade, several CIED manufacturers market thoracic impedance measurement algorithms integrated into their devices. Bioimpedance is an electrical principle which represents the resistive or capacitive changes that oppose a sinusoidal current to pass through the body. Since blood and fluids have a lower impedance to an electrical current compared to thoracic tissue, bioimpedance makes it possible to measure thoracic fluid changes. An inverse correlation exists between bioimpedance and the amount of body fluid [31-33]. Changes in bioimpedance measurements therefore reflect changes in intrathoracic fluid status and are evaluated based on a vendor-specific computer algorithm. As congestion is the major reason for HF-related hospitalizations and still remains difficult to accurately assess, the bioimpedance technique is promising for the early detection of fluid accumulation and hence impeding congestive HF [34, 35]. Bioimpedance therefore seems to be a logical parameter for fluid status follow-up. Furthermore, since a high-dose of intravenous admitted non-potassium sparing diuretics (i.e. loop diuretics) is currently considered the most widely used and relatively effective therapy for fluid removal, bioimpedance could be used to follow and guide treatment strategies accordingly [36]. However, despite early investigations showing promising results [32, 34, 35, 37], larger randomized trials have revealed disappointing outcomes [38-42]. The problem with bioimpedance monitoring is the insufficient knowledge about what is actually being measured and to what extent in- and external factors (i.e movement, posture, skin conditions, body composition, etc.) influence bioimpedance recordings.

NON-INVASIVE BIOIMPEDANCE MONITORING

Since not all patients with HF are equipped with a CIED, invasive bioimpedance data is only available in a limited patient population. To date, a few non-invasive portable bioimpedance devices exist (e.g. Maltron BioScan, Medis Niccomo, CardioDynamics BioZ Dx, NMT Zoe, etc.), but their form factor and difficulty to operate limit their use in clinical practice. Hence, non-invasive wearable devices for bioimpedance recordings provide an interesting alternative since their form factor enables longitudinal monitoring and trend analysis in a comfortable way [43-46]. There are only a handful of these devices, for example the Edema Monitor described by Shochat [47, 48], the Cova necklace from toSense and the AVIVO mobile patient management system from Corventis. Unfortunately, their level of clinical evidence is scarce and most of them are not yet commercially available. Recently, Philips published pilot results of a wearable bioimpedance vest intended for in-home monitoring. They reported a strong correlation of bioimpedance with daily weight changes and concluded that the vest could track recompensation during therapy for acute congestive HF [46]. Two years later, they reported that the vest could even provide a refinement in the prognostic assessment of patients admitted for HF [45]. Unfortunately, the vest is not commercially available and its form factor more or less limits the in-hospital use and is less convenient for continuous long-term in-home monitoring. Interestingly, Holst Centre/imec Netherlands (Eindhoven, The Netherlands) developed a multi-parametric wearable sensor, equipped with a bioimpedance module. This sensor could become an interesting alternative for long-term, continuous and non-invasive bioimpedance measurements in a comfortable way.

RESEARCH OBJECTIVES

This PhD project was performed within the Mobile Health Unit of Hasselt University in close collaboration with the Body Area Network group within the HUMAN++ department of the interuniversity microelectronics center (imec, Heverlee, Belgium) and Holst Centre/imec Netherlands and the Cardiology and Future Health department of Ziekenhuis Oost-Limburg.

This PhD thesis focuses on three main research objectives to further explore different remote monitoring strategies to improve HF disease management. Focus lies on gaining more insight in bioimpedance applications in HF. Better understanding of the measurement principles and external influences may shed light to novel individualized fluid monitoring strategies for HF patients.

OBJECTIVE 1 – To examine the impact of protocol-driven remote follow-up, in particular bioimpedance monitoring, of cardiovascular implantable electronic devices as part of a heart failure disease management strategy *(Part 1)*.

OBJECTIVE 2 – To explore the application potential of a novel, non-invasive multi-parametric wearable bioimpedance sensor in fluid status monitoring of heart failure patients *(Part 2)*.

OBJECTIVE 3 – To study the feasibility and safety of a smartphone application in combination with decision support algorithms and remote monitoring sensors to improve efficient implementation of guideline recommended drug therapy in heart failure *(Part 3)*.

Objective 1 will be tackled by using a structured database of standardized protocol-driven remote monitoring of CIEDs to closely analyze different remote monitoring notifications, triggered interventions and impact on clinical outcome. This will be done for patients with a CRT device, with a focus on all disease-related alerts (i.e. rhythm and bioimpedance-related alerts) (Chapter 1). Secondly, all bioimpedance-related notifications will be analyzed in detail in patients with either an ICD or CRT device, also comparing the different bioimpedance algorithms (Chapter 2). Next, two interesting case reports will be discussed concerning bioimpedance alerts from CIEDs in two pregnant women, to gain additional insight in bioimpedance alert handling and interpretation (Chapter 3 and 4).

For Objective 2, we will be focusing on wearable technologies from imec in the field of fluid monitoring in heart failure. This will be performed in different steps. In a first step, imec's electrocardiogram sensor will be validated against a gold standard Holter monitor (Chapter 5). Next, the feasibility of imec's bioimpedance sensor to detect fluid redistribution and accumulation will be tested in three different patient populations (Chapter 6). This sensor will then be used to study the applicability in a patient population suffering from acute decompensated heart failure (Chapter 7 and 8). And finally, also the ability and optimal electrode configuration of this bioimpedance sensor to detect respiratory parameters will be studied (Chapter 9).

Finally, for objective 3, we will study the feasibility of a two-way communication platform combined with decision support algorithms and remote monitoring sensors for active heart failure medication uptitration (Chapter 10).

A schematic overview of the different studies that were performed during this PhD thesis, is given in Figure 2.

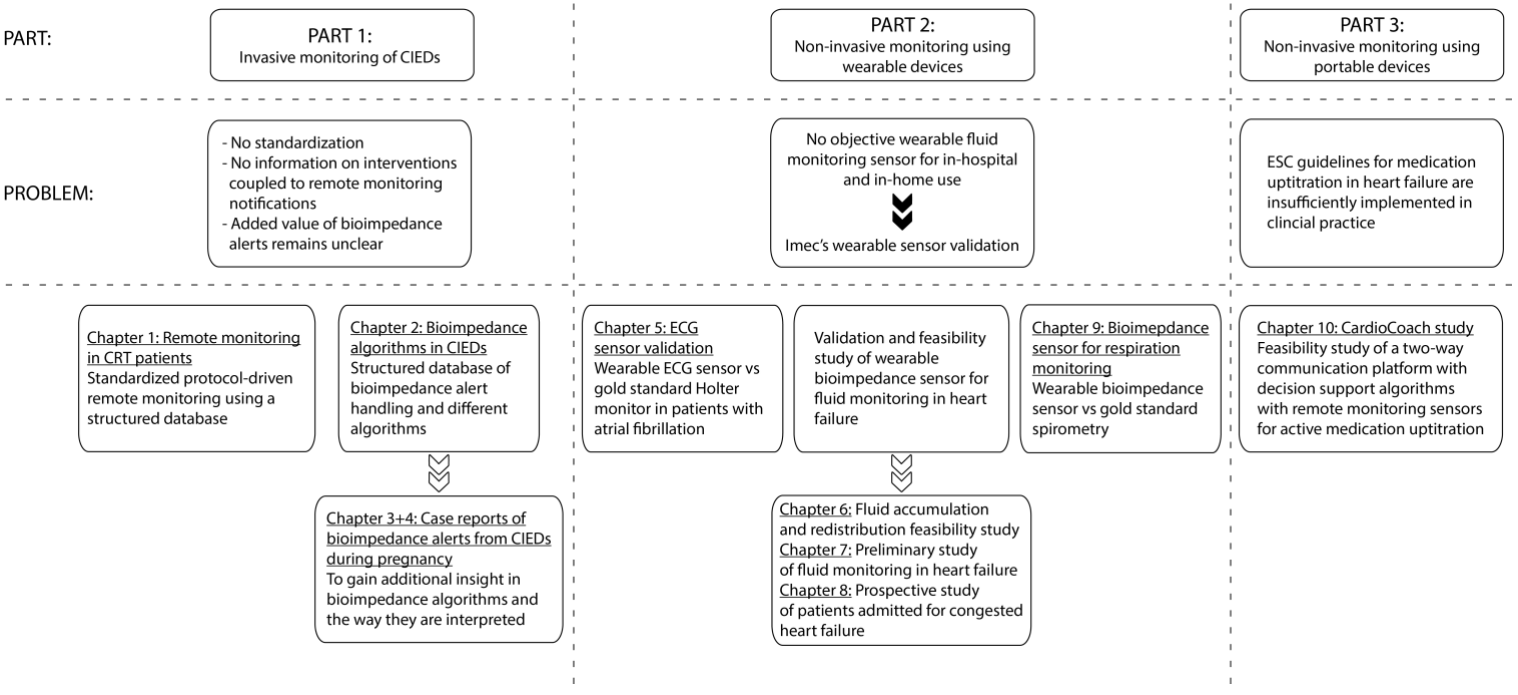

Figure 2: Schematic overview of the different studies that were conducted in this thesis.

PART I

REMOTE MONITORING OF CARDIOVASCULAR IMPLANTABLE ELECTRONIC DEVICES

CHAPTER 1

Protocol-driven remote monitoring of cardiac resynchronization therapy as part of a heart failure disease management strategy

Smeets CJ, Verbrugge FH, Vranken J, Van der Auwera J, Mullens W, Dupont M, Grieten L, De Cannière H, Lanssens D, Vandenberk T, Storms V, Thijs IM, Vandervoort PM

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ABSTRACT

Background: Cardiac resynchronization therapy (CRT) is an established treatment for heart failure (HF) with reduced ejection fraction. CRT devices are equipped with remote monitoring functions, which are pivotal in the detection of device problems, but may also facilitate disease management. The aim of this study was to provide a comprehensive overview of the clinical interventions taken based on remote monitoring.

Methods: This is a single center observational study of consecutive CRT patients (n=192) participating in protocol-driven remote follow-up. Incoming technical- and disease-related alerts were analyzed together with subsequently triggered interventions.

Results: During 34±13 months of follow-up, 1,372 alert-containing notifications were received (2.53 per patient-year of follow-up), comprising 1,696 unique alerts (3.12 per patient-year of follow-up). In 60%, notifications resulted in a phone contact. Technical alerts constituted 8% of incoming alerts (0.23 per patient-year of follow-up). Rhythm (1.43 per patient-year of follow-up) and bioimpedance alerts (0.98 per patient-year of follow-up) were the most frequent disease-related alerts. Notifications included a rhythm alert in 39%, which triggered referral to the emergency room (4%), outpatient cardiology clinic (36%), or general practitioner (7%), or resulted in medication changes (13%). Sole bioimpedance notifications resulted in a telephone contact in 91%, which triggered outpatient evaluation in 8% versus medication changes in 10%. Clinical outcome was excellent with 97% 1-year survival.

Conclusion: Remote CRT follow-up resulted in 0.23 technical- versus 2.64 disease-related alerts annually. Rhythm and bioimpedance notifications constituted the majority of incoming notifications which triggered an actual intervention in 22% and 15% of cases, respectively.

INTRODUCTION

Cardiac resynchronization therapy (CRT) is a guideline-recommended treatment for symptomatic heart failure with reduced ejection fraction and left bundle branch block or very wide QRS complex (>150 ms) [49, 50]. The use of CRT is rapidly increasing, with approximately 51,274 patients receiving a device yearly in Europe [51]. Remote follow-up of this group may offer distinct advantages to patients, healthcare workers, and society as well. Remote CRT monitoring incorporates surveillance for technical device problems (i.e., battery status, lead integrity and dislodgement), device programming, early detection of rhythm disorders, and in some devices changes in thoracic impedance [18-23]. Implementation of a remote monitoring program may substitute some of the scheduled outpatient device checks and therefore reduce the workload in outpatient device clinics [24-26]. Although some studies have shown a reduction of total number and duration of heart failure hospitalizations [27] and improved survival [28], other studies [29, 30] have shown conflicting results on a possible clinical benefit of remote monitoring.

In 2010, a dedicated remote follow-up program of heart failure patients with an implantable cardiac device was started in our center. A standardized protocol with pre-defined patient evaluation and treatment strategies, which has been proven to be critical in remote monitoring, was implemented [52]. Dedicated nurses, trained in electrophysiology, device follow-up as well as heart failure, reviewed all incoming alerts in a systematic and standardized manner with interventions triggered by protocol-based, guideline-recommended care and minimal involvement of physicians. All alerts and interventions taken were registered prospectively in a dedicated software program. The current observational study presents a detailed overview and analysis of all remote monitoring alerts and subsequently triggered interventions in 192 CRT patients included in this program. As such, the current research builds further on previous studies since these lack this level of detail [19].

METHODS

STUDY DESIGN

This is an observational registry study of CRT patients from a single tertiary care center (Ziekenhuis Oost-Limburg, Genk, Belgium), implanted between February 2010 and May 2013. Since February 2010, all CRT patients with a defibrillator (CRT-D) were asked to participate voluntarily in a remote follow-up program. Over time, also CRT patients without defibrillator (CRT-P) were included, since these devices did not possess remote monitoring features from the beginning but started to do so over time. For the current analysis, only patients enrolled in remote follow-up within six months after device implantation are included. All participants provided written informed consent and were followed until the 1st of February 2015. The study complies with the Declaration of Helsinki and the study protocol was approved by the local committee on human research.

PROTOCOL-DRIVEN REMOTE FOLLOW-UP AND ALERTS

All patients received a vendor-specific transmission device. The data collected from the CRT device were transmitted at night to the respective company databases, and subsequently transmitted to the multidisciplinary heart failure and device clinic's patient record. Dedicated nurses, trained in electrophysiology and heart failure, interpreted the notifications during working days; notifications received during the weekend were read on Monday. Patients participating in this program are encouraged to contact caregivers at low threshold for any question and the dedicated nurses subsequently play a pivotal role to decide the level of care that is needed (i.e. education by heart failure nurse, general practitioner, general cardiologist, heart failure specialist, electrophysiologist, etc.). Alert transmissions are generated when predefined alarm thresholds were crossed. These thresholds could be adjusted as needed in individual patients (e.g. the alert for atrial fibrillation may be turned off in patients with known atrial fibrillation). In addition, all devices, independent from device manufacturer, were programmed to send a scheduled transmission report on a monthly basis and alert transmissions on a daily basis. For the purpose of this analysis only alert-containing notifications (i.e. scheduled notifications including an alert or unscheduled alert transmissions) were considered and alerts were classified into five categories: rhythm alerts, bioimpedance alerts, technical device alerts, missed scheduled transmissions and a miscellaneous group (Table 1.1). Bioimpedance is an electrical principle which represents the resistance that opposes a current to pass through the body. An inverse correlation exists between bioimpedance and the amount of body fluid. Changes in bioimpedance

measurements therefore reflect changes in intrathoracic fluid status and can be used to detect emerging congestion. Bio-impedance alerts were only available for Medtronic or St. Jude devices (n=138). Since combinations of alerts were possible, it was not exceptional that one notification included multiple alerts.

Table 1.1: Overview of possible alerts/intervention triggers that were monitored.

Alert category	Alert type
Rhythm alert	Sinus tachycardia Supraventricular tachycardia New-onset atrial fibrillation <90% biventricular pacing Non-sustained ventricular tachycardia Sustained ventricular tachycardia Ventricular tachycardia + ATP Ventricular tachycardia + DC shock Ventricular fibrillation + ATP Ventricular fibrillation + DC shock High ventricular rate Premature ventricular complexes Miscellaneous rhythm alert (PMT, AMS, T-wave oversensing)
Bioimpedance* alert	Bioimpedance threshold crossing
Technical device alert	Battery end of life Lead problems (lead noise, lead impedance, malcapture, malsensing) Device malfunction (back up mode, inappropriate AMS)
Missed scheduled transmission	Gateway problem or patient absence
Miscellaneous alerts	Heart failure management Changes in daily activity Patient contacted the clinical call center

*Only for Medtronic devices (OptiVol and OptiVol 2.0) and St. Jude Medical devices (CorVue). AMS, automated mode switch; ATP, antitachycardia pacing; DC, direct current; ER, emergency room; GP, general practitioner; PMT, pacemaker mediated tachycardia.

INTERVENTION PROTOCOL

Incoming notifications, both scheduled transmission reports and alerts, were handled in a standardized manner with protocol-based interventions according to guideline recommendations (Figure 1.1) [17, 52, 53]. In case of an alert suggestive of a significant lead or device malfunction, a visit at the outpatient device clinic was arranged for troubleshooting. When a scheduled transmission report was missed, the patient was contacted by phone to identify the reason and exclude hardware malfunction. In case of a relevant disease alert, the interpreting nurse contacted the patient by phone for interrogation, using a custom-

made questionnaire (Table 1.2). Additional questions could be asked at the discretion of the caregiver in order to gain better insight in the reason for the alert. Subsequently, appropriate feedback and general heart failure education were always provided. If any orange or red flags were discovered during the interview, further action was planned in consultation with a dedicated heart failure specialist. A notification did not result in a patient contact when it was repetitive or related to a known condition, or when a clinical follow-up visit was already scheduled for the near future.

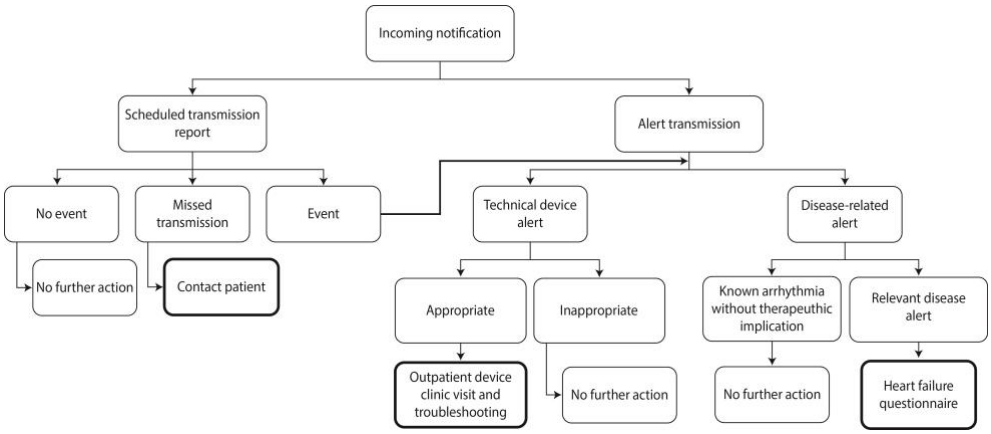

Figure 1.1: Schematic overview of notification handling.

OUTPATIENT FOLLOW-UP

Patients enrolled in remote follow-up visit the outpatient cardiology clinic for device and clinical heart failure follow-up at 6 weeks after implantation and subsequently every 6 months with a minimum of 2 visits per year, as per standard practice in our institution. Patients were followed until death, exclusion from remote follow-up, heart transplantation, or 1 February 2015, whichever came first.

STATISTICAL ANALYSIS

Continuous variables are expressed as mean ± standard deviation if normally distributed, or otherwise as median (interquartile range). Normality was assessed by the Shapiro-Wilk statistic. To define statistical differences between the different CRT manufacturers, the Kruskal-Wallis test and Mann-Whitney U test were performed for respectively rhythm and bioimpedance-related notifications. All statistical analyses were performed using the Statistical Package for Social Sciences release 23.0 (IBM® SPSS® Inc., Chicago, Illinois, USA).

Table 1.2: Custom-made questionnaire used for patient interrogation in case of a relevant disease alert. NYHA, New York Heart Association functional class.

Last visit by the general practitioner	Date: MM/DD/YYYY Reason & findings:……		
Daily activity	Unchanged	Worsened, but with few limitations	Significantly restricted
Dyspnea's	NYHA I or stable NYHA II	Worsening NYHA II or stable NYHA III	Worsening NYHA III or NYHA IV
Retrosternal pain	No	Stable	Unstable
Episodes of (pre-) syncope	No		Yes
Palpitations	No	Yes	
Increase in weight	No		Yes, …… kg
Edema	No	Limited and stable	Pronounced or increasing
Changes in diet	No	Yes, ……	
Changes in medication	No	Yes, ……	
			
Action	No further action	Discuss possible action with heart failure specialist	Plan action with heart failure specialist: 1. Visit general practitioner 2. Visit general cardiologist 3. Visit electrophysiologist 4. Visit heart failure specialist 5. Visit emergency room

RESULTS

STUDY POPULATION

From 344 eligible CRT patients, 110 patients were excluded due to the presence of a CRT-P device without remote monitoring capabilities and three patients refused study participation. 33 patients were included in the remote monitoring program more than six months after device implantation and were therefore also excluded and finally six patients were excluded due to follow-up in another center. A final study population of 192 patients was included in the study: 159 CRT-D patients (83%) and 33 CRT-P patients (17%). A study flowchart is provided in Figure 1.2. For 180 patients, there was a de-novo CRT implantation among which 25 patients already had a previous pacemaker or implantable cardioverter defibrillator (ICD) device and 12 patients already had a CRT device without remote monitoring enrolment and received an update or battery replacement. The median time interval between CRT implantation and start of remote follow-up was 1 day (IQR 1-2 days), with 161 (84%) patients included within one week. Patients were followed for 34 ± 13 months. The total number of elective follow-up visits to the outpatient heart failure clinic was 3.08 per patient-year of follow-up. When excluding the visits triggered by remote monitoring, this number was equal to 2.81 visits per patient-year of follow-up. Baseline characteristics of the study population at the time of implantation are provided in Table 1.3.

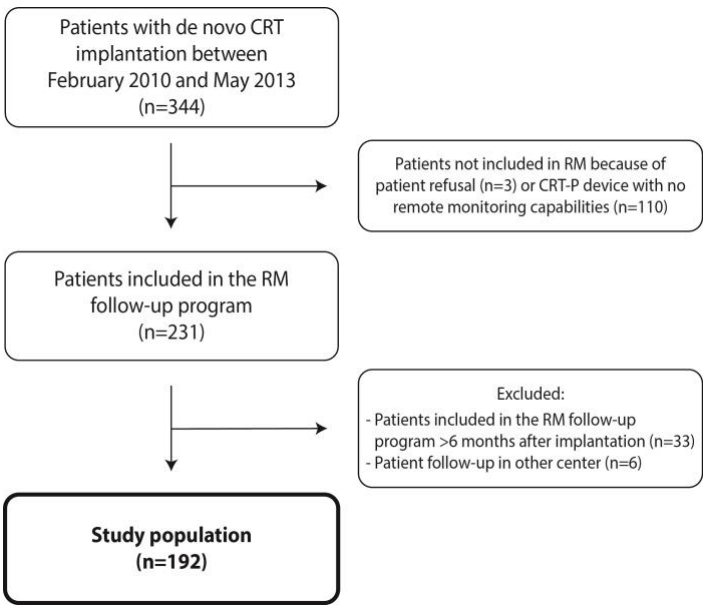

Figure 1.2: Flowchart of the study. CRT, cardiac resynchronization therapy; RM, remote monitoring.

Table 1.3: Baseline characteristics of the study population (n=192).

Variables	Study population (n=192)
Age, years	71 ± 11
Male gender	153 (80%)
NYHA functional class (II/III)	24/125 (16/83%)
Left ventricular ejection fraction, %	29 ± 9
QRS width, ms	148 ± 28
Ischemic heart disease	114 (59%)
Valvular surgery	21 (11%)
Atrial fibrillation	80 (42%)
Diabetes	44 (23%)
Chronic obstructive pulmonary disease	26 (14%)
Medication use	
Renin-angiotensin system blocker	161 (84%)
Beta blocker	183 (95%)
Spironolactone	135 (70%)
Loop diuretic	92 (48%)
Digoxin	29 (15%)
Statin	114 (59%)
CRT manufacturer	
Medtronic	83 (43%)
St Jude Medical	69 (36%)
Biotronik	38 (20%)
Boston Scientific	2 (1%)

Continuous data are expressed as mean ± SD if normally distributed and dichotomous data are expressed as n (%). NYHA, New York Heart Association.

REMOTE FOLLOW-UP NOTIFICATIONS AND ALERTS

A total of 1,372 alert-containing remote monitoring notifications were received in 176 patients (92%) during 543 cumulative patient-years of follow-up, corresponding to 2.53 notifications per patient-year of follow-up. In 60% (820) of all notifications the patient was eventually contacted, corresponding to 1.51 telephone contacts per patient-year of follow-up, leading to 837 interventions. 165 patients (86%) were contacted at least once during follow-up. The total of 1,372 alert-containing notifications comprised 1,696 unique alerts (3.12 alerts per patient-year of follow-up). An overview of the frequency of each alert category is presented in Figure 1.3. The large majority of these alerts (n=1434, 85%) were disease-related (i.e. 775 rhythm, 532 bioimpedance, and 127 miscellaneous), with missed scheduled transmissions (n=134) and technical device alerts (n=128) each representing almost 8%.

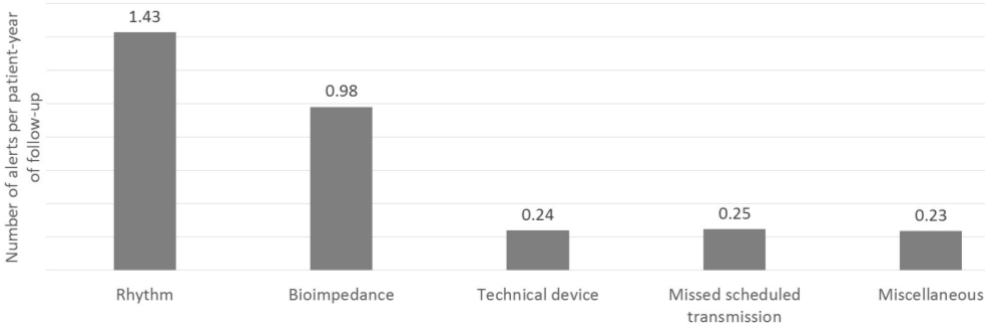

Figure 1.3: Frequency of alert categories with the number of alerts per patient-year of follow-up presented above.

An overview of the interventions that resulted from the alerts when the patient was contacted is shown in Figure 1.4. Telephonic heart failure education was deemed sufficient in 530 cases (63%). The alarm resulted in a hospital admission or an emergency room visit in 1%. 18% of cases were managed through the outpatient cardiology clinic. In 13% of cases, the patient was asked to consult the general practitioner and in 9%, the general practitioner was advised to change the patient's medication (i.e. 6% changes in (loop) diuretics and 3% changes in other medications). In the remainder of cases, technical support was provided (5%).

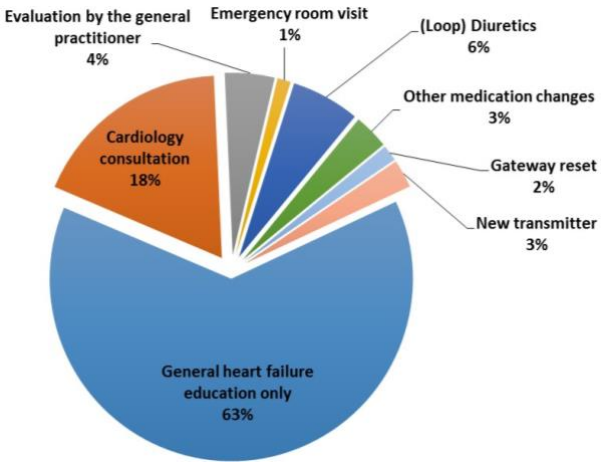

Figure 1.4: Overview of the interventions triggered by remote follow-up alerts when the patient was contacted.

For the purpose of the current study, no detailed time logging was performed. However, Ziekenhuis Oost-Limburg has currently over 900 patients in active remote monitoring

follow-up. The remote follow-up of these patients by the nurses takes about five to six hours a day. Therefore, it can be calculated that the time spent daily by the remote monitoring nurses to review all incoming alert-containing notifications for the 192 patients included in the current study is equal to 1.07 – 1.28 hours.

TECHNICAL DEVICE ALERTS

Over the total follow-up period, 128 technical device alerts were received for lead problems (n=81), loss of capture (n=24), device malfunction (n=17), a battery that was end of life (n=4), or technical support (n=2). This corresponded to 0.23 technical device alerts per patient-year of follow-up. In the four cases where a battery end of life alert was triggered, a device exchange was planned. In case of device, lead or lead thresholds problems, the patient was asked to visit the hospital for further evaluation and adjust device settings when appropriate. In addition, the clinical call center registered 134 missed scheduled transmissions, in which case the patient was contacted and a gateway reset or new transmitter was provided if needed.

APPROACH TO RHYTHM AND BIOIMPEDANCE ALERTS

Rhythm (775) and bioimpedance (532) alerts constituted the large majority of relevant disease-related alerts. The 775 rhythm alerts were comprised in 610 notifications which were received in 144 patients (75%) of the total population. A detailed overview of the distribution of rhythm alarms and the specific interventions that they triggered is shown in the supplemental material Table S 1.1. Notifications including a rhythm alert were deemed clinically relevant and thus warranting a phone call to the patient in 235/610 cases (39%) and initiated 248 interventions in total (Figure 1.5, left part). In 4% of cases, the patient was asked to visit the emergency room or an outpatient evaluation was arranged with the patient's cardiologist (36%) or general practitioner (7%) and medical therapy was adjusted in 13%. In 40% of cases no further action was taken and reinforcement of heart failure education was sufficient. No differences were found for the number of rhythm-related notifications across the different CRT manufacturers.

Of all bioimpedance-containing notifications (532), 485 notifications contained only a bioimpedance alert with no combination of other alerts. These sole bioimpedance notifications triggered 439 phone calls to which 445 interventions were coupled (Figure 1.5, right part). In the remainder 46 cases, the patient was not contacted due to a recent outpatient visit or an outpatient visit scheduled in the near future or because of a known

ongoing bioimpedance threshold crossing. Medication was changed in 10%, while an outpatient evaluation with the patient's general practitioner or cardiologist was arranged in both 4% of cases. In 82% of cases only general heart failure education was provided and no further action was implied since patient interrogation often did not reveal any acute signs of congestion. No differences were found for the amount of bioimpedance-containing notifications across the different CRT manufacturers.

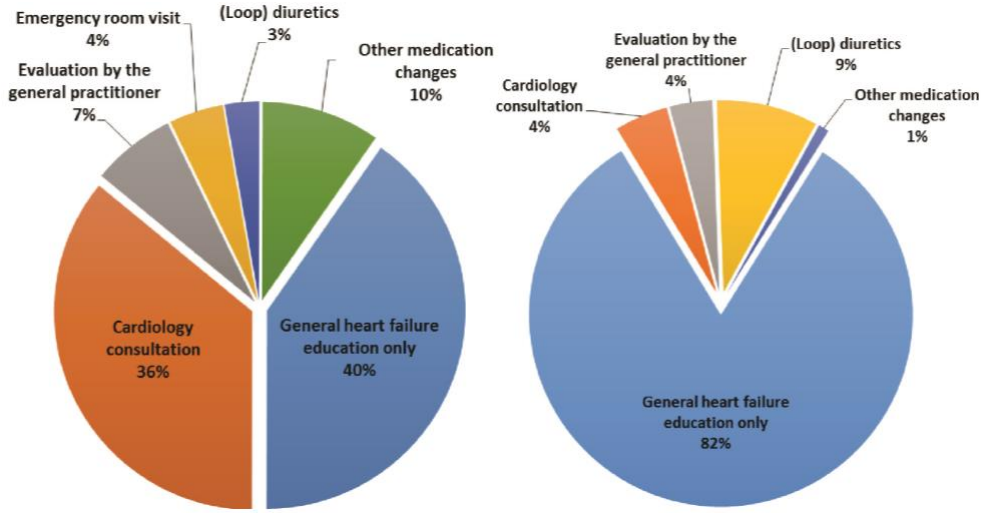

Figure 1.5: Overview of the interventions that resulted from relevant rhythm alerts (left) and bioimpedance alerts (right) for which the patient was contacted by phone.

CLINICAL OUTCOME

During the total follow-up 25 patients died, leading to 1-year and 3-year survival rates of 97% and 88%, respectively. After one year of follow-up, 176 patients (92%) were free from hospital admissions with a primary diagnosis of heart failure and 169 (88%) were free from death and heart failure readmission. At 3-year follow-up, these numbers were equal to 85% and 75% respectively. In total, there were 214 cardiac-related hospitalizations for 86 (45%) patients of which 133 were non-elective and 45 were heart failure related. For those who had at least one cardiac-related hospitalization, the median length of stay was 7 days (IQR 3-18).

DISCUSSION

CRT is an established therapy in the treatment of heart failure with reduced ejection fraction and conduction delay [49, 50]. In such patients, the presence of an implantable cardiac device offers the attractive possibility for remote monitoring. The current observational registry study provides a clear insight in a single center experience of standardized protocol-driven remote follow-up of a large cohort of patients with heart failure treated with CRT, who were followed in a dedicated heart failure clinic. It offers a comprehensive and detailed overview of incoming alarm notifications and individual alerts. The single Belgian tertiary care center where the study was performed accounts for approximately 15% of Belgian CRT implantations [54].

Major insights were: (1) in case of a remote monitoring notification, the patient was contacted for further evaluation in 60% of cases; (2) technical device alerts and missed transmissions were relatively infrequent, each constituting only 8% of the total number of incoming alerts; (3) rhythm (46%) and bioimpedance (31%) alerts constituted the majority of incoming disease-related alerts; (4) notifications including a rhythm alert triggered an actual intervention in 22%, while this was only 15% for sole bioimpedance notifications.

A shortcoming in current studies is the lack of information as to what clinical actions were taken based on the information gathered via remote monitoring, making it difficult to assess which components of a program are implied in perceived outcome benefits [19]. A better insight and standardization in remote monitoring strategies is therefore urgently needed. The current study provides helpful information in this respect as it provides a detailed description of a standardized remote monitoring protocol and reports both the frequency and therapeutic consequences of remote monitoring alerts in depth with a mean follow-up of almost three years.

A first observation is that alerts were frequent, with an incidence of approximately 3 per patient-year of follow-up. In the majority of cases (60%), these alerts resulted in the patient being contacted for further evaluation and/or therapeutic intervention. In addition, progress has been made in recent years to reduce transmission problems as these alerts represented only 8% of all incoming alerts. Furthermore, technical alarms for lead and device problems were also relatively infrequent (8%) and will probably decrease over time with further technical innovations. In contrast, rhythm alerts were the most frequent and triggered further therapeutic interventions in 22% of cases. Bioimpedance alerts triggered frequent phone contacts (91%), but led to few therapeutic interventions (15%), indicating a low specificity of these alerts. This may suggest that when financial or logistic constraints apply

to a remote follow-up program for CRT, prioritizing focus on rhythm alerts could be an efficient strategy. In this study, cardiology consultation was the most frequently triggered intervention (18%), but many patients were also helped through instructions by phone (63%) or via their general practitioner (13%). Only a very small proportion of alerts (<5%) resulted in hospital admission. Remote monitoring as organized in the current study did not lead to more frequent visits to the emergency room for trouble-shooting, as has been observed in some studies [38]. Overall admission rate in this study at one year of follow-up was 12%. Our results emphasize that remote follow-up of CRT patients is feasible with direct feedback loops that require minimal input from physicians, but rely on specialized caregivers trained in electrophysiology and heart failure with patients having a low threshold to contact caregivers for any question and the dedicated nurses subsequently play a pivotal role to decide the level of care that is needed. With such an approach, clinical outcome was comparable with the literature with one and three-year survival rates of respectively 97% and 88% and respectively 92% and 85% were free from hospital admissions with a primary diagnosis of heart failure [28].

This study should be interpreted in the light of some limitations. First, it was a relatively small and single-center study, which may impact its external validity. Secondly, while clinical outcomes may be compared to other contemporary CRT cohorts, study inclusion was based on voluntary participation to remote follow-up and there was no control group. Therefore, one cannot exclude the possibility that enrolled patients were more motivated for follow-up with better expected adherence to therapies. However, at our center, the overwhelming majority (>99%) of patients agrees with remote follow-up, reducing the risk for selection bias. Finally, remote monitoring options for CRT-P devices were limited at the start of the study, leading to less such patients included.

CONCLUSION

Remote follow-up of CRT patients resulted in 3.12 alerts per patient-year of follow-up: 0.23 technical device alerts versus 2.64 disease-related alerts per patient-year of follow-up. Rhythm and bioimpedance alerts constituted the majority of incoming alerts (respectively 1.43 versus 0.98 alerts per patient year of follow-up) and triggered an intervention in 22% and 15%, respectively. A transition from device to disease monitoring has been observed in recent years. By structured notification handling according to standardized questionnaires and decision trees in a well-organized remote monitoring follow-up program, survival rates reach comparable results as those from randomized controlled trials. In the future, this disease management will only improve by enhanced device algorithms and multi-parameter handling.

SUPPLEMENTAL MATERIAL

Table S 1.1: Detailed overview of the rhythm and sole bioimpedance alerts and the triggered interventions.

Type of alert	Number of alerts	Further action by investigational site	Triggered intervention				
			Diuretic adjustment	Other medication adjustment	General practitioner consultation	Cardiology consultation	Emergency room referral
Rhythm-related alerts							
VF	9 (1%)	6 (67%)	0	0	0	4 (67%)	2 (33%)
VT with shock	5 (1%)	2 (40%)	0	0	0	2 (100%)	0
VT with ATP	38 (5%)	14 (37%)	0	3 (21%)	0	8 (57%)	3 (21%)
VT without intervention	73 (9%)	19 (26%)	0	3 (16%)	5 (26%)	9 (47%)	3 (16%)
AF	138 (18%)	47 (34%)	2 (4%)	6 (13%)	6 (13%)	34 (72%)	4 (9%)
SVT not otherwise specified	100 (13%)	27 (27%)	2 (7%)	6 (22%)	8 (30%)	17 (63%)	0
Non-sustained VT	143 (18%)	13 (9%)	1 (8%)	4 (31%)	2 (15%)	7 (54%)	0
PVC	104 (13%)	18 (17%)	2 (11%)	2 (11%)	0	15 (83%)	0
<90% BIV pacing	136 (18%)	39 (29%)	4 (10%)	6 (15%)	2 (5%)	30 (77%)	3 (8%)
Decreased HR variability	18 (2%)	2 (11%)	0	0	0	2 (100%)	0
Other	11 (1%)	2 (18%)	0	0	0	2 (100%)	0
Sole bioimpedance alerts	485	73 (15%)	38 (52%)	4 (5%)	16 (22%)	20 (27%)	0

Data are expressed as n(%). VF, ventricular fibrillation; VT, ventricular tachycardia; ATP, antitachycardia pacing; AF, atrial fibrillation; SVT, supraventricular tachycardia; PVC, premature ventricular complexes; BIV, biventricular; HR, heart rate.

CHAPTER 2

Bioimpedance alerts from cardiovascular implantable electronic devices: observational study of diagnostic relevance and clinical outcomes

Smeets CJ, Vranken J, Van der Auwera J, Verbrugge FH, Mullens W, Dupont M, Grieten L, De Cannière H, Lanssens D, Vandenberk T, Storms V, Thijs IM, Vandervoort PM

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ABSTRACT

Background: The use of implantable cardioverter-defibrillators (ICDs) and cardiac resynchronization therapy (CRT) devices is expanding in the treatment of heart failure. Most of the current devices are equipped with remote monitoring functions, including bioimpedance for fluid status monitoring. The question remains whether bioimpedance measurements positively impact clinical outcome.

Objective: The aim of this study was to provide a comprehensive overview of the clinical interventions taken based on remote bioimpedance monitoring alerts and their impact on clinical outcome.

Methods: This is a single-center observational study of consecutive ICD and CRT patients (n=282), participating in protocol-driven remote follow-up. Bioimpedance alerts were analyzed with subsequently triggered interventions.

Results: A total of 55.0% (155/282) of patients had an ICD or CRT device equipped with a remote bioimpedance algorithm. During 34 (SD 12) months of follow-up, 1751 remote monitoring alarm notifications were received (2.2 per patient-year of follow-up), comprising 2096 unique alerts (2.6 per patient-year of follow-up). Since 591 (28.2%) of all incoming alerts were bioimpedance-related, patients with an ICD or CRT including a bioimpedance algorithm had significantly more alerts (3.4 versus 1.8 alerts per patient-year of follow-up, $P<.001$). Bioimpedance-only alerts resulted in a phone contact in 91.04% (498/547), which triggered an actual intervention in 15.90% (87/547) of cases since in 75.14% (411/547) reenforcing heart failure education sufficed. Overall survival was lower in patients with a cardiovascular implantable electronic device with a bioimpedance algorithm; however, this difference was driven by differences in baseline characteristics (adjusted hazard ratio of 2.118, 95% CI 0.845-5.791). No significant differences between both groups were observed in terms of the number of follow-up visits in the outpatient heart failure clinic, the number of hospital admissions with a primary diagnosis of heart failure, or mean length of hospital stay.

Conclusions: Bioimpedance-only alerts constitute a substantial amount of incoming alerts when turned on during remote follow-up and triggered an additional intervention in only 16% of cases since in 75% providing general heart failure education sufficed. The high frequency of heart failure education that was provided could have contributed to fewer heart failure-related hospitalizations despite significant differences in baseline characteristics.

INTRODUCTION

Cardiac resynchronization therapy (CRT) devices and implantable cardioverter-defibrillators (ICDs) are guideline-recommended treatments for heart failure with reduced ejection fraction, left bundle branch block, very wide QRS complex (>150 ms), or sudden cardiac death [49, 50]. The use of these cardiovascular implantable electronic devices (CIEDs) is rapidly increasing with 51,274 and 85,289 patients, respectively, receiving a CRT or ICD device in Europe in 2013 [51]. Remote follow-up of this group is slowly finding its way in routine clinical practice since it may hold major advantages for patients, health care workers, and society [18]. Over the last decade, several CIED manufacturers have marketed thoracic impedance measurement algorithms integrated into their devices. Changes in bioimpedance measurements reflect changes in intrathoracic fluid status and are evaluated based on a vendor-specific computer algorithm. Early investigations reported an inverse correlation with pulmonary capillary wedge pressure and fluid balance [32] and a higher sensitivity and lower unexplained detection rate compared to acute weight changes [37]. In addition, a decrease in bioimpedance happened even before clinical manifestation of heart failure worsening and before hospital admission for fluid overload [32]. These algorithms are therefore very promising for the early detection of impending decompensated heart failure and enable the possibility to adjust treatment strategies in order to prevent heart failure hospitalization [34, 35]. Despite early investigations showing promising results, larger randomized trials have revealed disappointing outcomes [38-41]. A shortcoming in current studies is the lack of standardization and information as to what clinical actions are coupled to remote bioimpedance alerts, making it difficult to conclude on its clinical impact.

In 2010, a dedicated remote follow-up program of heart failure patients with a CIED was started at Ziekenhuis Oost-Limburg (Genk, Belgium). Dedicated nurses, trained in electrophysiology, device follow-up, and heart failure pathophysiology, review all incoming alerts in a systematic and standardized manner with automatic interventions triggered by protocol-based, guideline-recommended care [55, 56]. In this observational registry study, we closely analyzed all bioimpedance alerts and subsequent triggered interventions from OptiVol and OptiVol 2.0 (Medtronic PLC) and CorVue (St. Jude Medical LLC) CIEDs using the default alert settings, and we studied their impact on clinical outcome. As such, the current research builds on previous studies since these lack this level of detail.

METHODS

STUDY DESIGN

This is an observational registry study of ICD and CRT patients from a single tertiary care center (Ziekenhuis Oost-Limburg, Genk, Belgium) implanted with the devices between February 2010 and May 2013. Since February 2010, all patients receiving either an ICD or CRT device with remote monitoring capabilities were asked to participate voluntarily in a remote follow-up program. The type of CIED that was implanted was solely based on the device's therapeutic capabilities (right ventricular pacing, biventricular pacing, and antitachycardia treatment) and was left to the discretion of the treating physician. For this analysis, only patients enrolled in remote follow-up within 6 months after device implantation are included. Patient baseline information is collected at the time of device implantation. All participants provided written informed consent and were followed until February 1, 2015. The study complies with the Declaration of Helsinki, and the study protocol was approved by the local committee on human research.

REMOTE FOLLOW-UP AND ALERTS

A vendor-specific transmission device, usually installed in the patient's bedroom, collected disease- and device-related data from the CIED that was transmitted to an online database accessible to the multidisciplinary heart failure team. All alerts were interpreted on weekdays by dedicated nurses trained in electrophysiology, device follow-up, and heart failure pathophysiology; notifications received during weekends were read on Monday. Daily alert transmissions were generated when predefined alarm thresholds were crossed. Besides alert transmissions, each device was programmed to send a scheduled transmission report monthly. Alerts were categorized according to their nature into technical (missed scheduled transmission and technical device problems) or clinical (rhythm, bioimpedance, and miscellaneous [changes in daily activity, heart failure management, etc]) alerts. Our study focuses on all bioimpedance-related alerts.

BIOIMPEDANCE MEASUREMENTS

Since bioimpedance is measured from the electrode lead to the device can, any thoracic fluid change including vascular, interstitial or alveolar fluid results in a change in its value. Therefore, bioimpedance measurements are not specific to one disease.

In 2004, Medtronic was the first company to introduce a bioimpedance algorithm, known as the OptiVol algorithm, in its CIEDs. For the OptiVol algorithm, bioimpedance is measured

in a semicontinuous way every 20 minutes between 12 AM to 5 PM. The algorithm starts 34 days postimplant and generates 2 separate graphs: 1 displays the raw bioimpedance data and the other indicates the accumulated change between the daily bioimpedance measurements and a dynamic reference impedance. The latter one, called the OptiVol fluid index, triggers an alarm when a predefined threshold is met, by default set at 60Ω [32]. The OptiVol fluid index graph may indicate an event, while the raw bioimpedance graph may indicate the severity of the event [42, 57]. In 2010, Medtronic launched OptiVol 2.0, an updated version of the initial bioimpedance algorithm. The updated version is intended to lower the number of false positive alerts. Alterations include a faster changing reference after initialization, a slower accumulating fluid index for an initial duration of the event in patients with higher day-to-day variability in impedance, and a fluid index which accumulates only over the last 30 days [42]. An initial study has reported a 40% decrease in unexplained detections [58]. In our study, the default OptiVol threshold settings were used.

In 2009, St Jude Medical introduced its own bioimpedance algorithm, known as CorVue. There are some fundamental differences compared to the OptiVol algorithms. CorVue also measures intrathoracic impedances in a semicontinuous way every 2 hours around the clock. In addition, depending on the type of lead, the impedance is measured in 1 (ie, unipolar leads) or multiple vectors. Within the first 2 weeks, the algorithm starts to build a reference impedance which is a long-term moving average (ie, over the last 144 or 168 measurements for CRT or ICD devices, respectively). Afterward, a short-term moving average (ie, over the last 12 measurements) of multivector impedance measurements builds the daily impedance. A bioimpedance alert is triggered when the daily impedance is lower than the reference impedance for a programmable duration known as the congestion trigger (ie, nominal 13 days for ICDs, 14 days for CRT-D, and 16 days for CRT-P) [42]. In our study, the default congestion trigger settings were used.

The presence of a bioimpedance algorithm is dependent on the CIED manufacturer: most Medtronic and St Jude devices are equipped with a bioimpedance algorithm and generate bioimpedance alerts, while Biotronik and Boston Scientific devices do not generate any bioimpedance alerts. In our study, the choice of CIED brand implanted in a particular patient is completely random. Therefore, the presence or absence of a bioimpedance algorithm in this patient population is also randomly assigned.

INTERVENTION PROTOCOL FOR BIOIMPEDANCE ALERTS

All incoming bioimpedance alerts were deemed to be of potential clinical relevance and resulted in a phone contact between the interpreting nurse and the patient. In exceptional cases, where the patient had an in-hospital check-up very recently or had one planned in the near future, a phone contact was not initiated. A custom-made heart failure questionnaire was used to identify potential causes for the bioimpedance alert [56, 59]. Additional questions could be asked at the discretion of the health care worker in order to gain better insight. Appropriate feedback and general heart failure education (ie, stress the importance of the conservation of a salt-free diet and fluid restrictions) were always provided. Further action was protocol-driven in consultation with a dedicated heart failure specialist.

OUTPATIENT FOLLOW-UP

Patients enrolled in remote follow-up visit the outpatient cardiology clinic for device and clinical heart failure follow-up at 6 weeks after implantation and subsequently every 6 months with a minimum of 2 visits per year as per standard practice in our institution. Patients in this study were followed until death, exclusion from remote follow-up, heart transplantation, or February 1, 2015, whichever came first.

STATISTICAL ANALYSIS

Demographic and functional characteristics were compared using descriptive statistics. Continuous variables are expressed as mean and standard deviation (SD) if normally distributed or median and interquartile range (IQR) otherwise. Survival curves were constructed according to the Kaplan-Meier method, with the log-rank test used for comparison among groups. Unadjusted and adjusted hazard ratios (HRs) were calculated by Cox regression analysis with Firth's penalized likelihood correction. To define statistical differences between both groups, the independent samples student *t* test and Mann-Whitney U test were used for normally and not normally distributed continuous variables, respectively, and the chi-square test and Fisher exact test were used accordingly for categorical variables. To define statistical differences between the different bioimpedance algorithms, the Kruskal Wallis test was used. The significance level for tests was 2-sided with alpha = .05. All statistical analyses were performed using IBM SPSS Statistics 24.0 (IBM Corp); SAS 9.4 (SAS Institute Inc) was used for Cox regression with Firth's penalization.

RESULTS

STUDY POPULATION

From a total of 506 patients with a CIED implanted during the study period, 110 patients were excluded due to the presence of a cardiac resynchronization therapy pacemaker (CRT-P) device without remote monitoring capabilities, 82 patients were excluded because the remote monitoring program was started more than 6 months after device implantation, 22 patients refused study participation, and 10 patients were excluded due to follow-up in another center. The final study population consisted of 282 patients: 155 (55.0%) patients with a CIED equipped with a bioimpedance algorithm (CIED^{+}) and 127 (45.0%) patients with a CIED without an available bioimpedance algorithm (CIED^{-}) (Figure 2.1). In total, 110 (39.0%) Medtronic, 105 (37.2%) St. Jude Medical, 61 (21.6%) Biotronik, and 6 (2.1%) Boston Scientific CIEDs were implanted.

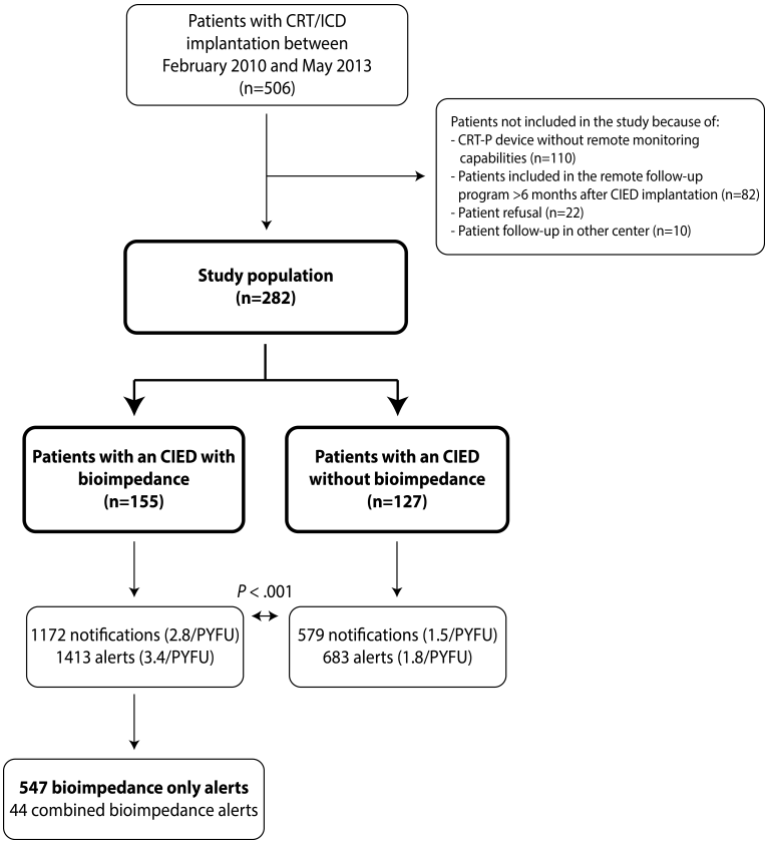

Figure 2.1: Flowchart of the study. CRT, cardiac resynchronization therapy; ICD, implantable cardioverter defibrillator; CIED, cardiovascular implantable electronic devices; PYFU, patient-years of follow-up.

Respectively, 26.4% (41/155), 43.2% (67/155), and 30.3% (47/155) of patients in the CIED+ population had a device implanted with Optivol, Optivol 2.0, and CoreVue algorithm. The median time interval between CIED implantation and start of remote follow-up was 1 day (IQR 1 to 2 days), with 81.9% (231/282) of patients included within 1 week. Patients were followed for 34 (SD 12) months leading to 801 cumulative patient-years of follow-up. The number of follow-up visits in the outpatient device clinic was 3.25 per patient-year of follow-up of which 93% were elective and 7% were triggered by remote monitoring. Baseline characteristics of the study population at the time of implantation are shown in Table 2.1.

Table 2.1: Baseline characteristics of the study population (n=282).

Variables	CIED with bioimpedance (n=155)	CIED without bioimpedance (n=127)	*P* value
Age, years	72 ± 12	70 ± 13	.12
BMI	27 ± 5	28 ± 6	.54
Male gender	123 (79%)	108 (85%)	.22
ICD	31 (20%)	59 (46%)	**< .001**
CRT-D	102 (66%)	57 (45%)	**< .001**
CRT-P	22 (14%)	11 (9%)	.15
Bioimpedance algorithm			
OptiVol	41 (27%)	/	
OptiVol 2.0	67 (43%)	/	
CorVue	47 (30%)	/	
NYHA functional class (II/III)	17 (16%) / 90 (83%) (n=109)	14 (24%) / 43 (73%) (n=59)	.42
Left ventricular ejection fraction, %	31 ± 12	34 ± 12	**.01**
QRS width, ms	145 ± 31	127 ± 32	**< .001**
Heart failure etiology			
Ischemic heart disease	86 (55%)	86 (68%)	**.04**
Dilated	13 (8%)	5 (4%)	.13
Valvular	3 (2%)	1 (1%)	.63
Hypertrophic	5 (3%)	3 (2%)	.73
Toxic	1 (1%)	2 (2%)	.59
Idiopathic	40 (26%)	17 (13%)	**.01**
Other etiology or no heart failure	7 (5%)	13 (10%)	.06
Comorbidities and risk factors			
Valvular surgery	18 (12%)	11 (9%)	.42
Atrial fibrillation	62 (40%)	51 (40%)	.98
Chronic obstructive pulmonary disease	23 (15%)	16 (13%)	.59
Chronic kidney disease	42 (27%)	31 (24%)	.61
Diabetes	32 (21%)	25 (20%)	.84
Family history of cardiovascular disease	34 (22%)	40 (31%)	.07
Arterial hypertension	59 (38%)	57 (45%)	.25
Hypercholesterolemia	59 (38%)	48 (38%)	.96
Smoking	151 (97%)	122 (96%)	.74
Medication use			
Renin-angiotensin system blocker	125 (81%)	102 (80%)	.94
Beta blocker	144 (93%)	109 (86%)	.052
Spironolactone	105 (68%)	68 (54%)	**.02**
Loop diuretic	76 (49%)	48 (38%)	.06
Digoxine	23 (15%)	18 (14%)	.88
Statin	85 (55%)	82 (65%)	.10
Calcium channel blockers	8 (5%)	15 (12%)	**.04**
Anti-diabetic medication	27 (17%)	22 (17%)	.98

Continuous data are expressed as mean ± SD if normally distributed or otherwise by median and IQR and dichotomous data are expressed as n(%). CIED, cardiovascular implantable electronic device; BMI, body mass index; ICD, implantable cardioverter-defibrillator; CRT, cardiac resynchronization therapy; NYHA, New York Heart Association.

REMOTE FOLLOW-UP NOTIFICATIONS/ALERTS AND INTERVENTIONS

During follow-up, the clinical call center handled 1751 remote monitoring notifications. Since a notification can contain multiple alerts, a total of 2096 unique alerts were received (ie, 2.6 alerts per patient-year of follow-up). Patients with a CIED^{+} had significantly more alerts than those with a CIED^{-}: 1413 (67.41%, 3.4 per patient-year of follow-up) and 683 (32.59%, 1.8 per patient-year of follow-up), respectively, P<.001. The amount of technical and arrhythmia alerts was similar in both patient groups. The higher number of alerts in the CIED^{+} population can be entirely attributed to bioimpedance alerts. The distribution of the different alert categories among both groups is shown in Figure 2.2.

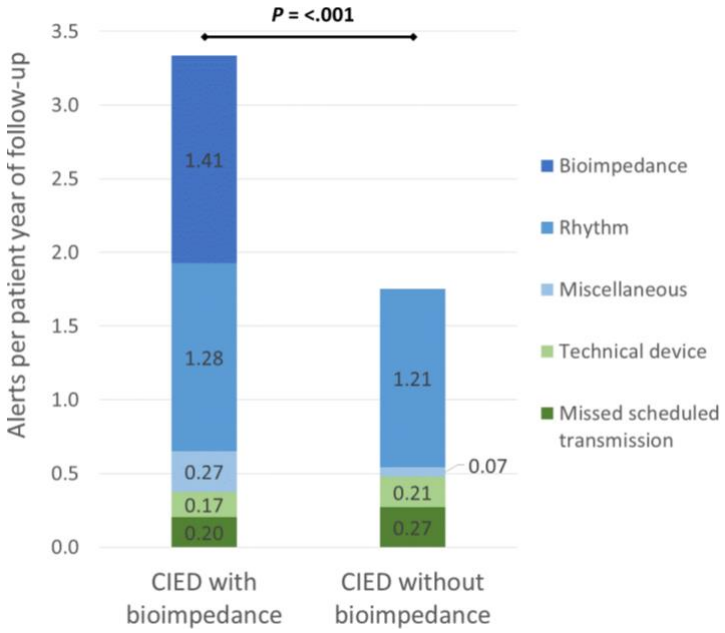

Figure 2.2: Frequency of alert categories with the number of alerts per patient year of follow-up for patients with a CIED with or without a bioimpedance algorithm. Disease-related alerts are marked in blue color tints and technical-related alerts in green color tints. CIED, cardiovascular implantable electronic device.

BIOIMPEDANCE NOTIFICATIONS AND INTERVENTIONS

During follow-up, 591 notifications including a bioimpedance threshold crossing were received for 111 of 155 (71.6%) patients. In 44 of these notifications, 1 or more additional alerts were combined resulting in 547 bioimpedance-only notifications. In 498 (91.0%) of bioimpedance-only notifications, the patient was contacted by phone and a standardized heart failure questionnaire was used. In 9.0% (49/547), a phone contact was not initiated

since the patient had an in-hospital check-up very recently or had one planned in the near future. In 75.1% (411/547) of bioimpedance-only notifications, only general heart failure education was given. An additional intervention was triggered in 15.9% (97/547) of cases (Figure 2.3, Left). In total, 97 interventions were performed (Figure 2.3, Right), including medication changes in 49.5% (48/97), referral to the general practitioner or cardiologist in 26.8% (26/97) and 22.7% (22/97) of cases, respectively, and in 1.0% (1/97) the patient was asked to visit the emergency room. A combination of different interventions for 1 bioimpedance alert is also possible.

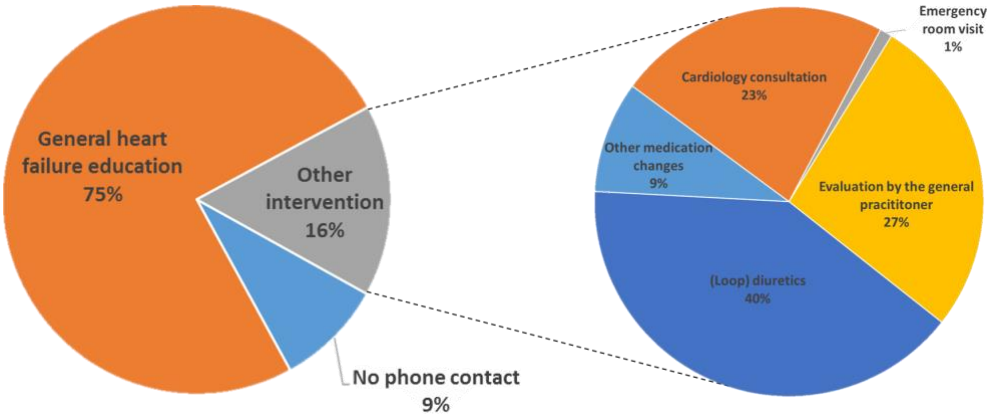

Figure 2.3: Overview of the interventions triggered during remote follow-up in the case of a bioimpedance-only alert.

DIFFERENT BIOIMPEDANCE ALGORITHMS

There was a statistically significant difference in number of bioimpedance alerts per patient-year between the different bioimpedance algorithms (χ^2=12.643, *P*=.002) (Figure 2.4). The updated OptiVol 2.0 algorithm (0.79 alerts per patient-year of follow-up) triggered significantly fewer bioimpedance alerts than OptiVol (1.67 alerts per patient-year of follow-up; *P*=.02) and CorVue (1.97 alerts per patient-year of follow-up; *P*=.005). No differences were observed concerning the distribution of interventions triggered by the different bioimpedance algorithms.

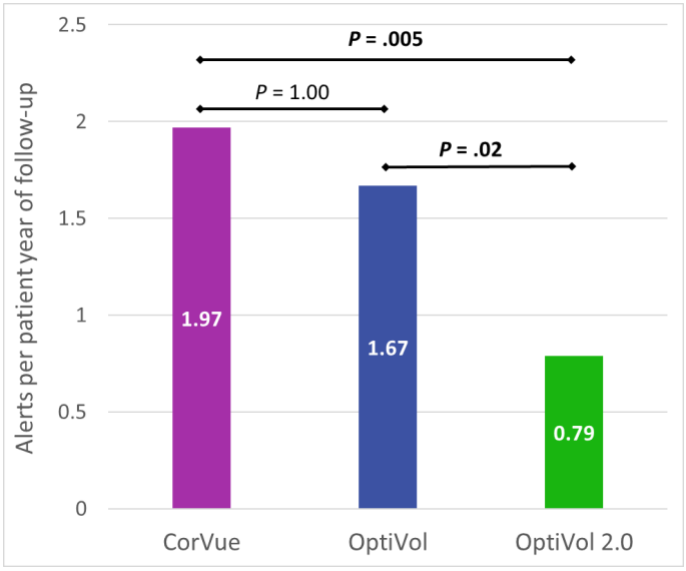

Figure 2.4: Overview of the amount of remote monitoring bioimpedance alerts per patient year of follow-up triggered by the different bioimpedance algorithms.

CLINICAL OUTCOME

At mean time of follow-up (ie, 34 months) 26 patients had died, leading to an overall survival rate of 90.8%. Seven patients died in the CIED$^-$ population compared to 19 in the CIED$^+$ population, leading to all-cause survival rates of 94.5% and 87.7%, respectively (*P*=.047) (Figure 2.5A). Most deaths were due to cardiovascular causes, with 6 in the CIED$^-$ population compared to 15 in the CIED$^+$ population (*P*=.10). No significant differences in survival rate were observed for the different bioimpedance algorithms.

At mean time of follow-up, 40 patients were hospitalized with a primary diagnosis of heart failure and hence 85.8% (242/282) of patients were free from heart failure–related hospitalization. No significant difference was observed between both groups (23/155, 85.2%, for CIED$^+$ versus 17/127, 86.6%, for CIED$^-$ at mean time of follow-up, *P*=.76) (Figure 2.5B), nor for the different bioimpedance algorithms (*P* = .95) (Figure 2.5C).

No significant differences were observed between both groups with respect to the number of elective follow-up visits in the outpatient heart failure clinic (*P*=.45) or the number of cardiac-related hospital admissions (*P*=.32). For those who had at least 1 cardiac-related hospital admission, median length of hospital stay was 6 (IQR 3 to 14) days. There was no significant difference for length of hospital stay between both groups or for the different bioimpedance algorithms.

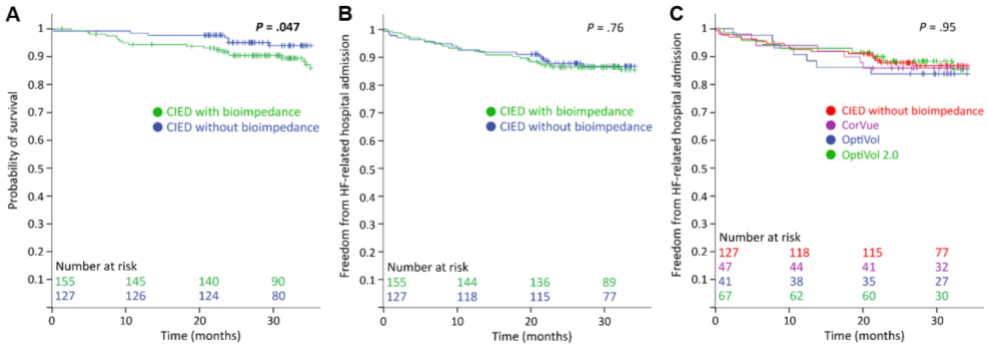

Figure 2.5: A: Probability of survival for patients with a CIED with or without a bioimpedance algorithm; B: Freedom from hospital admission with a primary diagnosis of heart failure for patients with a CIED with or without a bioimpedance algorithm; C: Freedom from hospital admission with a primary diagnosis of heart failure for the different bioimpedance algorithms. CIED, cardiovascular implantable electronic device.

Table 2.2 provides an overview of the unadjusted and adjusted Cox regression analysis with Firth's penalization. Presence of bioimpedance algorithms in the CIED resulted in a nonsignificant adjusted hazard ratio of 2.118 (95% CI 0.845-5.791) for all-cause death and 2.335 (95% CI 0.852-7.020) for cardiovascular death. Multivariate analysis indicated that age, ejection fraction, and QRS time contribute to the observed difference in survival rate between both groups.

Table 2.2: Cox regression analysis with Firth's penalization for clinical outcome measures.

Variables	Unadjusted hazard ratio			Adjusted hazard ratio*		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value
All-cause mortality	2.342	1.029-5.996	.047	2.118	0.845-5.791	.13
Cardiovascular mortality	2.168	0.881-6.082	.10	2.335	0.852-7.020	.12
Heart failure hospitalization	1.103	0.592-2.097	.76	1.284	0.655-2.562	.47

CI, confidence interval; HR, hazard ratio. *Hazard ratios were adjusted for significant differences in baseline characteristics including ICD use, CRT-D use, left ventricular ejection fraction, QRS width, ischemic etiology of heart failure and spironolacton use and clinically relevant parameters including age, gender and loop diuretic use.

DISCUSSION

Although many newly implanted CIEDs have a built-in bioimpedance algorithm, it remains unclear whether bioimpedance measurements contribute to improved clinical outcome when incorporated in a standardized heart failure care path including remote follow-up. In this paper, we present a comprehensive overview of bioimpedance alerts and subsequent triggered interventions in patients with either a CRT or ICD device enrolled in a dedicated, protocol-driven, remote follow-up program in a single Belgian tertiary care center.

Major insights include the following:

(1) Patients with a CIED equipped with a bioimpedance algorithm have significantly more remote monitoring notifications
(2) In 75% of bioimpedance-only alerts, reenforcing heart failure education was the only action taken; in 16% of cases, an additional intervention was triggered; and in 9%, the patient was not contacted
(3) For the different bioimpedance algorithms, significant differences were observed for the number of bioimpedance alerts but not triggered interventions or clinical outcome
(4) Although patients with a CIED equipped with a bioimpedance algorithm have a significantly lower survival rate driven by differences in baseline characteristics, there was no difference in heart failure–related hospitalizations.

An important observation that merits further attention is the high number of patients with bioimpedance-only alerts who were contacted and were given heart failure education only without any additional interventions. This may indicate a high sensitivity but low specificity of these alerts to detect emerging congestion as well as the existence of a temporal lag between a bioimpedance alert and clinical manifestation of heart failure worsening [32, 34, 35, 38-41, 60-62]. Therefore, a possible explanation for the rather low number of additional interventions could be that due to these bioimpedance alerts, patients are contacted in the early phase of emerging congestion. By the fact that patients are contacted and general heart failure education is repeated, it is possible that their perception of disease awareness strengthens (i.e. importance of fluid and salt restriction, heart failure medication intake and physical activity), avoiding further worsening of congestion.

The updated OptiVol 2.0 algorithm triggered significantly fewer bioimpedance alerts than the other two bioimpedance algorithms. This corresponds to literature, where a 40% decrease in unexplained bioimpedance alerts was observed [58]. However, no changes in

intervention strategy or impact on clinical outcome compared to the other bioimpedance algorithms was observed. Although improvements to bioimpedance algorithms have already been made, this could still indicate that intrathoracic impedance is currently wrongly measured, handled, or interpreted. In the majority of cases, the bioimpedance alarm threshold is set to default. These thresholds should be individually adjusted in order to improve sensitivity and specificity rates, as suggested by previous research [34, 35, 42]. Another possibility to improve intrathoracic impedance measurements is controlling the circumstances in which measurements are performed. Currently, measurements are performed under different circumstances throughout the day. Since bioimpedance measurements are also influenced by motion and body posture, reliability could be improved by a lower number of measurements that are all performed under the same posture (eg, during the night when lying in a particular posture). Finally, instead of alerts triggered by bioimpedance crossings alone, integration with other parameters currently monitored by implantable electrical devices (eg, patient activity, heart rate variability, average ventricular rate) will provide a more efficient tool to predict heart failure worsening [59].

Patients with a CIED$^+$ showed a lower overall survival rate. However, this difference can be explained by differences in baseline characteristics between both groups rather than the presence of a bioimpedance algorithm. Indeed, multivariate analysis indicated a significant hazard ratio for age, ejection fraction, and QRS time and a nonsignificant adjusted hazard ratio for the presence of a bioimpedance algorithm in the CIED. Concerning heart failure–related hospitalizations, both groups showed similar results. This could indicate a potential benefit of bioimpedance algorithms on clinical outcome since, based on baseline characteristics, one would expect a higher number of heart failure–related hospitalizations in the CIED$^+$ group. This could mean that the high frequency of heart failure education provided in cases of a bioimpedance alert could have prevented heart failure–related hospitalizations.

When reviewing available literature, it is clear that the success rate of remote monitoring is strongly dependent on optimal workflow with standardized protocols and appropriate feedback loops. The DOT-HF (Diagnostic Outcome Trial in Heart Failure) trial [38], where patients received an audible alert in case of a bioimpedance crossing, showed that providing wrong feedback can even induce an increase in hospital admissions. In the LIMIT-CHF (Lung Impedance Monitoring in Treatment of Chronic Heart Failure) trial [42], bioimpedance alerts triggered empirical changes in diuretic dose, which did not significantly prevent heart failure–related hospitalizations. Moreover, the OPTILINK-HF (Optimization of Heart Failure

Management using OptiVol Fluid Status Monitoring and CareLink) trial [41] employed a similar approach of protocol-driven remote monitoring as used in our center and reported no significant improvements in clinical outcome. Shortcomings in this trial were the single-parameter follow-up, suboptimal data transmission, and the absence of a centralized monitoring team. In our study, a multiparameter approach was used and all incoming alerts were handled in a standardized way. In addition, remote follow-up in our center is performed by a small team of dedicated heart failure nurses who have close personal contact with the patients. Furthermore, our nurses are operating from inside our tertiary care center and hence have daily contact with the treating physician. This approach facilitates protocol standardization and has already been shown to be effective in the IN-TIME (Influence of Home Monitoring on Mortality and Morbidity in Heart Failure Patients With Impaired Left Ventricular Function) trial [28]. It is clear that there is not just one remote monitoring approach, but a high variability exists and hence each approach needs to be assessed on its individual merit. In our study, the question remains to what extent reinforcement of heart failure education is crucial in remote bioimpedance monitoring and impacts clinical outcome.

STUDY LIMITATIONS

This study should be interpreted in the light of some limitations. First, this is a relatively small single-center observational registry study with classic limitations associated with this type of study design, thereby making the study results mainly hypothesis-generating. Although a nonsignificant adjusted hazard ratio was obtained for the presence of bioimpedance algorithms in the CIED, a potential power problem can be present in the all-cause survival analysis due to the rather low sample size and low event rates. Next, since the presence of a bioimpedance algorithm is dependent on CIED manufacturer and is therefore random, our study is a nonrandomized clinical trial. A possible selection bias could be present due to the device indication. However, the assignment of the type of CIED that was implanted was solely based on the device's therapeutic capabilities (RV pacing, biventricular pacing, and antitachycardia treatment) and was left to the discretion of the treating physician. Other diagnostic information, for example, the presence or absence of bioimpedance algorithms in the CIED, was not taken into consideration when assigning the CIED type or brand. In the CIED$^+$ population, more CRT-D devices are present since these devices were first equipped with bioimpedance algorithms. In general, patients who receive a CRT-D device have more advanced heart failure than patients who receive an ICD device. This can explain the differences in baseline characteristics (eg, older population with a lower

left ventricular ejection fraction and broader QRS complex). Finally, study inclusion was based on voluntary participation to remote follow-up. Therefore, one cannot exclude the possibility that enrolled patients were more motivated for follow-up with better expected adherence to therapies. However, the majority (>95%) of patients agree to remote follow-up, reducing the risk for selection bias.

CONCLUSION

In patients with a CIED with a bioimpedance algorithm, bioimpedance alerts constitute almost half (42%) of incoming alerts when turned on during remote follow-up. Repeating general heart failure education by phone sufficed in 75%, and an additional intervention was performed in 16% of cases. The high frequency of heart failure education that was provided could have contributed to fewer heart failure–related hospitalizations despite significant differences in baseline characteristics. Future trials are needed to verify whether bioimpedance algorithms can only be used to trigger heart failure education or if they have an intrinsic value to change treatment strategies. In addition, future improvements in the way bioimpedance is measured, handled, or interpreted could further increase its clinical relevance. Before bioimpedance measurements can be widely implemented in clinical practice, larger multicenter randomized controlled trials are required.

CHAPTER 3

Detection of subclinical transient fluid accumulation during pregnancy in a patient with an implantable cardioverter defibrillator and OptiVol® fluid monitoring algorithm

Smeets CJ*, Lanssens D*, Gyselaers W, Bertrand PB, Grieten G, Vandervoort PM

*shared first authorship.

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CASE PRESENTATION

The case of a 32-year-old female patient who developed an OptiVol 2.0 fluid index crossing at $7^{3/7}$ weeks of pregnancy, primigravida, is reported. An implantable cardioverter defibrillator (ICD, Protecta™ XT VR, Medtronic, Brussels, Belgium) with second generation fluid build-up detection algorithm, was implanted in 2011 after an episode of sudden cardiac death related to the Marfan syndrome with secondary heart failure [63, 64]. In 2013, she underwent valve sparing aortic root replacement and mitral valve repair surgery because of aortic root dilation and severe mitral valve regurgitation (prolapse). She has been in routine follow-up since, with dilated left ventricular dimensions and borderline ejection fraction. The patient was included in the remote monitoring follow-up program of Ziekenhuis Oost-Limburg (Genk, Belgium) prior to conception by oocyte donation in April 2014.

In the early phase of pregnancy, at $7^{3/7}$ weeks, the patient developed an OptiVol 2.0 fluid index crossing (Event 1) (Figure 3.1). This crossing triggered an alert that was handled by specialized remote monitoring nurses. After thorough analysis of the alert and investigation of the other parameters, which seemed to be normal, the patient was contacted by phone interview to identify possible causes of this fluid buildup alert. The interview contained a structured questionnaire that can identify (early) signs of fluid retention, including shortness of breath and the presence of edema. The patient was asymptomatic, responded negative to all questions and consequently no further actions were undertaken. The OptiVol 2.0 fluid index crossing was closely monitored further.

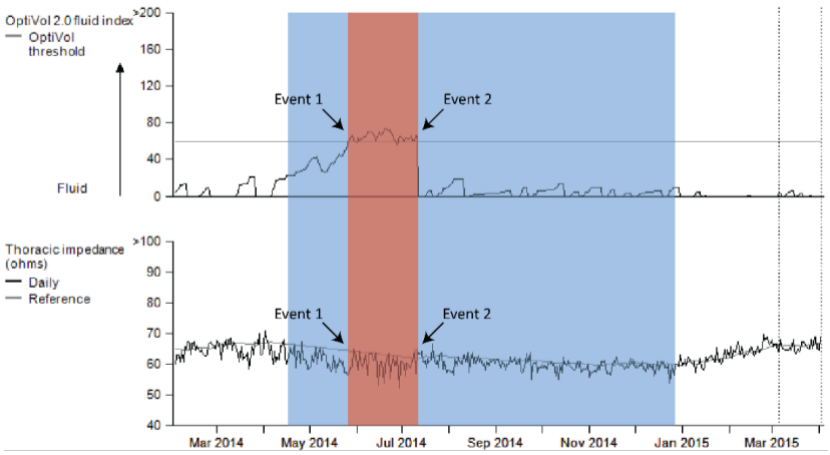

Figure 3.1: Overview of the OptiVol 2.0 information from an implantable cardioverter defibrillator. Blue box: gestation period; Red box: period of fluid index crossing; Red arrows: OptiVol crossing which triggers the fluid built up alert (Event 1); Green arrows: reset of the fluid index which corresponds to the end of the fluid built up alert (Event 2).

During the gestational period, thoracic impedance values kept decreasing (i.e. fluid accumulation). Significant difference in thoracic impedance values is found between the means before pregnancy vs. the second trimester of pregnancy ($p<0.01$) and second trimester of pregnancy vs. post-pregnancy ($p<0.01$). After delivery, thoracic impedance values recovered to pre-pregnancy values ($p=0.79$) (Figure 3.2).

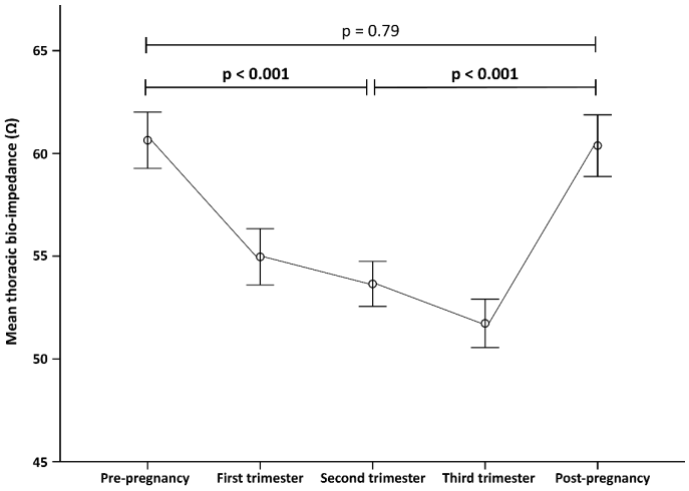

Figure 3.2: Mean thoracic bio-impedance values with 95% confidence intervals. p-values were calculated via independent t-test.

Interestingly, the OptiVol fluid index already recovered at week $13^{3/7}$ because of a crossing event between the daily thoracic impedance value and the reference signal (Event 2). No further OptiVol events were identified during the rest of the pregnancy (Figure 3.1). At 38 $^{4/7}$ weeks of gestation, a healthy boy of 3370g was delivered by C-section (breech presentation) with an Apgar score of 9 - 10 - 10. There were no obstetric complications for the mother, neither for the neonate.

DISCUSSION

The case of a pregnant woman, suffering from the Marfan syndrome, who received an OptiVol 2.0 fluid index crossing alarm through an implantable cardioverter defibrillator at $7^{3/7}$ weeks of pregnancy was presented. At pregnancy onset, thoracic impedance values decreased significantly. It is known that during pregnancy total fluid content, especially extracellular water, of the pregnant mother increases [65, 66]. These results are well in line with our findings indicating that a possible explanation for the OptiVol crossing is due to fluid buildup during pregnancy and after delivery the total fluid content shifts back to normal values. Current findings indicate a significant decrease in thoracic impedance, indicating an

increase in thoracic fluid content, at gestation onset. Based on the bioimpedance signal, the thoracic fluid content remained at a higher level during the whole pregnancy and started to recover to initial pre-pregnancy values immediately after delivery.

Importantly, the OptiVol crossing alert was only present from week $7^{3/7}$ and already disappeared at week $13^{3/7}$, although the raw bio-impedance remained at the same level and even slightly decreased further during pregnancy, indicating a further increase in thoracic fluid content. OptiVol is a fluid index measurement and indicates an accumulation of the difference between the daily impedance and dynamic reference impedance and is more an indication whether an event may occur in the near future or has occurred in the past. Since the fluid index takes into account a dynamic reference impedance value, it constantly adjusts for the new bio-impedance values. In fact, the reference impedance works as the patient's own control and the fluid index resets when the reference line is met. The thoracic impedance on the contrary gives a better estimation of thoracic fluid content since it plots the raw data measured from the right ventricular coil to the device can pathway and clearly represents the status of the patient's impedance or thoracic fluid status. Since the OptiVol alert is triggered only by the fluid index and not by the raw bioimpedance data, it can give a false sense of security, the alert can disappear, although fluid has accumulated and may be still present or ongoing. This clearly demonstrates the importance on how a remote fluid accumulation alert is handled in daily practice. In this case, a pregnancy has a controlled change in thoracic fluid content, but in other pathologies such as congestive heart failure, these changes are causing disease worsening. It should be considered that OptiVol is only an alert indicator but not an indicator to monitor progression of fluid status since the index is not a quantified measure. Thus, for good clinical practice it is not only important to look at the fluid index, which triggers the alert, but more importantly, the raw bioimpedance data has to be considered, even when the alert disappears.

CONCLUSION

This case clearly demonstrated the presence of a significantly higher thoracic fluid content during the total gestational period, with a rapid recovery to initial pre-pregnancy values after delivery, measured with an implantable cardioverter defibrillator. It was demonstrated that fluid accumulation, which is subclinical and transient, already starts very early during pregnancy and stays present until delivery. In addition, it became clear that the way remote OptiVol fluid crossing alerts are currently evaluated in clinical practice needs to be handled with caution.

CHAPTER 4

Intrathoracic fluid changes from preconception to postpartum as measured by bioimpedance monitoring

Smeets CJ*, Lanssens D*, Vandervoort PM, Grieten L, Gyselaers W

*shared first authorship.

Submitted

ABSTRACT

Background: The OptiVol fluid status monitoring system of implantable cardioverter defibrillators (ICD) continuously measures intrathoracic impedance, which strongly relates to intrathoracic fluid content and allows timely diagnosis of intrathoracic fluid retention. Postconceptional maternal systemic vasodilatation is reported, triggering a cascade of cardiovascular adaptive changes.

Case presentation: Intrathoracic impedance was remotely monitored from preconception to postpartum in a woman with an ICD. At 6 and 20 weeks, 2 significant changes were recorded, suggestive for thoracic fluid accumulation. After normal outcome, postpartum intrathoracic impedance returned to preconception values.

Conclusions: Intrathoracic impedance monitoring allows remote follow-up of gestational changes in maternal body fluid status. When these changes could be measured non-invasively, intrathoracic impedance monitoring may be a potential beneficial monitoring asset during high-risk pregnancy for longitudinal assessment of maternal hemodynamic changes in early pregnancy and should be evaluated in clinical trials.

BACKGROUND

The case of a pregnant woman with an implantable cardioverter defibrillator (ICD, Evera™ XT DR, Medtronic, Brussels, Belgium) and second generation fluid build-up detection algorithm, implanted for the presence of the Long QT Syndrome, is presented. She was included in two remote monitoring follow-up programs, a cardiac remote monitoring program for her ICD device and an obstetric remote monitoring program for the early detection of hypertension in high risk pregnancies. In contrast to first generation cardiovascular implantable electronic device, modern ICD devices also enable device-based diagnostic remote monitoring[1]. The OptiVol® fluid status monitoring system continuously measures intrathoracic impedance which strongly relates to intrathoracic fluid content and allows for timely diagnosis of thoracic fluid retention. Using the broad concept of Ohm's law, intrathoracic impedance can be measured by delivering a small alternating current between the defibrillator's right ventricular coil and the device, meanwhile measuring the corresponding voltage drop and hence the electrical resistance. There is an inverse relation between intrathoracic impedance and thoracic fluid content [33]. Important intrathoracic impedance changes are remotely signaled to clinicians by automated alerts. The OptiVol system takes into account a dynamic reference intrathoracic impedance value and constantly adjusts for newly measured bioimpedance values. The OptiVol fluid index measure indicates the accumulation of the difference between the daily (raw) impedance and dynamic reference impedance and therefore increases gradually. It triggers an alarm when a predefined threshold is crossed, by default set at 60Ω. In the current study, the default OptiVol threshold setting was used. The reference impedance works as the patient's own control and the fluid index immediately resets when a new (raw) bioimpedance measure crosses the reference line. The raw intrathoracic impedance measurements give an estimation of changes in a patient's thoracic fluid content. It is known that important cardiovascular adaptations occur during pregnancy to accommodate for fetal requirements [67]. Vasodilatation has been observed within the first weeks after conception, before placentation is complete, and triggers a cascade of cardiovascular adaptive changes throughout pregnancy until postpartum [67]. In addition, several research groups reported an early gestational increase of thoracic fluid content, especially the extracellular component [65, 66]. However, these groups only performed bioimpedance measurements at specific moments during and after the gestational period. This is the first case report showing longitudinal and semi-continuous thoracic bioimpedance measurements before, during and after an uncomplicated pregnancy.

CASE PRESENTATION

The case of a 31-year-old female patient who experienced a thoracic impedance alert twice during gestation, is presented. This was observed via an implantable cardioverter defibrillator (ICD, Evera™ XT DR, Medtronic, Brussels, Belgium) with second generation fluid build-up detection algorithm (OptiVol® 2.0), implanted in 2003 after an episode of sudden cardiac arrest related to the Long QT Syndrome type intrathoracic impedance [68]. She has been in routine follow-up since and was included in a cardiac remote monitoring follow-up program since February 2015, prior to conception. Five weeks before conception, the patient developed an OptiVol 2.0 fluid index crossing (Event 1) (Figure 4.1). This crossing triggered an alert that was handled by specialized cardiac remote monitoring nurses, who assessed technical aspects and other cardiovascular measurements associated with this event. Because these were all normal, the patient was contacted by phone to identify possible causes of the fluid buildup alert. An interview was taken, consisting of a structured questionnaire towards identification of (early) signs of fluid retention, including shortness of breath and the presence of edema. The patient mentioned having a flu since a couple of days, for which NSAIDs were taken. It is reported that infectious intrathoracic processes, such as pneumonia or a flu, can affect intrathoracic impedance measurements [33]. The OptiVol 2.0 fluid index crossing recovered a few days later. In the early phase of gestation, at 6 $^{2/7}$ weeks, the patient developed a second OptiVol 2.0 fluid index crossing, the first one during pregnancy (Event 2) (Figure 4.1). The very first signs of this signal already started at 4 $^{4/7}$ weeks. She was again contacted by phone, but confirmed being asymptomatic and responded negative to all questions. At 20 $^{2/7}$ weeks of gestation, the patient developed a third OptiVol 2.0 fluid index crossing (Event 3) (Figure 4.1). Again, she was asymptomatic and responded negative to all questions. The alert disappeared at 28 $^{1/7}$ weeks of gestation, despite a continuing decrease of thoracic impedance (i.e. fluid accumulation) until delivery.

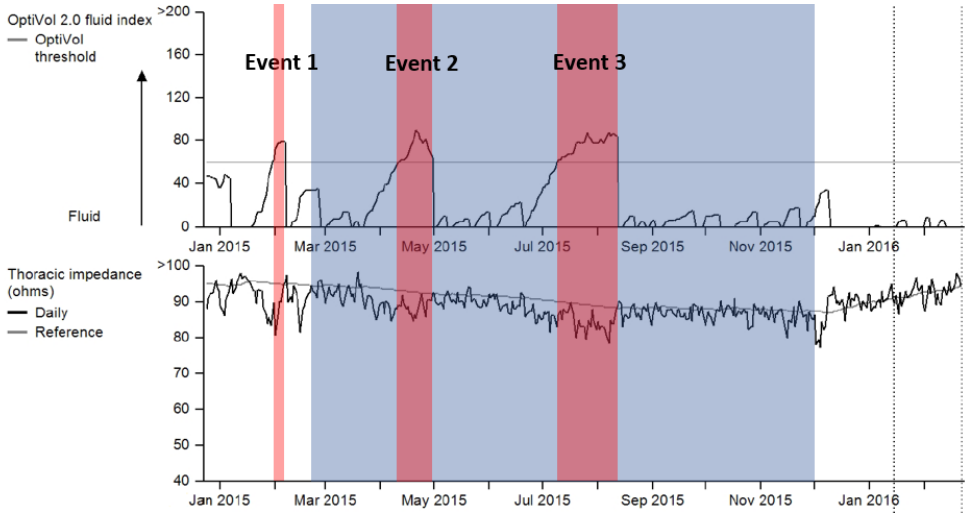

Figure 4.1: Overview of the OptiVol® 2.0 information from an implantable cardioverter defibrillator. Blue-marked areas: gestational period; Red-marked areas: period of fluid index crossing; Event 1: OptiVol crossing which triggered the fluid built up alert for the first time due to an episode of flu; Event 2: OptiVol crossing which triggered the fluid built up alert for the second time at 6 $^{2/7}$ weeks. Event 3: OptiVol crossing which triggered the fluid built up alert for the second time at 20 $^{2/7}$ weeks.

Thoracic impedance values pre-, per- and post- pregnancy were significantly different (Figure 4.2). The patient was also included in an obstetric remote monitoring follow-up program for pregnant women who are at risk for the development of gestation-induced hypertensive disorders (GHD). Because of the presence of the Long QT Syndrome, the patient was invited to participate in this program from 15 $^{6/7}$ weeks of pregnancy. In this follow-up program, two blood pressure measurements and one weight measurement a day are communicated wirelessly to the clinical call center. A team of obstetricians and midwives monitor all measured parameters remotely, and initiate interventions when necessary. There were no blood pressure values recorded above 140/90 mm Hg, and gestational weight gain was 11 kg, which is within the normal range. No phone contact was triggered based on the transmitted data. At 27 $^{2/7}$ weeks of gestation, a maternal cardiovascular assessment was performed as reported elsewhere [65, 69]. During this examination, maternal cardiac, arterial and venous function are evaluated using ICG and ECG- Doppler ultrasonography, to assess maternal hemodynamic function non-invasively. All cardiovascular parameters were normal. At 40 $^{6/7}$ weeks of gestation, she delivered a girl of 3295 grams with normal Apgar score. There were no maternal or neonatal complications. At 6 weeks of age, the neonate was also diagnosed with Long QT Syndrome type II.

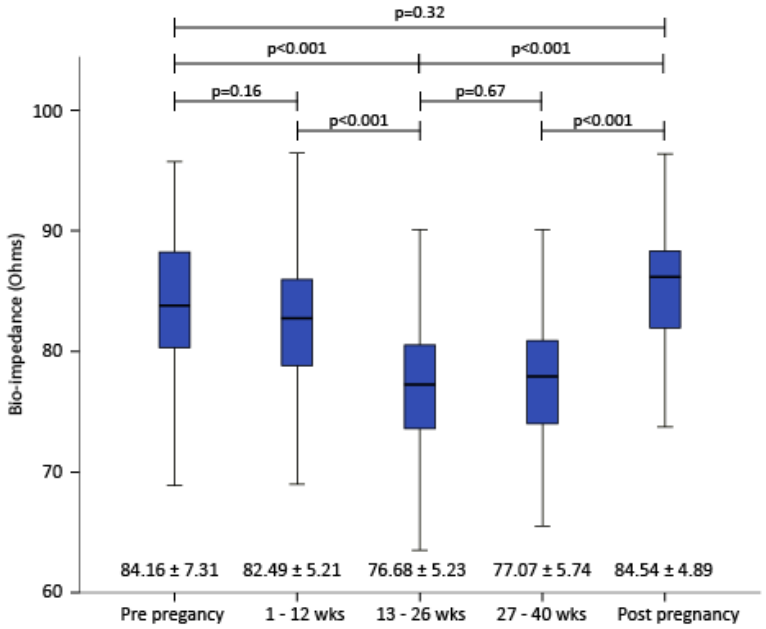

Figure 4.2: Thoracic impedance (ohms) values from an implantable cardioverter defibrillator pre-, per-and post pregnancy. Differences in means (± SD) were tested using Paired Student's two sampled *t*-test, at nominal level α = 0.05. Of the 319 thoracic impedance values, 34 were pre-pregnancy, 82 were in the first trimester (1 – 12 weeks of pregnancy), 105 were in the second trimester (13 – 26 weeks of pregnancy), 55 were in the third trimester (27 – 40 weeks of pregnancy) and were 43 post-pregnancy.

CONCLUSIONS

A decrease in thoracic impedance, indicating an increase in thoracic fluid content, started already shortly after fertilization (i.e. 4 $^{4/7}$ weeks of pregnancy). This increase in thoracic fluid content persisted during the course of pregnancy and immediately recovered to initial pre-pregnancy values after delivery. This clearly demonstrates the presence of a higher thoracic fluid content during pregnancy, which already starts at the early beginning of gestation [67]. Women with the Long QT Syndrome are known to have a reduced risk for cardiac events during pregnancy, but have increased risk during the 9-month postpartum period [68]. In our case, no severe cardiac events were recorded during pregnancy. Nevertheless, two events of OptiVol fluid index crossing were observed during gestation. Both crossing alerts can be explained by well-known physiological cardiovascular changes during the corresponding gestational stages. The event at 6 weeks is observed during the gestational window where maternal systemic vasodilation is reported which could result in a higher blood pressure volume and lower intrathoracic impedance, one of the earliest observed changes in the body of the pregnant women [67]. This causes a fall in systemic

vascular resistance and triggers physiological changes in the cardiovascular and renal systems. In early pregnancy, osmoregulation is 'reset' at a lower osmolality around a new steady state which facilitates water retention [67]. The second gestational OptiVol fluid index is observed around the moment previous research reported a maximum increase in cardiac output [70]. This is associated with increased flow in the pulmonary circulation. Pulmonary vascular resistance is reduced and the increase in plasma volume is accompanied by a decrease in plasma colloid osmotic pressure of about 10-15%. Consequently, the colloid osmotic pressure/pulmonary capillary wedge pressure gradient falls by about 30%, increasing susceptibility to pulmonary edema in pregnant women [71]. Since the patient was not experiencing any symptoms related to fluid overload, these events can be attributed to normal cardiovascular changes during pregnancy. From data received through the obstetric remote follow-up program, the maternal cardiovascular profile at 27 weeks and the normal clinical outcome, we conclude that maternal hemodynamic changes in our case can be labeled as "normal".

This case report is the first one in which the earliest maternal cardiovascular changes are detected and registered longitudinally until full recovery in postpartum. Our observation illustrates the feasibility to use the bioimpedance technology for continuous monitoring of gestational cardiovascular changes. Our observations were made using the remote monitoring technique of an implanted cardioverter defibrillator. Today, innovative research is producing more and more devices to evaluate cardiovascular function by non-invasive mode, including external bioimpedance patches[7]. When these new devices would allow cardiovascular monitoring at similar quality, the way is open towards exploring periconceptional cardiovascular monitoring as a new tool to discriminate normal from abnormal maternal cardiovascular adaptations and identify pregnancies at risk for GHD already at the very first post-implantation stages.

PART II

REMOTE MONITORING BY NON-INVASIVE WEARABLE DEVICES

CHAPTER 5

Clinical validation of a low-power and wearable ECG patch for long term full-disclosure monitoring

Smeets CJ*, Torfs T*, Geng D, Berset T, Van der Auwera J, Vandervoort PM, Grieten L

*shared first authorship.

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ABSTRACT

Background: Detection of intermittent atrial fibrillation (AF) is done using a 24h-Holter. Holter recordings are powerful but lack the comfort and have limited recording times resulting in under diagnosing of intermittent AF.

Objective: Within this work we evaluated and compared a novel miniaturized three-channel electrocardiogram (ECG) monitoring patch versus a 24h-Holter system.

Methods: Both patients with a chronic AF rhythm (n=5) as well as patients with an AF rhythm (n=5) that underwent electrical reconversion were equipped with both a 24h-Holter and ECG patch.

Results: Alignment of raw data of both ECG systems allowed cross-correlation analysis. Overall good correlations up to 85% were obtained. RR-interval analyses of both systems resulted in very high correlations of 99% and higher. AF analysis showed correct identification of AF on both ECG systems.

Conclusions: The performance of our ECG patch matches those of the Holter and could provide a suitable tool for long-term monitoring applications.

INTRODUCTION

Atrial fibrillation (AF) is the most common heart rhythm disorder, with increasing incidence with age. It is a cardiac arrhythmia that often proceeds asymptomatic and can causes severe comorbidities such as embolic stroke. Short episodes of AF (48 hours) are sufficient for thrombus formation in the left atrial appendage which can dislocate and cause severe (cerebral) damage. For these reasons, the management of AF puts a high burden on healthcare costs, accounting for up to 6.5 billion dollar in the US [72-74]. It is therefore essential that the diagnosis of AF occurs as early as possible. The problem here, however, is that it is a disease, which can manifest in intermittent episodes (i.e. paroxysmal AF), making detection very challenging. Since decades, the gold standard method for investigation of patients with suspected arrhythmias, including AF, in the ambulatory setting is the 24-hour Holter monitor. This method has already proven its beneficial effect in many occasions. However, with its current form factor, there are some limitations in its use and applicability. Due to the short measurement period (i.e. 24 hours) of the Holter monitor, its diagnostic yield is reported to range from 15% to 39%. This is due to the fact that intermitted periods of paroxysmal AF, which do not manifest during the 24-hour monitoring period, remain unnoticed [75-84]. Event recorders and 7-day electrocardiogram (ECG) monitors have due to their longer measurement period a higher diagnostic yield. However, like the 24-hour Holter monitor they contain a lot of cables and are therefore rather cumbersome to wear [75, 76, 82, 84, 85]. The highest diagnostic yield is achieved with implanted devices, such as loop recorders [78]. But due to high costs and invasive character they are limited to a certain subset of patients. Therefore, new non-invasive diagnostic devices capable of monitoring for longer time periods, with a high quality and comfort are needed. These devices will have to be made small, with few or no electrodes/cables and without losing diagnostic accuracy. In addition, to provide optimal patient follow-up, they will need to be equipped with wireless communication capabilities. Patches would be able to exhibit these properties and would have additional advantages and reduced lead-noise sensitivity due to fixed leads. Such devices have recently been developed and have already been proven to capture more significant arrhythmias compared to 24-hour Holter monitoring [72, 74, 86-88]. However, most of the time, these devices are limited to single lead ECG information and are not completely optimized for low-power applications causing a reduction in monitoring time. A comparison between commercial patch systems and our ECG application can be found in the work of Lobodzinski *et al.* and Buxi *et al.* [86, 87, 89].

In this work, we compared an innovative low-power ECG patch from imec versus a gold standard 24-hour Holter monitor on raw signal quality, clinical significance, lead redundancy and AF detection performance.

REFERENCE HOLTER SYSTEM

A Seer Light Holter from General Electric Company (GE) Healthcare (Little Chalfont, United Kingdom) was used as gold standard medical device and served as a reference system. Dimensions of this device are 8.5 cm x 5.4 cm x 1.5 cm, with a total weight of 72 grams and is worn by the patient in a pouch. A connector cable provides 7 leads resulting in three full disclosure bipolar ECG channels. The system has a digital sampling rate of 125 frames per second and an analog to digital conversion of 10 bits, with 8 ms sampling. A voltage peak-to-peak input ranges within 16 mV and recordings are made with a bandwidth between 0.05 Hz to 40 Hz. The device is equipped with an event button and memory card for local storage. The event button can either be a mechanical button (located on the lower right part of the device) or a software algorithm based on accelerometer input (tapping motion). Device set-up and interrogation is done by infrared communication with the provided Seer Light connect device. In Figure 5.2, one can see how the 24-hour Holter is attached to the human body.

ARCHITECTURE ECG PATCH

Imec's low power ECG patch consists of 2 stacked printed circuit board modules, a sensor board and a radio/controller board [89]. Together, the stacked modules with the housing measures 4.9 cm x 3.2 cm x 1.9 cm, with a total weight of 25 grams (including battery). Depending on the measurement requirements a larger battery can be used resulting in a slight increase of total weight. Figure 5.1 shows the overall architecture of the proposed ECG patch monitor and its photograph. The system contains imec's proprietary ultra-low power (40μW), low noise (80 nV/√Hz) three-channel ECG analog front-end application-specific integrated circuit with electronically selectable gain/bandwidth and on-chip 12 bit ADC and a 3D accelerometer ADXL326 by Analog Devices. A microcontroller (TI MSP430F1611) is used to control the system and streaming the data to a 2.4 GHz Radio (Nordic nRF24L01), or storing the data on a micro SD card. The system also contains an optional digital signal processing (DSP) unit, called CoolBio, which is not used in the current study. For the purpose of this study the micro SD card was used for data storage. However, the Nordic radio has the ability to transmit all recorded data with low-power to a receiving unit for the duration of the recording. Transmitted data can either be real-time ECG data as well as the processed data from the on-chip digital signal processor. For the duration of this study this radio feature was only used to check the integrity of the signal but had no additional added value for the data collection.

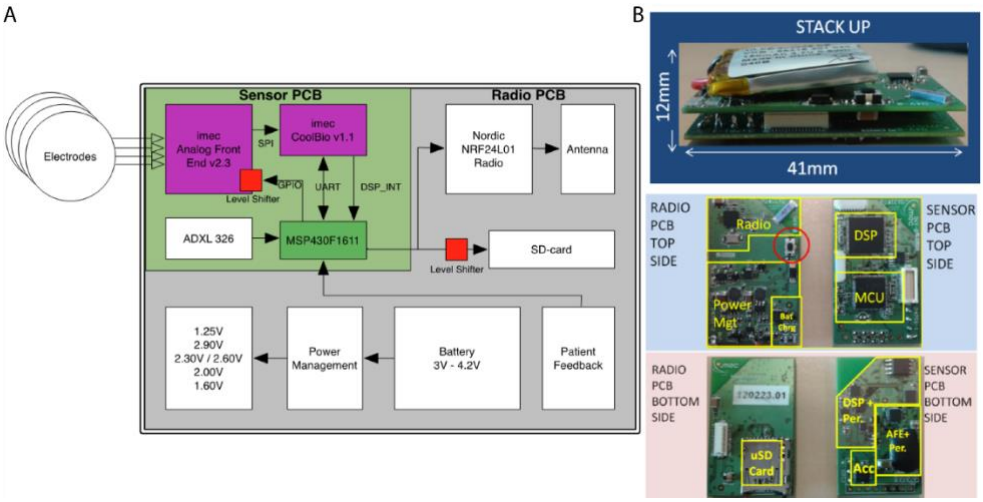

Figure 5.1: A: The system architecture with the different modules of the low-power ECG patch. B: A photograph of the two stacked modules. DSP, Digital Signal Processor; MCU, Microcontroller; uSD Card, micro SD-card; Acc, Accelerometer; AFE+Per., Analog Front End and additional circuitry; DSP+Per., peripheral circuitry connected to the DSP unit.

The system is powered by a single-cell Li-polymer battery, which supplies a voltage from 3.2 to 4.2 V. This enables the device to measure up to 48 hours when recording to SD card and up to seven days when streaming via radio.

The patch records full disclosure ECG signals of up to three (unconventional) leads, together with tissue-contact impedance and a 3D-accelerometer for physical activity monitoring. By measuring tissue-contact impedance, the patch provides real-time information on the sensor contact quality. This can be used to evaluate data quality and to filter (adaptive filtering) for motion artifacts. The device is also equipped with an event button to record symptomatic events. To attach the device to the human body, it is clicked in an integrated disposable patch with fixed electrode position. In Figure 5.2 one can see how the ECG patch is attached to the human body and the lead configuration of both the ECG patch and reference Holter system.

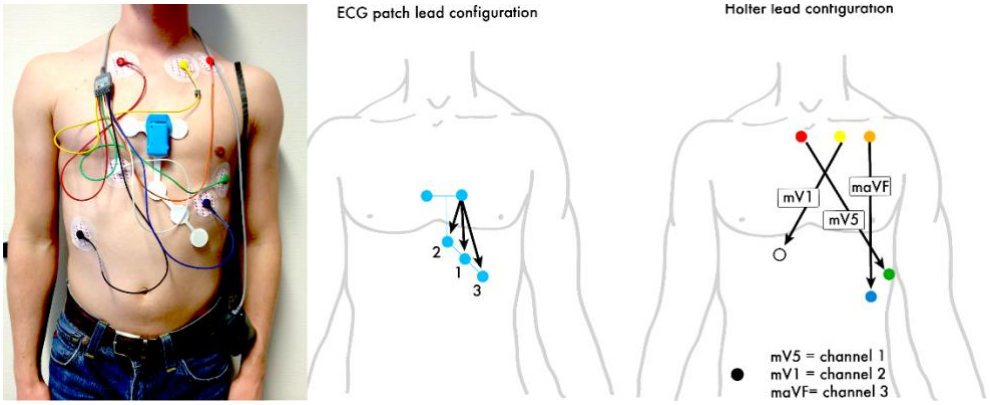

Figure 5.2: Left: Photograph of the measurement setup for a subject wearing the reference Holter system and the ECG patch for validation purposes. Middle: Unconventional lead configuration of the ECG patch. Right: Lead configuration of the reference Holter monitor from General Electric Company (GE) Healthcare (Little Chalfont, United Kingdom).

STUDY SETUP

Patients (n=5) where a diagnostic ECG showed an AF rhythm and patients (n=5) with AF, which were admitted to our hospital for electrical reconversion to normal sinus rhythm, were equipped with the Seer Light 24-hour Holter monitor. In addition, the patients were also equipped with our ECG patch monitor. For the former group, both devices were attached for about 24 hours. For the latter group, both devices were attached two to three hours before the electrical reconversion, detached during the reconversion (to prevent system damage) and reattached after reconversion for another two to three hours. Holter data were analyzed by specialized nurses and validated by cardiologists following standardized procedures.

SIGNAL ANALYSIS AND STATISTICS

The analog front-end in the ECG patch is configured for a sample rate of 512Hz, with bandwidth from 0.5Hz (1^{st} order highpassfilter) to 200Hz (2^{nd} order lowpassfilter). The reference device uses a sample rate of 125Hz. Raw data was offline analyzed afterwards. Since sampling rates and initial startup moments were different for both devices a proper alignment was required. These alignment algorithms were developed in MATLAB® 8.1 (The MathWorks Inc., Massachusetts, United States). First, raw ECG signals were fragmented into sections of 5 minutes at random intervals. After beat-detection, using a Mexican-hat continuous wavelet transform (CWT) algorithm, the RR-interval was obtained. These RR intervals were subsequently cross-correlated between both signals. Next, these fragment

signals could be aligned and the temporal delay between both signals could be determined allowing full data alignment and calculation of the exact 'real' sampling frequencies required for accurate re-sampling of both signals.

After this alignment procedure, the following actions were performed in signal comparison: (1) a normalized absolute-value cross correlation (xcorr) of raw signal (1 = complete correlation, 0 = no correlation) for each lead compared to each other, resulting in a total of 9 combinations. (2) After calculating the RR-intervals from all leads, they were correlated for a more clinical-relevant correlation (1 = complete correlation, 0 = no correlation) [74]. Finally, the entire dataset was fragmented in sequential fragments of 5 minutes and in each segment a standardized detection algorithm of AF was applied, i.e. the Linker Algorithm [90, 91]. If this algorithm indicated the presence of AF, a score of 2 is obtained for that entire 5-minute section. Applying this standardized algorithm on both unconditioned signals, provides insight on data quality and the ability to detect AF between both devices. Since both devices each have three leads, the option of a majority vote is possible to indicate the presence or absence of AF.

RESULTS

In this section, the results of the alignment, cross correlations and AF analysis are shown. All analyses were based on the raw ECG signals without any pre-processing or filtering. As proof of concept, one example of each case will be discussed in detail. One for a subject with persistent AF and one for a subject undergoing cardiac reconversion. For all the other recorded subjects, only the means are given.

SIGNAL ALIGNMENT

Cross correlation of the RR-intervals showed the highest peak after 26.244 seconds, indicating the temporal offset of the ECG patch towards the Holter device (data not shown). The exact real sample rate was also determined using this approach: arbitrarily assuming the ECG patch to have a sample rate exactly equal to its nominal value of 512 Hz, the real sample rate of the Holter system was calculated as 124.987Hz (compared to a nominal value of 125 Hz). The obtained results of the RR-interval correlation and the corresponding raw ECG signal alignment are shown in the upper and lower panel of Figure 5.3, respectively.

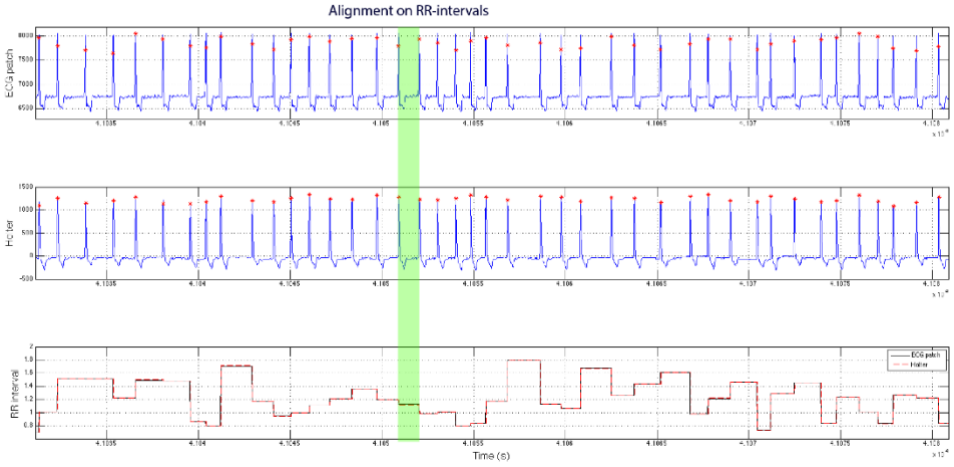

Figure 5.3: Results on an alignment set of ECG data from both the ECG patch and the Holter system. Peak detection and RR-interval analysis allows cross-correlation analysis to align both signals based on RR intervals. Based on the obtained delay the, the ECG patch could be delayed in order to match the alignment of the Holter. Upper graph: RR-intervals of the ECG patch. Middle graph: The ECG signal obtained from the Holter. Lower graph: Aligned RR-intervals. The green translucent bar shows the alignment of the two ECG traces and the corresponding RR-interval.

The sampling frequencies and temporal offset varied for all recordings, therefore a new alignment procedure was needed for each recording. The success of alignment was determined on the mathematical outcome of the cross correlation and confirmed by manually measuring the RR-intervals at random recording intervals.

CROSS CORRELATION OF RAW ECG SIGNALS

After the alignment procedure, a cross correlation of all combinations of the ECG signals was performed. Here fore, all 3 leads of both the Holter and ECG patch signals were compared with each other, resulting in 9 cross-correlations (Figure 5.4).

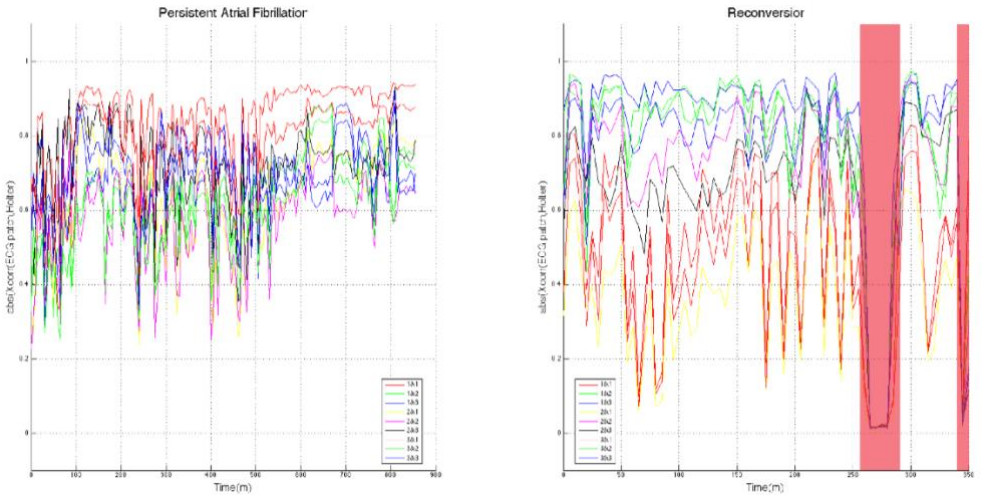

Figure 5.4: Cross correlation results of raw ECG signals. All leads of the ECG patch were compared to the Holter leads, resulting in nine different correlations. The correlations were made absolute indicating that 1 represents a perfect correlation and 0 represents no correlation. Left panel: Cross correlations of a patient suffering from persistent AF. Right: Cross correlations of a patient undergoing cardiac reconversion. The red translucent bar indicates the disconnection of the system during the electrical reconversion and at the end of the recording.

For the patients with persistent AF, the example showed the best result for the combination of lead 1 of both devices Holter lead 1 and ECG patch lead 1, with an xcorr of 0.85. When this combination is looked in more detail, one can see that there are great similarities in both the QRS morphology and RR-intervals, but a clear difference in signal amplitude (Figure 5.5). The worst correlation was obtained in the combination for ECG patch lead 3 with Holter lead 1, with an xcorr of 0.23. For this combination, one can see great dissimilarities in ECG morphology and amplitude, and only the RR-intervals remain the same (Figure 5.5). The other lead combinations for the persistent AF patient are shown in Table 5.1. Focusing on

the total population of persistent AF and taking into account the best lead configuration for each subject, a mean correlation of 0.89 ± 0.05 was obtained. For the reconversion subjects, similar results were obtained pre- and post-reconversion. In all these recordings, again lead 1 of both devices showed the best correlation (Figure 5.4).

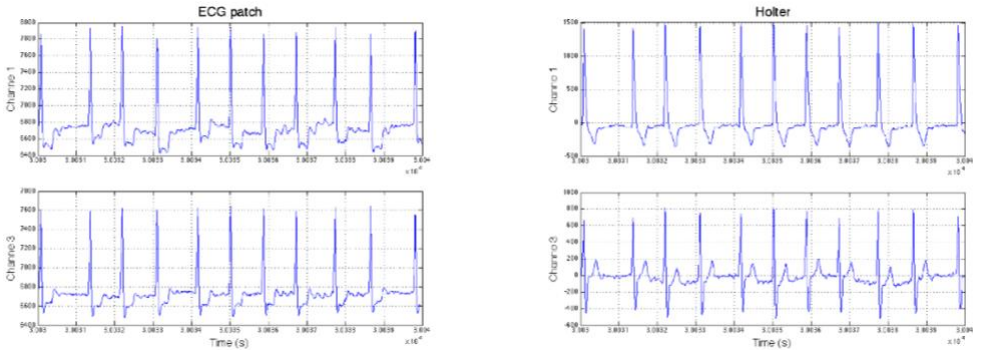

Figure 5.5: Showing the highest and lowest cross correlations between the ECG patch and the Holter. The aligned ECG results of lead 1 and lead 3 of the ECG patch are shown on the left, and for the Holter system on the right. Lead 1 of the ECG patch had the highest correlation with lead 1 of the Holter (xcorr=0.8569). While lead 1 of the ECG patch had the worst correlation with lead 3 of the Holter (xcorr=0.2315). Comparing lead 3 of the ECG patch with lead 3 of the Holter resulted in an overall reduced correlation (xcorr=0.4031).

Table 5.1: Matrix representing the different leads for both the ECG patch and the Holter system. The combination results in cross correlations of the entire recording time.

	ECG patch Lead 1	ECG patch Lead 2	ECG patch Lead 3
Holter Lead 1	**0.8569**	0.5953	**0.2315**
Holter Lead 2	0.6317	0.3148	0.6162
Holter Lead 3	0.7711	0.3749	0.4031

CROSS CORRELATION OF RR-INTERVAL ANALYSIS

To compare the clinical performance of the ECG patch to the Holter system, an analysis was made based on the recorded QRS complexes (i.e. RR-intervals). Figure 5.6 shows the result of RR-interval cross-correlation for lead 1 of both devices. A cross correlation, of 0.9968 was obtained with minor deviations in the signal. For the patients suffering from persistent atrial fibrillation, a mean overall RR-interval cross correlation of 0.9977 ± 0.0012 was obtained. In addition, data of the subjects who were admitted to the hospital with AF and underwent reconversion, showed an xcorr of 0.9912 in the pre-reconversion state and an xcorr of 0.9952 post reconversion. In the example subject, both devices were disconnected in the

time window from 258 to 270 minutes. The noise collected in this time window was not considered as relevant information and was left out from the analysis.

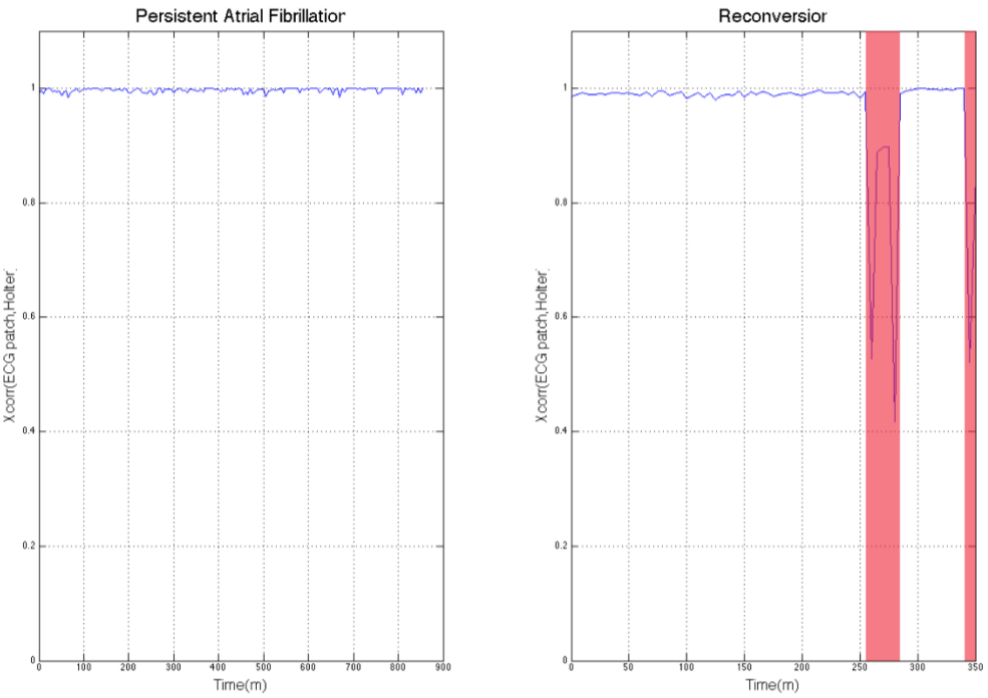

Figure 5.6: Cross correlation results of RR-interval analysis. Graphs only show lead 1 of both the ECG patch and the Holter system. Similar results were obtained for all the other leads (data not shown). Left: A high correlation was obtained for the patient with persistent AF (xcorr=0.9968). Right: Very high correlation was obtained for the reconversion patient (xcorr-pre-reconversion=0.9912, xcorr-post-reconversion=0.9952).

ATRIAL FIBRILLATION ANALYSIS

In order to assess the viability of the ECG patch system as a clinical tool, a comparison was made in the performance of an AF algorithm on the raw ECG data. The well-known *Linker* algorithm was used [90, 91]. An episode of AF is represented by a score of 2, while normal sinus rhythm is represented by a score of 0. In order to perform AF analysis, the signals from all ECG leads were fragmented into 5-minute blocks. Each block of aligned ECG traces were analyzed using the Linker algorithm [90, 91]. If within such a block the rhythm went back to normal sinus rhythm or did have irregularities in signal quality, the entire 5-minute fragment was given a score of 0. Figure 5.7 shows the results for the patients suffering from persistent AF, for all three leads of both systems. In all cases, the ECG patch system had a better overall performance compared to the reference Holter system. In all cases, a drop to 0 was

caused by a loss of signal quality or false peak detection instead of normal sinus rhythm. A majority vote was performed and if the result of the analysis (a score of 2 or 0) was equal to a score of 2 for more than two of the three leads, this would favor the majority and the majority vote of the signal was considered as the true signal, and would be considered as AF in this case (score of 2). In all subjects with persistent AF, the majority vote of our analysis resulted in 100% AF detection for both devices. When the reconversion subjects are considered, one can see that in the pre-reconversion period, the algorithm indicated 100% AF burden (Figure 5.7). After reconversion to normal sinus rhythm, the score of the algorithm dropped to 0. Also here the presence of a majority vote corresponded with the initial diagnosis. A clinical reference was made based on the standard Holter readings and they were 100% conform to the findings of the ECG patch.

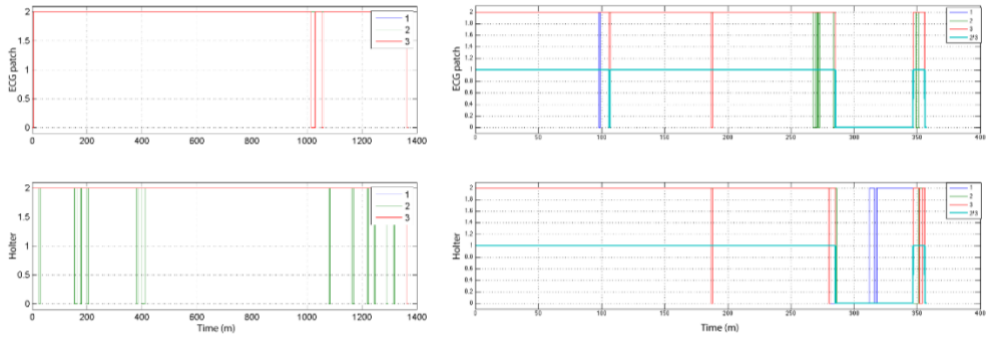

Figure 5.7: AF detection. Left: The outcome of the Linker algorithm [90, 91] for the patient with persistent AF. A score of 2 represents the presence of AF while a score of 0 indicates normal sinus rhythm or noise. Right: The results for the reconversion patient. A majority vote was applied to indicate the accuracy of the system.

DISCUSSION

With the increasing prevalence of cardiovascular rhythm disorders, the tools for their diagnosis need to further evolve in order to expand the functionalities of the Holter system, the current gold standard. The most important aspects that need to be improved are the measurement time and miniaturization, in order to favor patient comfort. Within this study, the raw signal quality of a medical reference system, a 24h Holter, was compared with a new three lead patch system from Imec. In total 10 subjects were analyzed, from which five were suffering from persistent AF and five were admitted to the hospital for reconversion of AF. The study focused on 3 different aspects: (1) comparing raw signal quality between both systems, (2) cross correlation of the obtained RR-intervals between both systems and (3) comparison of the ability to detect AF using the same standard algorithm on both signals.

The alignment procedure was crucial before signal comparison could be made. Since the recordings lasted for 24 hours and both systems did not have a synchronized clock, the alignment was done based on the RR-intervals. In all subjects, a good signal alignment was obtained. However, due to the use of leads in the reference system, there were sometimes long periods of motion artefacts, making the alignment difficult. Another limitation of the alignment procedure can be present in subjects with perfect RR-intervals (i.e. pacemaker rhythm), since their RR-intervals do not vary significantly.

The cross correlation of the raw ECG traces between different lead combinations of the Holter and the ECG patch showed both similarities and differences in all cases. Since the ECG patch system is using three non-conventional lead configurations and the positioning of the Holter leads is not completely the same as the ECG patch electrodes, this results in different morphologies of the QRS signal, both in shape and amplitude. In case of good correlation, there are clear similarities (Figure 5.5), while poor correlations were accompanied by great morphological differences due to the different vectors that are recorded. However, this does not indicate failing of the system, but rather makes it difficult to assess and compare the functionality and performance of both systems based on the correlation of raw signals. It is more an indication on the overall signal comparison and at the area's where the correlation drops to a score of 0, it is worth to investigate the cause. In all cases there was noise present in one or more leads, resulting in signal differences. The results for the obtained signals from the reconversion subjects also showed good correlations. During the reconversion both systems were disconnected to prevent electrical damage, which results in a drop of the correlation. After reconversion, all subjects were back

in normal sinus rhythm and the overall raw data correlation increased and approximated a score of 0.

A more important and relevant parameter to compare the functionality of both systems, is by focusing on the RR-intervals, which are independent on the signal morphology and amplitude and solely rely on the intervals between two adjacent RR-peaks. The cross correlation between all leads of both systems indicated very good correlation above 99%. The small differences, which were observed, were due to the down sampling of the ECG patch ECG to 125 Hz and some noise artifacts which could result in wrong peak detection resulting in differences in RR-intervals. When comparing the overall correlation of the RR-intervals of the different subjects, a very good correlation of 0.9977 ± 0.0012 was obtained. This indicates that both systems have the same performance in QRS detection ability and that general algorithms have nearly the same performance on both signals. For the reconversion subjects similar results were obtained, both for the AF episodes as well as the normal sinus rhythm. Since the ECG patch has the ability to monitor multiple leads it is possible to combine the three signals in a sample-by-sample sum of squares approach to enhance the R-peak detection.

To further investigate the application ability of the ECG patch, the ECG traces were analyzed to obtain a diagnosis for normal sinus rhythm or AF. All the obtained Holter results were in parallel analyzed by a cardiologist using the standard analysis procedure. For the persistent AF patients, it was found that these subjects were 100% in AF. For the patients undergoing electrical reconversion, the results showed that they were in AF before the treatment and returned back to sinus rhythm afterwards. To verify these clinical findings based on only the Holter data, all the raw ECG tracings were analyzed with an AF algorithm. Since the major focus is on the performance differences between the Holter and the ECG patch, a well-known AF algorithm (i.e. the Linker algorithm) was used [90, 91]. Because of computational limitations in the post-processing and analysis of all ECG traces with this algorithm, the data was segmented into blocks of 5 minutes, which were consecutively analyzed by the algorithm. Every time a score of 0 was obtained, a cardiologist was asked to review these fragments and distinguish between, (1) normal sinus rhythm, (2) AF and (3) noise. In all cases, the drops in AF score to 0 were due to noise. Since both signals have three leads, it is possible to create a majority vote allowing to strengthen the clinical diagnosis. In all cases, both the Holter and ECG patch showed 100% AF in the group of patients suffering from persistent AF. Similar results were obtained in the patient population who underwent

reconversion. Here, 100% of the time the subjects were in AF prior to reconversion and 100% in sinus rhythm after reconversion.

The proposed study has some limitations that should be taken into account. The main purpose of this study was to compare the developed hardware functionalities and the acquisition of raw data of a new ECG patch versus the medically approved gold standard Holter system. The ECG patch has additional features for motion artifact reduction and on-chip beat detection capabilities, however, these features were not applied in this study since the main focus was on raw-data comparison. Additional digital signal processing on the raw data will further improve the signal quality and therefore also the diagnostic power for future applications. Additionally, the experiments took place in a small patient population with little diversity in the nature of their arrhythmias. Also the comparison between both systems based on different electrode positions is rather difficult since the ECG patch records the ECG vectors in a non-conventional way. However, the layout of these patch systems are variable and can be changed into any form factor towards future applications.

CONCLUSION

Within this work we compared the measurement functionality and the hardware performance of a proprietary developed ECG patch with a medical gold standard 24h Holter device. Based on the obtained results, it was difficult to conclude the functionality between both devices on raw signal quality, since electrode positions were at different locations. However, the main focus was on the detection of rhythm disorders (i.e. AF) the detection of QRS peaks and RR-interval analysis. The application of a standardized AF algorithm on the recordings resulted in good correlation between both devices. Based on the obtained results in 10 subjects, one can conclude that the new ECG patch has the same performance as a medical gold standard Holter. It is important to state that the ECG patch in its current form factor will not replace the Holter, but extends the functionalities in cases were long-term comfortable monitoring is required. Important to note is that the ECG patch has been used in its basic structure without the capabilities of digital signal processing to compensate for motion artefacts and on chip beat detection. Additional improvements in electronics miniaturization and patch optimization, both in layout and adhesives, should enhance stability on the chest wall and further improve the performance during physical activity.

CHAPTER 6

A wearable multi-parametric bioimpedance device for monitoring fluid redistribution and accumulation

Smeets CJ, Lee S, Nijst P, De Cannière H, Vandecasteele M, Van Hoof C, Grieten L, Vandervoort PM

Submitted

ABSTRACT

Background: Few methods exist for the objective evaluation of thoracic fluid (re-)distribution and accumulation, an important indicator for disease progression in heart failure patients. Bioimpedance provides a promising tool and is already well established in implantable cardiac devices. However, few wearable applications are known and the combination with other vital parameters is rather rare.

Objective: Study the impact of different use cases and feasibility of a multi-parametric wearable bioimpedance monitoring device to assess acute thoracic fluid redistribution and corresponding physiological responses in controlled environments.

Methods: A compact-sized, multi-parametric, wearable monitoring device capable of recording continuous bioimpedance, electrocardiogram and accelerometer data was used. Bioimpedance was recorded at a fixed frequency of 50 kHz to monitor baseline impedance changes. A pilot study was performed in three different populations: (1) subjects undergoing rapid fluid challenge and forced diuresis afterwards (n=4), (2) subjects undergoing a tilt table test (n=8) and (3) healthy control subjects (n=3).

Results: During fluid challenge, impedance decreased after fast fluid injection and restored to baseline values after admission of loop-diuretics. During tilt table testing, impedance decreased when tilted 30 degrees anti-Trendelenburg and restored to baseline values when set back to 0 degrees. For the control subjects, no changes in impedance were observed.

Conclusion: The wearable bioimpedance device was able to measure changes in thoracic fluid redistribution and physiological responses both during fluid challenge and position shifts. These recordings in controlled environments show promising results to study the effect of thoracic fluid changes and apply these concepts in heart failure patients.

INTRODUCTION

Both acute and chronic thoracic fluid (re-)distribution and accumulation are an important indicator for disease progression in heart failure (HF) patients. Unfortunately, few methods exist for the objective evaluation of thoracic fluid content and HF condition. Accurately assessing a patient's congestion status remains difficult and is mainly done by physical examination (i.e. dyspnea, orthopnea, edema, etc.), echocardiography (e.g. left ventricular ejection fraction, E/e' ratio, inferior vena cava diameter, etc.), biomarkers (e.g. pro-BNP, troponins, etc.) or radiographic signs on chest X-ray (i.e. interstitial edema, pleural effusion, etc.). Unfortunately, these are characterized by a low sensitivity and poor predictive value [36, 92, 93]. The current gold standard is cardiac catheterization to assess pressure overload by measuring right atrial and pulmonary capillary wedge pressure [94]. Unfortunately, its invasive nature limits its routine use in daily practice. Bioimpedance provides a promising non-invasive tool to evaluate fluid status. Bioimpedance is an electrical signal which represents the resistance and reactance that opposes an electrical AC current to pass through the body. As a result of the passing current, a voltage is generated. Bioimpedance is then calculated by the magnitude and phase shift of the recorded voltage signal compared to the injected AC current. Since blood and fluids have much lower resistances than thoracic tissue, it is possible to measure thoracic fluid changes using bioimpedance. Namely, if fluid is being accumulated in the thorax, this will decrease the overall bioimpedance and vice versa. In addition, besides monitoring bioimpedance changes due to the fluid content, the thoracic impedance also represents a dynamic system of respiratory induced bioimpedance changes [95] and even cardiovascular changes such as stroke volume and cardiac output monitoring [96]. These physiological components contain a higher frequency than fluid changes and are superimposed on the baseline bioimpedance.

To date, several devices are able to measure thoracic impedance. The best-known examples are implantable cardiac devices (i.e. cardiac resynchronization therapy and implantable cardioverter defibrillators) that have a bioimpedance-based congestion monitor [42]. This added tool allows additional insight in disease progression and possible worsening of HF. Literature indicates that bioimpedance is a very sensitive tool, but shows a lack of specificity as a single indicator to monitor HF congestion [32, 34, 35, 38]. Since implantable cardiac devices are invasive, they can only be used in a very limited patient population. Non-invasive devices for bioimpedance recordings provide an interesting alternative, especially when the recording capabilities of these monitors can be enhanced to record additional physiological parameters (electrocardiogram (ECG), respiration, activity, etc.). Adding these multiple

parameters increases sensitivity and specificity to predict HF worsening (MUSIC-study) [97, 98]. Wearable applications, in contrast to discrete recordings of fixed or portable systems, leverage their form factor to enable longitudinal monitoring and trend analysis in a comfortable way. Unfortunately, there are only a handful of these devices, for example the Cova necklace from toSense and the AVIVO mobile patient management system from Corventis. However, their level of clinical evidence is very scarce. Recently, Philips published pilot results of a wearable bioimpedance vest intended for in-home monitoring. They reported a strong correlation of bioimpedance with daily weight changes and concluded that the vest could track recompensation during therapy for acute decompensated HF [46]. Two years later, they reported that the vest could even provide a refinement in the prognostic assessment of patients admitted for HF [45]. Unfortunately, the vest is not commercially available and its form factor more or less limits the in-hospital use and is less convenient for continuous long-term in-home monitoring. In this work, a novel wearable multi-parametric bioimpedance monitor was used. We studied the feasibility and ability of the device to study acute thoracic fluid changes and the corresponding physiological responses in different groups of healthy subjects under controlled environment.

SYSTEM ARCHITECTURE BIOIMPEDANCE MONITOR

The proposed wearable bioimpedance device is a battery-operated, compact-sized, wirelessly-connected monitoring unit. Its dimensions are 4.8 cm (width) x 3 cm (length) x 2 cm (height), which makes it suitable for wearable use. The device is composed of 2 stacked modules, i.e. a sensor and controller module. The sensor module contains our custom-designed low-power analog-front end application-specific integrated circuit with a square-wave current generator. The controller module provides embedded signal processing, wireless connectivity, and data storage functionality. Figure 6.1 shows the overall architecture of the proposed bioimpedance monitor and its photograph [43].

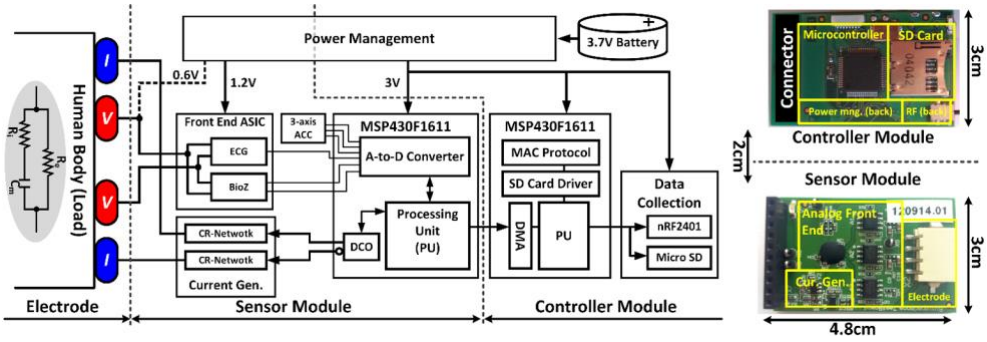

Figure 6.1: System architecture and photograph of the two stacked modules.

The system consumes 0.9 mW when idle and 14.4 mW during measurement, which enables longitudinal data collection. The system has an accuracy of 0.5 Ω and a resolution of 0.2 Ω on both the resistance and reactance measurements. A tetrapolar electrode configuration (see Figure 6.2, Right) was chosen in order to suppress the effect of skin-electrode contact impedance, which is much larger than the thoracic impedance. Bioimpedance is measured at 50 kHz [99] with a sampling rate of 32 Hz for both resistance and reactance. Additional ECG and accelerometer data were collected simultaneously with a sampling rate of 128 and 32 Hz respectively. For the results, only the resistance is shown due to the dominant resistive component of fluid changes. The left side of Figure 6.2, shows how the bioimpedance monitor is attached to the human body. This electrode configuration has been previously used and shows good signal quality for the aimed purpose [44].

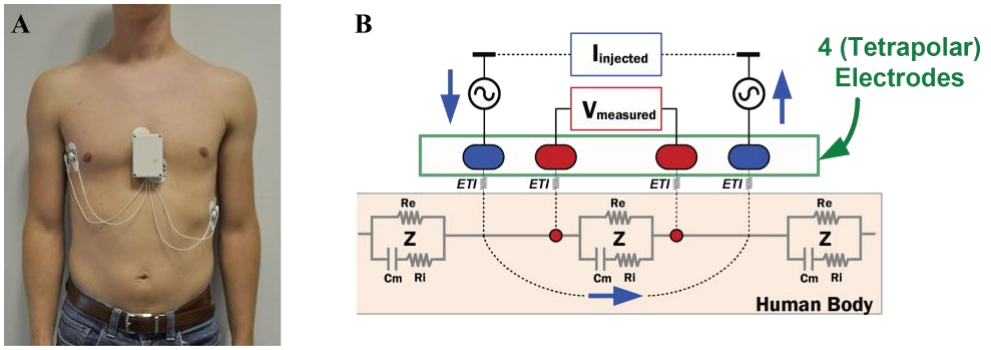

Figure 6.2: A. The optimal configuration of the wearable bioimpedance monitoring device; B. Tetrapolar electrode configuration.

STUDY POPULATION AND SETUP

The device's functionality and ability to monitor fluid changes and physiological signals were studied in three different healthy subject populations. Prior to protocol initialization, subjects were put in supine position for 15 minutes to ensure stabilization of the bioimpedance signal. All participants provided written informed consent. The study complies with the Declaration of Helsinki and the study protocol was approved by the local committee on human research. The following populations were studied (Figure 6.3):

1. **Fluid challenge:** Healthy volunteers were put in a supine position for about 7 hours while the experiment was being performed. When the experiment started, the first baseline impedance was measured. Then, 500 ml of isotonic hydroxyethyl starch (Volulyte) was administered intravenously in a time period of about 10-15 min (fast fluid challenge, FFC). Volulyte is an artificial colloid for plasma volume replacement which remains in the bloodstream. By increasing the total blood volume, it causes vascular expansion. To maintain vascular expansion, the FFC was followed by a slow fluid challenge (SFC), where another 500 ml of Volulyte was administered intravenously to the subject in a time period of 3-4 hours. Finally, a loop-diuretic (i.e. 1 mg bumetanide) was administered intravenously to enhance diuresis/fluid excretion and reduce total body fluid. Seven consecutive hours of physiological data were recorded for each subject. The goal of this protocol is to induce acute changes in body fluid content and study whether these changes could be detected using bioimpedance. Subjects were only allowed to drink a maximum of 150 ml water during the entire experiment and were given a salt-free meal in order not to influence the fluid balance. Detailed information of this study protocol can be found in [100].

2. **Tilt table test:** Eight healthy volunteers were put in a supine position for 15 minutes while the experiment was being performed. 5 minutes after the experiment started, the table was tilted in a minus 30-degree angle for 5 minutes. Next, the table was returned to its original position for 5 minutes. The purpose of this protocol was to verify whether fluid redistributions, induced by posture changes, would influence thoracic impedance measurements.
3. **Control group:** As a negative control, three healthy volunteers were equipped with the bioimpedance monitor. They were put in a supine position for 3 hours without any intervention. They entered the hospital with an empty stomach and were not allowed to eat, drink or move during the entire measurement in order not to influence the bioimpedance recording.

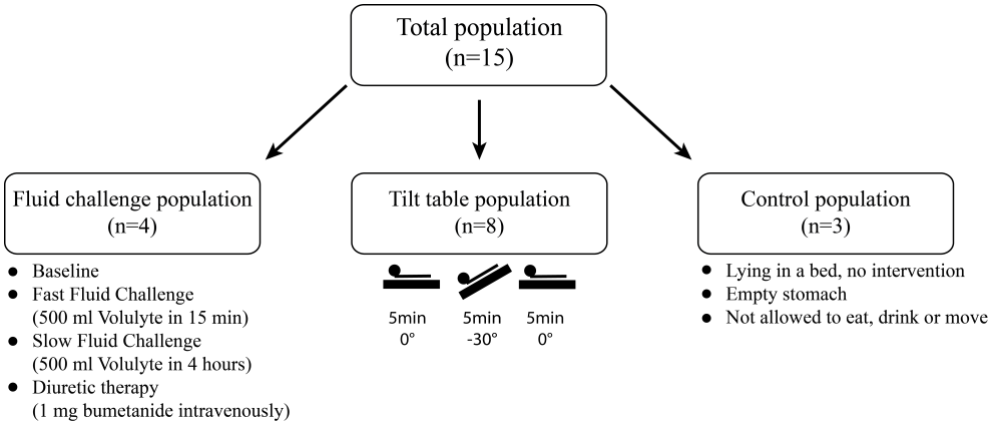

Figure 6.3: Graphical overview of the different study populations.

FLUID CHALLENGE

After a stable bioimpedance signal was obtained, the FFC phase was initiated by injecting 500 ml of Volulyte intravenously. During the fluid challenge protocol, patients were not constantly in the same body posture. Therefore, 10-min interval analysis was only performed for stable data parts under constant posture. Figure 6.4 summarizes the entire experiment (6-7 hours) of a representative patient in mean and standard deviation over intervals of 10 minutes. In this patient, a total difference of -6 Ohms was observed during the FFC. The FFC is followed by a period of SFC. During this phase, the bioimpedance signal is slowly increasing and stabilizing. After the fluid challenge, 1 mg of bumetamide (loop diuretic) was administered intravenously to the subject. As the fluid was excreted, the bio-impedance increased by 6 Ohms. Besides bioimpedance, the heart rate obtained from the ECG, was also plotted. The subject was in a resting position with a baseline heart rate around 45 beats per minute (bpm). During the FFC, the heart rate increased by almost 10 bpm and returned to baseline values after bumetanide treatment.

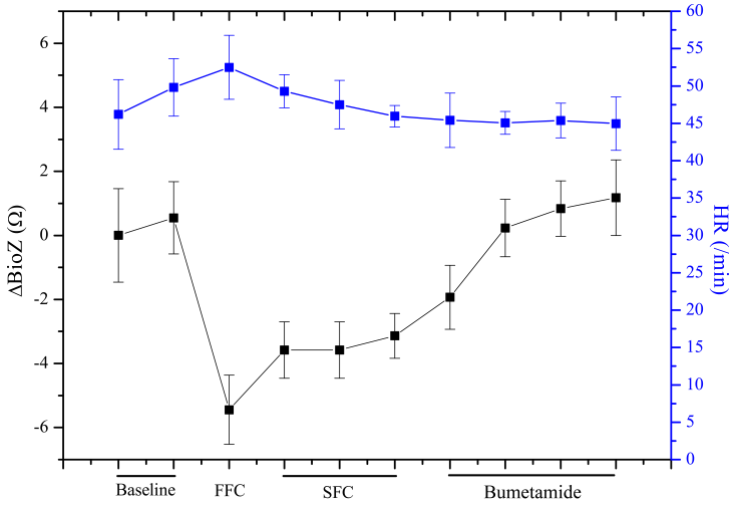

Figure 6.4: Mean and standard deviation of the absolute change in bioimpedance (ΔBioZ) signal (in Ω) on the left y-axis and heart rate (HR) (bpm) on the right y-axis during the fluid challenge protocol for a representative patient. The different events in the fluid challenge protocol are shown in the X-axis. Each point corresponds to the mean value and standard deviation of 10 minutes of data. Only data recorded in the same body posture is included. FFC, fast fluid challenge; SFC, slow fluid challenge.

TILT TABLE TEST

At the start of the tilt table test, subjects were in a supine position allowing stabilization of the bioimpedance signal. Figure 6.5 summarizes the results of a representative patient in mean and standard deviation over intervals of 30 seconds of the start and end of each part of the protocol. When the posture was changed from 0° to -30° for five minutes, a sudden decrease in bioimpedance of -20 Ω was observed. This decrease in bioimpedance was inverted when the subject was put back to 0°. Plotting the heart rate with the bioimpedance signal allows physiological interpretation of the event. When tilting the subject in a negative angle, a decrease in heart rate is observed which slowly returns to baseline values afterwards.

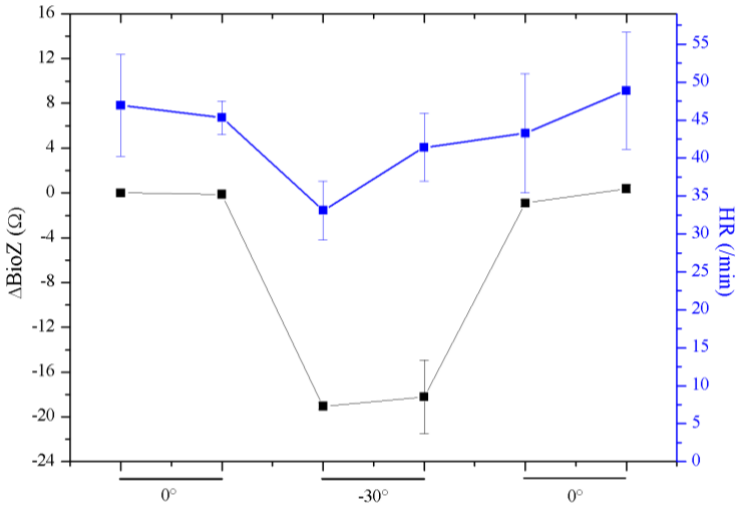

Figure 6.5: Mean and standard deviation from 30 seconds intervals of the absolute change in bioimpedance (ΔBioZ) signal (in Ω) on the left y-axis and heart rate (HR) (bpm) on the right y-axis during tilt table test for a representative patient. The protocol used was 5 minutes at 0°, followed by 5 minutes at -30° and finally 5 minutes at 0°.

CONTROL SUBJECTS

As a negative control study, three subjects were measured for about three hours. It is clear that no significant changes can be observed in baseline bioimpedance. Figure 6.6 summarizes the entire experiment of a representative patient in mean and standard deviation of 10 minutes every 30 minutes of the protocol.

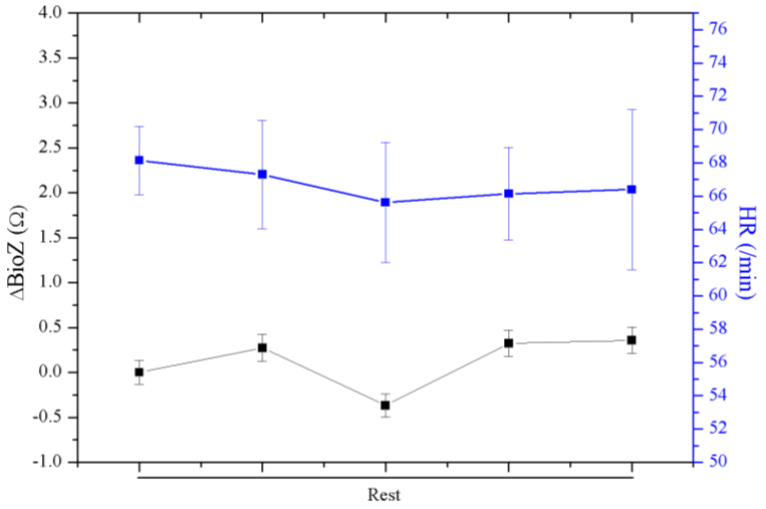

Figure 6.6: Mean and standard deviation of the absolute change in bioimpedance (ΔBioZ) signal (in Ω) on the left y-axis and heart rate (HR) (/bpm) on the right y-axis for a representative patient. Each point corresponds to the mean value and standard deviation of 10 minutes of data every 30 minutes of the protocol.

DISCUSSION

In the current pilot study, the feasibility of a wearable multi-parametric bioimpedance device to measure changes in fluid balance and fluid redistributions was studied. This was done by performing bioimpedance measurements in three different populations; i.e. subjects undergoing a fluid challenge protocol, subjects undergoing a tilt table test and control subjects. Such a wearable bioimpedance device capable of measuring fluid changes would be a useful tool in monitoring different diseases which are characterized by problems with fluid homeostasis.

During the fluid challenge protocol, an increase of total body fluid is induced and thus a decrease in overall bioimpedance was observed almost immediately after the fast Volulyte infusion. Heart rate increased during this phase and this phenomenon originates from the Bainbridge reflex, which is activated by low pressure sensors in the atria of the heart. These sensors become activated when atrial volumes in the heart increase [101]. Afterwards, a stabilization in both bioimpedance and heart rate was observed during the slow fluid challenge. This stabilization in bioimpedance is probably due to pooling of fluid and redistribution in the abdominal and peripheral system [100]. This redistribution will strive to re-settlement of normal body homeostasis. Due to this fluid redistribution and obtaining an equilibrium during the SFC, the heart rate decreases gradually since the atrial filling is reduced. After the intravenous administration of Bumetamide, bioimpedance values returned to baseline values. Bumetamide acts on the Na^+-K^+-$2Cl^-$ cotransporter in the thick ascending limb of the loop of Henle. This will inhibit sodium and chloride reabsorption resulting in an increase urinary production and thus overall decrease in total body water [102]. Due to the intravenous administration of the diuretic, these physiological effects are observed very rapidly. In less than 15 minutes, the subjects needed to urinate due to the forced diuresis. This decrease in overall body fluid causes the bioimpedance to increase. The re-stabilization of the signal to baseline levels at the end of the protocol indicates the recurring homeostasis and the fluid-equilibrium of the body. After the start of forced diuresis, the heart rate further returned to their baseline.

During the tilt table test, an immediate decrease in bioimpedance and increase in heart rate was observed when the subject was tilted in a minus 30-degree angle. The decrease in bioimpedance can probably be explained by the acute shift of blood from the lower parts of the body towards the head and upper thorax. This fluid increase causes the thoracic impedance to decrease in an acute way. The observed changes in bioimpedance can also

be provoked by organ shifts. However, a decrease in heart rate was also observed, which can be explained by the fact that since more blood flows to the head, the high pressure baroreceptors in the carotid artery and aortic arch become activated. In order to physiologically reduce the intra-vascular pressure, the activation of the baroreceptors lead to a decrease in heart rate. This phenomenon is known as the Baroreflex [101]. Therefore, the change in bioimpedance is probably a combined effect of changes in thoracic fluid and organ shifts. After repositioning the subject back to 0°, the blood can be redistributed over the body and both the bioimpedance and heart rate re-stabilize to baseline values. These results demonstrate the importance of a subject's posture when conducting bioimpedance measurements.

Results from the control subjects verify that the observed changes in the other two subject populations were caused by changes in fluid level or fluid redistributions. This can be concluded since no changes in bioimpedance or heart rate were observed for these subjects. Control subjects were in a resting position with no induced changes in total body water or fluid redistributions.

A limitation of the current study is the small sample size. However, this is a first pilot study on patients and controls which is intended to gain an insight in the possibilities of a novel wearable bioimpedance device to measure fluid redistribution and accumulation.

CONCLUSION

The novel wearable bioimpedance device was able to measure changes in thoracic fluid redistribution and physiological responses both during fluid challenge and position shifts. The wearable bioimpedance device enables the physician to longitudinally monitor various physiological signals and could provide a useful tool in monitoring several pathologies that characterized by a disturbed fluid balance, such as congestive HF. Future studies will focus on this application domain.

CHAPTER 7

Congestive heart failure patient monitoring using wearable bio-impedance sensor technology

Lee S*, Squillace G*, **Smeets CJ***, Vandecasteele M, Grieten L, de Francisco R, Van Hoof C

* shared first authorship

Conference Proceedings IEEE Engineering in Medicine and Biology Society. August 2015:438-441.

Abstract

A new technique to monitor the fluid status of congestive heart failure (CHF) patients in the hospital is proposed and verified in a clinical trial with 8 patients. A wearable Bio-impedance (BioZ) sensor allows a continuous localized measurement which can be complement clinical tools in the hospital. Thanks to the multi-parametric approach and correlation analysis with clinical reference, BioZ is successfully shown as a promising parameter for continuous and wearable CHF patient monitoring application.

INTRODUCTION

One of the symptoms of Congestive Heart Failure (CHF) is pulmonary fluid accumulation (hence the name "congestive") due to the inability of the heart to adequately serve the needs of the body with oxygen saturated blood. This pumping failure can result in fluid effusion and accumulation in the pulmonary and peripheral system. Patients admitted to the hospital with CHF, are suffering from symptoms such as dyspnea and edema and are treated with diuretic therapy to promote fluid excretion. During the treatment, daily thoracic X-ray images of the lung and detailed fluid balance measurements are taken so that the patients disease progression can be accurately tracked. These methods are costly and very labor intensive. In most cases, CHF patients reside in the high or medium intensive care units for 3 to 7 days. Depending on the status of their condition they will be discharged to return to a home environment or worsen in their disease status and eventually die.

A more straight forward method to quantify the amount of thoracic fluid built up could pose a valuable tool to direct and organize faster and more efficient treatment strategies that in turn could improve the outcome. This monitoring could be done in real-time during the hospitalization period. Today there is no gold standard technique that can provide a quantitative assessment of the patient. Current clinical practice is based on taking into account the manifestation of clinical symptoms as well as the recorded vital parameters.

Despite the fact that some research groups are focusing on bio-impedance (BioZ) techniques to detect pulmonary fluid build-up from CHF patients and showed promising results as a diagnostic tool for this application [103], it is still not applicable in an in-hospital environment due to their bulky form factor. This bulky and non-wearable form factor makes it almost impossible to be simultaneously used with existing clinical equipment.

In this paper, we present a new technique to monitor CHF patients in the hospital setting based on our wearable BioZ sensor, which was introduced for the first time in [43]. We also present the basic concept and initial results of an observational clinical trial. Different from other BioZ monitors, the proposed technique measures BioZ in a localized area in the lower left thoracic region so that it is able to detect the fluid build-up status without making any disturbance to the existing clinical equipment. Furthermore, a multi-parametric approach including an ECG sensor, a 3-axis accelerometer as well as BioZ is adopted in order to compensate for movement or posture artefacts during the measurement. Even though our BioZ sensor is capable of measuring at multiple frequencies in sweep mode, only single frequency analysis results will be shown in this paper.

WEARABLE BIOIMPEDANCE SENSOR

For wearable healthcare applications, imec has developed low-power and compact-sized bio-signal monitoring device featuring BioZ and ECG sensors as well as 3-axis accelerometers as shown in Figure 7.1 and [43]. The system includes a custom-made analog front-end (AFE) chip for ECG and BioZ sensor and 3-axis accelerometer IC, microcontroller (MCU), power management unit, micro SD card, and 2.4GHz RF transceiver. The target frequency of BioZ measurement can be chosen by changing the control bit of Digitally Controlled Oscillator (DCO) in the MCU, and 27 different frequencies from 10KHz to 211KHz are chosen to be repeatedly swept every 17 seconds for this application.

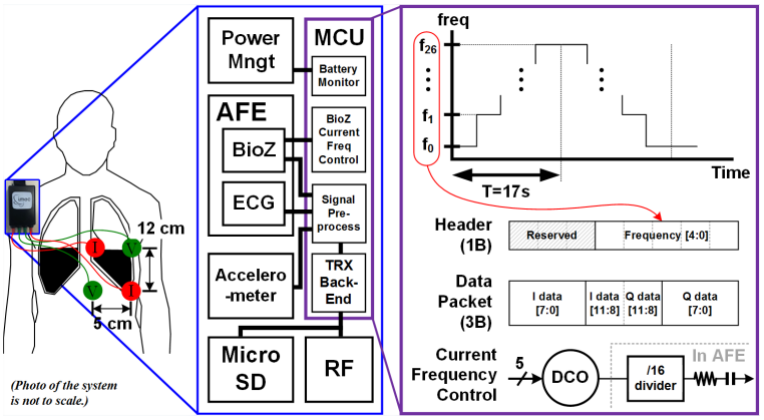

Figure 7.1: Overview of wearable BioZ sensor and electrode configuration for CHF patient monitoring application.

The electrode configuration used for data collection on CHF patient is also shown in Figure 7.1. In order to reduce the number of electrodes to be attached on patients, two voltage electrodes (V) are shared by the BioZ and ECG sensor while two other current electrodes (I) are only used in the BioZ sensor to inject an AC current into the body. Four electrodes are attached on the skin over the lower left thoracic region in a 2 by 2 array configuration with 5cm and 12cm center-to-center distance for horizontal and vertical direction, respectively. This electrode configuration was chosen to achieve a compact size, and a higher sensitivity to the lung fluid build-up, while being less sensitive to other body components such as body fat.

CLINICAL DATA COLLECTION POTOCOL

The target population for data collection with the wearable BioZ sensor is the group of heart failure patients who were admitted with decompensation and receiving diuretic therapy. When the patient is admitted to the hospital, the purpose and method of data collection is explained to patients before asking for participation. This study complied with the Declaration of Helsinki, the protocol was approved by the local institutional ethics committee, and written informed consent was obtained from all participating patients. Prior to the start of the data collection, clinical research forms with baseline patient characteristics are filled in. These include age, gender, height, weight, chest circumference, and body fat at the level of the thorax. Data recording is performed every morning and evening for about one hour each time while the patient is staying in hospital. The system is attached to the patient according to the defined electrode configuration in Figure 7.1, and patients are asked not to move too much during data recording. During the first few days of the data collection period, the fluid balance of the patient, i.e. the amount of intake and outtake in time, and one or two RX thorax images per day, are also collected in order to be used as clinical references.

DATA ANALYSIS

For each patient, the collected data is hierarchically organized in days and parts. The measurement lasts three to seven days, and each day has one to three parts of measurements depending on the patient's status. Each measurement part generates separated raw data files for electrical sensors, while the clinical data of fluid balance and RX thorax images are available in one file for the entire hospitalization period. In order to automate signal processing even with different number of measurements among patients, four steps are followed as shown in Figure 7.2.

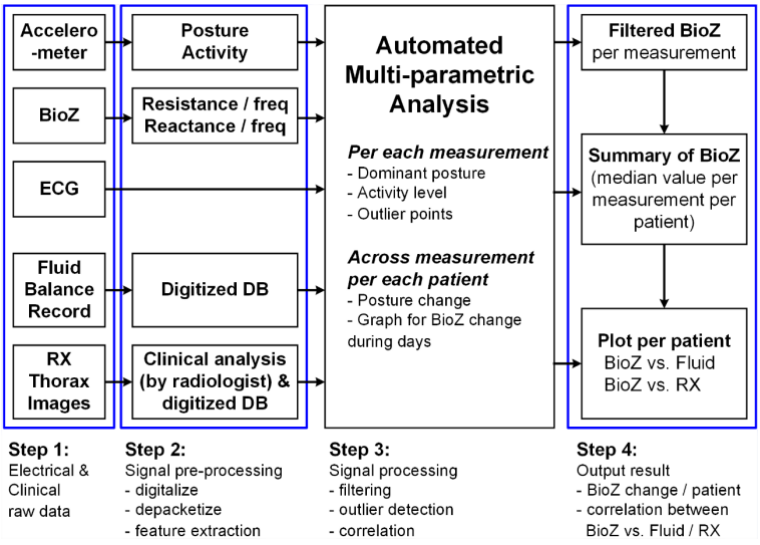

Figure 7.2: Signal processing flow chart: from raw data to output result.

SIGNAL PRE-PROCESSING

Once raw data from electrical sensors per each part of measurement is ready to be processed, it is de-packetized and its features are extracted. First of all, BioZ data is de-packetized and converted into resistance (R, in ohm) and reactance (X, in ohm) per each frequency. Since the frequency sweep of the BioZ measurement takes 17 seconds, the accelerometer and ECG data is also segmented based on each sweep cycle of BioZ and numbered with the corresponding sequence order of BioZ. Two features are available for 3-axis accelerometer data. One of them is classified posture, which is based on θ and φ in spherical coordinate system, and the other is activity level. In Figure 7.3 (a) and (b), the effect of different body posture and activity level on BioZ measurement are presented respectively, from an example of our clinical data collection. Even though the fluid status of

the patient remains the same, a different posture can result in more than 5Ω variation which is more dominant than the impedance change due to fluid build-up or removal which is only up to a few ohm change. Our proposed multi-parametric analysis can detect these abrupt confounding changes in BioZ and filter them out by classifying the posture at the moment of the BioZ measurement, which will be described in more detail in Section III-B. In addition, BioZ data have a larger standard deviation within a segmented window when there is any motion like talking or deep breathing during the BioZ measurement, and corresponding activity level is shown to be higher. In this case, the data is not as accurate as the one measured under static condition. To achieve a higher signal quality of BioZ, data measured under dynamic motion are excluded in the multi-parametric analysis. ECG signal has not been actively used so far for the analysis, but further works will include basic ECG features such as heart rate and heart rate variability hence to be used in the multi-parametric analysis.

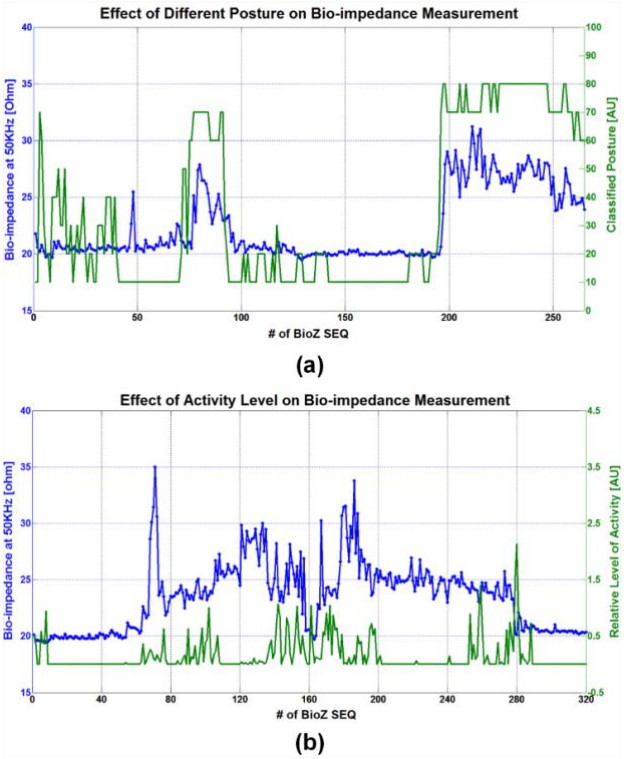

Figure 7.3: Effect of physical parameters posture of the subjects (a) and activity level (b) on BioZ measurement.

Clinical raw data of the fluid balance record are available as hand-written recordings and are only digitized after data collection is finished. On the other hand, RX thorax images are only available in the form of electronic files, so they need to be analyzed first by clinicians to be used in digital signal processing. For this purpose, three radiologists are asked to give their own score between -2 (the patient is significantly deteriorating) to +2 (the patient is strongly improving) about two consecutive images for whole patient image set. Each mean value from the these scores is accumulated over days for further signal processing.

SIGNAL PROCESSING BY MULTI-PARAMETRIC ANALYSIS

In multi-parametric analysis, noisy BioZ data is excluded based on the subject's posture and activity level when each measurement cycle or segment of BioZ data was measured. As a criteria for filtering BioZ, the dominant posture per patient is evaluated in three stages of segment, part, and day according to the measurement structure as shown in Figure 7.4.

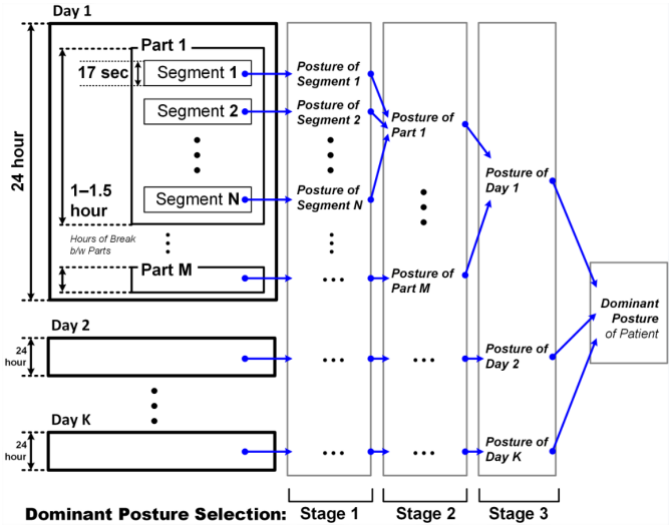

Figure 7.4: Measurement structure of clinical data collection.

In the first stage, the posture within each segmented data is examined. Accelerometer was sampled at 32Hz and each segmented data is 17 seconds long so that there are 544 posture data points per each segment. The median is selected as the posture of the specific segment. In the second stage, the most frequently occurred posture for each part is taken and marked as posture of the specific part. Since each part lasts around one hour, the number of segments per part is roughly between 200 and 250. At the last stage, the dominant posture of the patient is finally determined. Depending on how many days for hospitalization period and how many parts were performed per day, there can be several

postures of the part since the number of the part per patient varies from 4 to 13, and the average number of the parts is 8.125 for 8 patients. If the postures of the part across whole measurement per patient are constant, it becomes the dominant posture of the patient and used for filtering BioZ. However if the postures of the part are varied across measurements indicating that the patient was not in the same posture during the entire measurement, the dominant posture needs to be specifically selected so that change in BioZ can only be the outcome of fluid status, not due to the physical or environmental effect. In this case, all individual postures of the entire parts in the dataset are examined again to investigate whether different postures were presented during the measurement even though it occurred only for the short time during that part of measurement. The posture which can cover the most number of parts is selected as dominant posture of the patient. In some parts the dominant posture is not available and data analysis cannot be performed on those parts.

On the other hand, activity level is only evaluated per each segment. The average value of the activity level per segment becomes the criteria to filter BioZ by threshold method. Once dominant posture of the patient is determined, median value of the BioZ data measured only under the dominant posture of the patient and smaller activity level than the threshold is calculated as the representative value for each part. These values are used for correlation analysis with clinical data.

CORRELATION WITH CLINICAL DATA

Since the timespan between two clinical data points are different, two individual approaches are adopted for correlation analysis. Fluid balance data are summated into 1 hour intervals. Only the fluid data that is matched with parallel BioZ recordings are being used for both qualitative and quantitative correlation analysis. Quantitative analysis is only available when the database includes more than 5 independent data points. The number of points can be limited by BioZ due to either insufficient number of parts or the different posture across the parts, but also by fluid balance due to logistic issues depending on the department the patient was hospitalized. The other data than the one used for correlation analysis can be referred for patient status trend afterwards.

In contrast, RX thorax images are only taken once a day, and not parallel recorded with the BioZ measurement. Since the time is indicative, two graphs for both BioZ and analysis results of RX thorax images by radiologists in time are drawn separately, and qualitative analysis is performed on them. The positive slope of both graphs indicates an improved patient's status. So it is considered good correlation between them to have the same sign of the slope, e.g. positive, negative, or zero meaning no changes.

DATA ANALYSIS RESULT

In Figure 7.5, the results of correlation analysis between BioZ and clinical data from three patients, whose data has enough number of points to make quantitative correlation analysis with fluid balance, are shown as an example. Among 27 frequencies for BioZ measurement, impedance measured at 50KHz is chosen to be analyzed, because it is often used in single frequency measurement and the impedances at higher frequencies sometimes saturated in some subject. This saturation can be observed at 100KHz and 150KHz in Figure 7.5(b) and (c). In those cases, reactance channel is saturated while resistance channel is still within operational range so that the change in BioZ magnitude is smaller than non-saturated case at 50KHz.

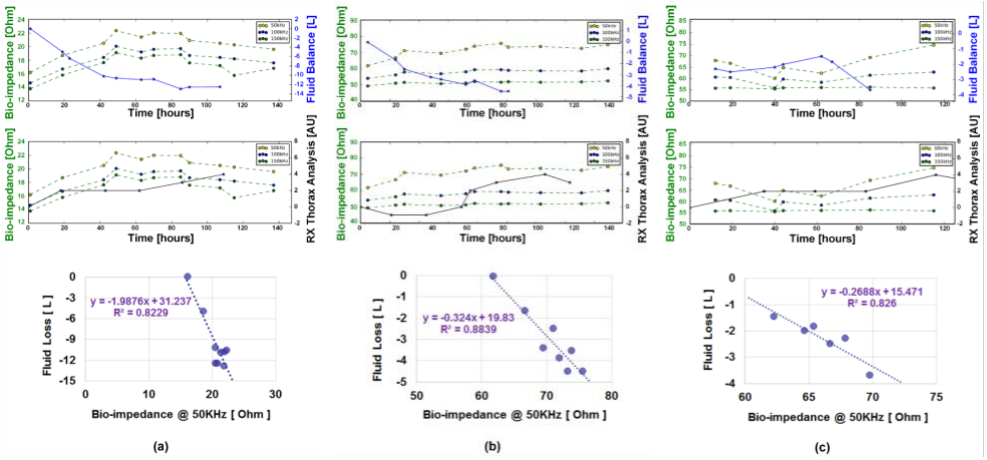

Figure 7.5: Data analysis result of 3 patients: Patient 2 (a), Patient 5 (b) and Patient 7 (c).

As shown in Figure 7.5, individual patients have its own linear characteristics for BioZ versus fluid status with correlation factors larger than 0.8. The slope represents the amount of fluid loss per impedance change. It varies among patients because the fluid is lost from the whole body while BioZ is measured only in localized lung area. Interestingly in one patient there was more fluid extracted from other body parts rather than from the lung indicating a stiffer slope of the graph. This indicates BioZ is less sensitive to fluid loss. It was from the right heart failure (HF) patient, whose accumulated the fluid in her legs rather than the lung. She lost up to 2L fluid in total but her thoracic BioZ kept almost constant, resulting in no correlation between BioZ and fluid loss as shown in Figure 7.6. For other patients, the slope varies between 0.25L/Ω and 2 L/Ω, so it would be able to measure the fluid change larger

than 50 – 400mL since the sensor has resolution of 0.2Ω as described in [43]. The x-intercept of the line represents the baseline BioZ which means the original BioZ value when there is no fluid accumulated. It also varies considerably from 20Ω for one patient to 70Ω for the other patient, but relevant physiological parameters have not been found yet.

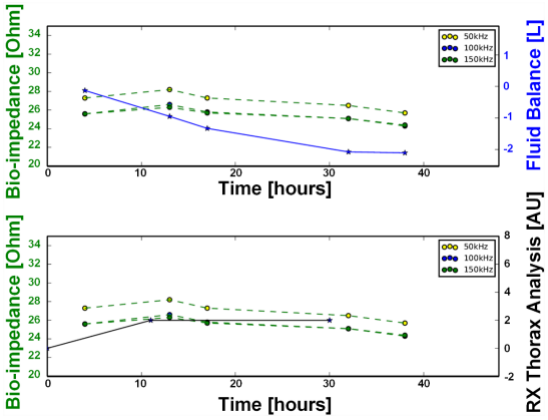

Figure 7.6: Result of data collection on right HF patient.

FUTURE WORKS

It is known that body composition or body fat has an impact on whole body impedance, but it is unknown whether it is also applicable in localized BioZ value or not. By verifying the root causes for different baseline BioZ among patients, estimation of fluid status can be personalized. Multi-parametric analysis including ECG features will also tell more about patient status, which is expected to result in better estimation of fluid status. Last but not least, multi-frequency analysis on the same data has been performed and compared to the single frequency analysis.

CONCLUSION

Our new technique to monitor CHF patients with a wearable BioZ sensor technology during hospitalization is shown in this paper. Fluid balance and RX thorax images are proposed to be used as clinical references for BioZ assessment in this application. In order to achieve a better indication of fluid status by BioZ, multi-parametric analysis based on posture and activity level are performed. After filtering BioZ data based on dominant posture and threshold of maximally allowed activity level, high correlations between BioZ and fluid balance is observed with a correlation factor larger than 0.8. Therefore it is concluded that the localized BioZ measurement can be used as status indicator of CHF patient in hospital environment.

CHAPTER 8

Feasibility and prognostic value of a wearable thoracic impedance sensor in acutely decompensated heart failure with volume overload

Smeets CJ, Lee S, Squillace G, Groenendaal W, Vranken J, De Cannière H, Van Hoof C, Grieten L, Mullens W, Nijst P, Vandervoort PM

Submitted

ABSTRACT

Background: Incomplete relief of congestion in acute decompensated heart failure (HF) relates to poor outcome. However, congestion can be difficult to evaluate, stressing the urgent need for new objective approaches. Continuous bioimpedance monitoring might be an effective way for serial fluid status assessment due to the inverse correlation with tissue hydration. We studied the feasibility of a wearable bioimpedance sensor to assess longitudinal changes in fluid status and their relation with HF hospitalization and all-cause mortality.

Methods and results: A wearable bioimpedance monitoring device was used for thoracic impedance measurements. Thirty-six patients with signs of acute decompensated HF and volume overload were included. Changes in the resistance at 80 kHz (R_{80kHz}) were used for analyses and patients' fluid balance (fluid in/out) was taken as a reference. Patients were divided in two groups, i.e. those with an increase (n=24) or decrease in R_{80kHz} (n=12) during hospitalization. Clinical outcome at both 30 days and one year of follow-up was significantly better for patients showing an increase in R_{80kHz} (at one year 88% versus 50%, p=0.005 for all-cause mortality and 75% versus 25%, p=0.001 for the composite of all-cause mortality and HF hospitalization). A decrease in R_{80kHz} resulted in a significant hazard ratio of 4.96 (95% CI 1.82-14.37, p=0.003) on the combined endpoint.

Conclusions: The novel wearable bioimpedance device was able to track longitudinal changes in fluid status. Patients who do not show an improvement in thoracic impedance show a worse clinical outcome, indicating its use as a prognostic parameter for clinical outcome.

INTRODUCTION

Heart failure (HF) is a major and increasing public health problem worldwide, characterized by frequent (re)hospitalizations which are mainly caused by congestion [1, 50]. Congestion is related to water and sodium retention and is defined as a high left ventricular end-diastolic pressure (i.e. pressure overload) followed by signs and symptoms such as dyspnea, rales, and edema (i.e. volume overload) [36, 104]. At present, a high-dose of intravenously administered loop diuretics is the most widely used and effective therapy for fluid removal [36]. Accurately assessing a patient's congestion status remains difficult and is mainly done by physical examination (i.e. dyspnea, orthopnea, edema, etc.) or radiographic signs on chest X-ray (i.e. interstitial edema, pleural effusion, etc.). Unfortunately, these are characterized by a low sensitivity and poor predictive value [92, 93]. The current gold standard is cardiac catheterization to assess pressure overload by measuring right atrial and pulmonary capillary wedge pressure [94]. This approach also showed to be effective when remotely monitored using an implantable continuous hemodynamic pressure monitor [105-107]. However, its invasive nature limits its routine use in daily practice. Guidelines or specific criteria to define treatment efficacy and discharge readiness of patients presenting with acute decompensated HF are vague or missing. Consequently, thirty percent of patients still have symptoms of congestion on discharge, which negatively influences patients' prognosis [108].

In recent years, thoracic impedance measurements, provided by implantable or external devices (i.e. OptiVol and CorVue), have been investigated as a tool to assess a patient's fluid status and detect volume overload [32, 38, 109]. Bioimpedance is an electrical principle which represents the resistance that opposes a sinusoidal current to pass through the body. Since blood and fluids have a lower resistance to an electrical current compared to thoracic tissue, it is theoretically possible to measure thoracic fluid changes. An inverse correlation exists between bioimpedance and the amount of body fluid. To date, several invasive or portable devices are able to measure bioimpedance. However, due to their invasive or bulky character, they are only used in a limited patient population. Non-invasive wearable devices for bioimpedance recordings provide an interesting alternative since they enable longitudinal monitoring and trend analysis in a comfortable way [43-46]. Previous research already showed a strong agreement between non-invasive thoracic impedance measurements and fluid changes [44, 46] and even hypothesized the potential use in predicting prognostic outcome [45].

In the current study, the feasibility of a novel wearable multi-parametric bioimpedance monitoring device to assess longitudinal changes in a patient's fluid status and their relation with HF hospitalization and all-cause mortality was studied.

METHODS

STUDY DESIGN

This is a prospective cohort study of patients admitted in a single tertiary care center (Ziekenhuis Oost-Limburg, Genk, Belgium). Consecutive patients admitted with signs of acute decompensated HF, for which diuretic therapy was started, were included. Treatment was not dictated by the study protocol and left to the discretion of the treating physician. Besides bioimpedance measurements, no additional tests or treatments were performed beyond those of standard practice. Bioimpedance measurement results were blinded for the treating physician. Patients were divided in two groups according to the relative change in bioimpedance and were clinically followed for 12 months. Clinical outcome measures were the number of cardiovascular hospitalizations, all-cause mortality, HF hospitalization and the composite of all-cause mortality and HF hospitalization both at 30 days and one year of follow-up. All participants provided written informed consent. The study complies with the 1975 Declaration of Helsinki and the study protocol was approved by the local committee on human research.

STUDY POPULATION

Patients admitted to the emergency room with signs or symptoms of acute decompensated HF with volume overload, assessed by a dedicated HF specialist, were approached as soon as possible after triage. Symptoms of congestion were defined as pitting edema, worsening in shortness of breath or orthopnea, paroxysmal nocturnal dyspnea, wheezes, rales, or signs of congestion on chest X-ray such as the presence of pulmonary venous congestion, vascular redistribution, Kerley B lines or blunted costophrenic angles. Study inclusion was only performed when the anticipated date of discharge was >48 hours after enrollment.

WEARABLE BIOIMPEDANCE MONITOR

A novel wearable multi-parametric bioimpedance monitoring device from Holst center/imec Netherlands (Eindhoven, The Netherlands) was used for local bioimpedance measurements (Figure 8.1). The device continuously measures multi-frequency bioimpedance, non-standard one lead electrocardiogram and accelerometer data [43, 44, 110]. Due to the dominant resistive component of fluid changes, changes in resistance at 80kHz (R_{80kHz}) were used for the analyses. Since individual bioimpedance values vary widely and no normative bioimpedance value exist, it is impossible to directly compare the bioimpedance recordings. Therefore, relative bioimpedance values were used to minimalize this inter-individual variability. Patients were divided into two groups, i.e. those with a relative increase in R_{80kHz} and those with a relative decrease in R_{80kHz} from admission to coronary care unit discharge.

A fixed tetrapolar electrode configuration [44] was used to reduce the influence of the electrode-skin impedance.

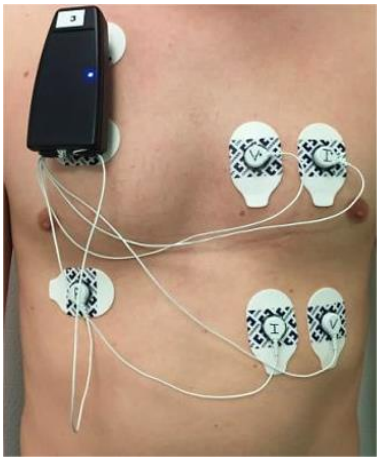

Figure 8.1: The multi-parametric wearable bioimpedance monitoring device.

MEASUREMENT PROTOCOL OF DECOMPENSATED HEART FAILURE PATIENTS

Thoracic impedance measurements, using the wearable device were performed twice a day for about 10 minutes per measurement on at least three consecutive days, using a fixed electrode configuration (Figure 8.1). In between consecutive measurements, the device was detached but whenever possible the electrodes were left in place. A skin marker was used to mark the location of the electrodes in case electrodes were removed. To eliminate possible posture influences, patients were always positioned in a 20/30-degree semi Fowler's position and were asked not to move or talk during measurements. In addition, patients' input/output fluid balances were documented every hour as a reference measure for changes in fluid status. Fluid balance information was available until patients move from the coronary care unit to the low intensive care unit.

STATISTICAL ANALYSIS

Continuous variables are expressed as mean ± standard deviation if normally distributed, or otherwise as median (interquartile range (IQR)). Normality was assessed by the Shapiro-Wilk statistic. To define statistical differences between the two groups, the independent samples student's t-test and Mann-Whitney U test were used for respectively normally and not normally distributed continuous variables and the Chi-Square test was used for categorical variables. Correlation analysis between changes in fluid balance and changes in thoracic impedance values was performed using Spearman correlation in a one-tailed

hypothesis test. Survival curves were constructed according to the Kaplan Meier method, with the log-rank test used for comparison among both groups. Cox regression analysis with Firth's penalized likelihood correction was used to calculate unadjusted and adjusted hazard ratios. Factors with a $p<0.05$ were maintained in the multivariate model. A significance level of 0.05 was used for all tests. All statistical analyses were performed using the Statistical Package for Social Sciences release 24.0 (IBM® SPSS® Inc., Chicago, Illinois, USA) and SAS 9.4 (SAS Institute Inc, Cary, North Carolina, USA) for Cox regression with Firth's penalization.

RESULTS

STUDY POPULATION

Thirty-six patients admitted to the cardiology ward with acute decompensated HF were included (mean age 81 ± 8 years, left ventricular ejection fraction 45% (IQR 36-55), 39% ischemic HF etiology). Mean duration of measurement period was 5 ± 2 days.

BIOIMPEDANCE CHANGES

For the total population, a moderate negative correlation was found between changes in fluid balance and relative changes in R_{80kHz} (r= -0.51, p<0.001). Patients were divided into two groups according to the relative change in R_{80kHz} from admission to coronary care unit discharge, i.e. patients with a relative increase in R_{80kHz} and patients with a relative decrease in R_{80kHz}. Baseline population characteristics are provided in Table 8.1. From the 36 patients, 24 (67%) patients showed a relative increase in R_{80kHz} and 12 (33%) patients showed a relative decrease in R_{80kHz} (Figure 8.2A).

Both groups showed comparable baseline patient characteristics. Significantly less patients with atrial fibrillation or under diuretic therapy were present in the group with a relative increase in R_{80kHz}. As expected, a significant difference in relative R_{80kHz} change from admission to coronary care unit discharge was observed for patients with an increase in R_{80kHz} (109%, IQR 105-122) versus (94%, IQR 85-97) for those with a decrease in R_{80kHz} (p<0.001).

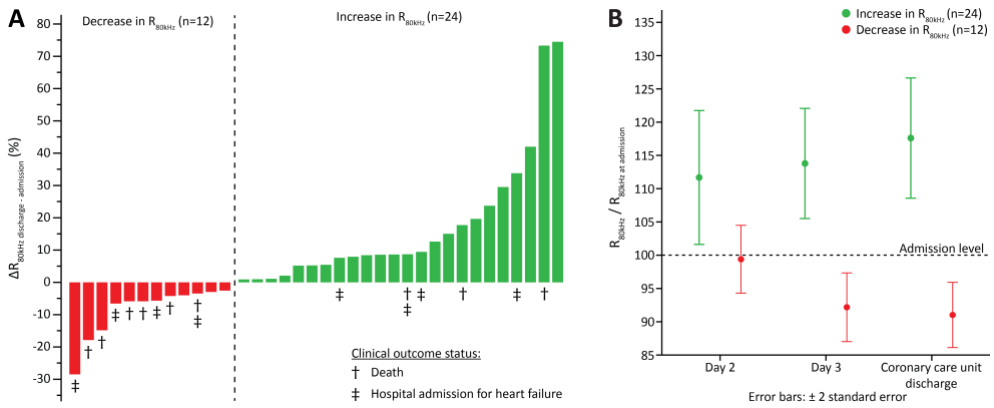

Figure 8.2: A. Relative changes in R_{80kHz} from admission to coronary care unit discharge by patient, including clinical outcome status († all-cause mortality and ‡ hospital admission with a primary diagnosis of HF); B. Relative changes in bioimpedance from admission to coronary care unit discharge (mean and two times standard error) for patients with a relative increase in R_{80kHz} (green) and patients with a relative decrease in R_{80kHz} (red).

Table 8.1: Baseline characteristics of the study population.

Variables	Decompensated HF patients (n=36)		
	Increase in R_{80kHz} (n=24)	Decrease in R_{80kHz} (n=12)	p-value
Age, years	80 ± 9	83 ± 6	0.239
Male gender	10 (42%)	6 (50%)	0.635
BMI, kg/m²	31 ± 8	30 ± 4	0.862
Left ventricular ejection fraction, %	55 (IQR 39-55)	44 (IQR 26-47)	0.057
Heart rate, bpm	86 ± 25	90 ± 19	0.653
Systolic blood pressure, mmHg	144 ± 23	147 ± 33	0.727
Diastolic blood pressure, mmHg	74 ± 18	72 ± 26	0.856
NT-proBNP	3,027 (IQR 1,681-6,161)	12,181 (IQR 3,307-17,352)	0.052
R_{80kHz} at admission, Ω	42 ± 20	46 ± 18	0.522
R_{80kHz} at coronary care unit discharge, Ω	48 ± 22	44 ± 18	0.598
Relative R_{80kHz} change from admission to coronary care unit discharge, %	109 (IQR 105-122)	94 (IQR 85-97)	**<0.001**
Heart failure etiology			
Ischemic heart disease	10 (42%)	4 (33%)	0.727
Dilated cardiomyopathy	0 (0%)	1 (8%)	0.333
Valvular disease	5 (21%)	3 (25%)	1.000
Other	9 (38%)	4 (33%)	0.258
Comorbidities			
eGFR <60 ml/min/1.73m²	15 (63%)	11 (92%)	0.121
Atrial fibrillation	11 (46%)	10 (83%)	**0.031**
Chronic obstructive pulmonary disease	1 (4%)	3 (25%)	0.098
Diabetes	7 (29%)	6 (50%)	0.281
Maintenance therapy			
Renin-angiotensin system blocker	12 (50%)	6 (50%)	1.000
Beta blocker	16 (67%)	7 (58%)	0.720
(Loop)diuretic	14 (58%)	12 (100%)	**0.015**

Continuous data are expressed as mean ± SD if normally distributed and dichotomous data are expressed as n (%). BMI, body mass index; BNP, Brain natriuretic peptide; eGFR, Estimated Glomerular Filtration Rate.

In those patients with a relative increase in R_{80kHz}, the biggest change was observed between the day of admission and the day after (+12%) (Figure 8.2B). During the subsequent days, a smaller relative change in R_{80kHz} of respectively +2% (between day 2 and day 3) and +4% (between day 3 and the day of coronary care unit discharge) was observed. For the population with a relative decrease in R_{80kHz}, smaller relative changes in R_{80kHz} were observed (respectively -0.5%, -7% and -1%).

CLINICAL OUTCOME

During follow-up, 9 patients died, leading to a one-year survival rate of 75%. Patients with a relative increase in R_{80kHz}, had a significant higher probability of survival than patients with a relative decrease in R_{80kHz} (respectively 88% versus 50%, p=0.005) (Figure 8.3A). This difference was already present at 30 days of follow-up (respectively 100% versus 58%, p<0.001). After one year of follow-up, 28 patients (78%) were free from hospital admissions with a primary diagnosis of HF, but no significant difference was found between both groups (respectively 83% versus 67%, p=0.283). At 30 days these numbers were respectively 96% versus 92% (p=0.628). Finally, 21 (58%) were free from death and HF readmission at one year of follow-up (75% for patients with a relative increase in R_{80kHz} and 25% for patients with a relative decrease in R_{80kHz}, p=0.001) (Figure 8.3B), which was respectively 96% and 50% (p=0.001) at 30 days of follow-up. Clinical outcome status is also included in Figure 8.2A. In total, there were 28 cardiac-related hospitalizations for 15 (42%) patients of which 27 were non-elective and 13 were HF-related. Clinical outcome results are summarized in Table 8.2.

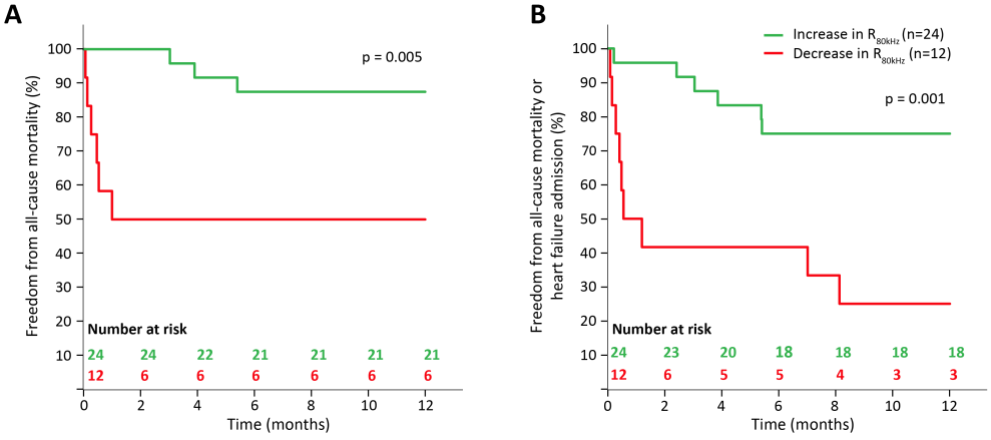

Figure 8.3: Freedom from all-cause mortality (A) or freedom from all-cause mortality or hospital admission with a primary diagnosis of heart failure (B) for patients with an increase in R_{80kHz} (green) versus patients with a decrease in R_{80kHz} (red).

Table 8.2: Clinical outcome results at both 30 days and one year of follow-up.

Endpoint	30 days of follow-up			One year of follow-up		
	Increase in R_{80kHz} (n=24)	Decrease in R_{80kHz} (n=12)	p-value	Increase in R_{80kHz} (n=24)	Decrease in R_{80kHz} (n=12)	p-value
HF hospitalization and all-cause mortality	75.0	25.0	**0.001**	95.8	50.0	**0.001**
All-cause mortality	87.5	50.0	**0.005**	100.0	58.3	**<0.001**
HF hospitalization	83.3	66.7	0.283	95.8	91.7	0.628

Table 8.3 provides an overview of the Cox regression analysis. A decrease in R_{80kHz} from admission to coronary care unit discharge resulted in a significant hazard ratio of 4.96 (1.82 to 14.37) on the combined endpoint, mainly driven by all-cause mortality. After a model building exercise, multivariate analysis revealed that significant differences in baseline characteristics (i.e. presence of atrial fibrillation and diuretic use) and clinically relevant parameters (i.e. age and left ventricular ejection fraction) had no significant influence on clinical outcome.

Table 8.3: Cox regression analysis with Firth's penalization for clinical outcome measures.

Endpoint	Hazard ratio*	95% Confidence interval	*P*-value
HF hospitalization and all-cause mortality	4.96	1.82-14.37	**0.003**
All-cause mortality	5.51	1.55-23.32	**0.015**
HF hospitalization	2.10	0.54-8.14	0.294

* Multivariate analysis revealed no significant influence of significant different baseline characteristics (i.e. presence of atrial fibrillation and diuretic use) or clinically relevant parameters (i.e. age and left ventricular ejection fraction) on clinical outcome.

DISCUSSION

To date, different invasive and non-invasive bioimpedance applications are studied for their potential applications in HF treatment and follow-up. The current study provides preliminary evidence about the feasibility and prognostic value of a novel wearable thoracic impedance sensor to assess longitudinal changes in a patient's fluid status and their relation with clinical outcome. A significant inverse relation was found between daily fluid balance and thoracic impedance measurements. Moreover, an increase in thoracic impedance during initial treatment related to a significant better clinical outcome compared to patients who failed to show an increase in thoracic impedance.

Wearable bioimpedance devices enable longitudinal monitoring and trend analysis in a low-cost, feasible, reproducible and non-invasive manner. In addition, thoracic impedance changes correlate well with a patient's fluid balance and could therefore be used to track volume overload [44]. Furthermore, Cuba-Gyllensten et al. found the highest correlation between daily fluid levels and thoracic impedance measurements compared to other clinical parameters [46]. Due to the poor prognostic value, serial echocardiographic (e.g. left ventricular ejection fraction, E/e' ratio, etc.) or biomarkers (e.g. pro-BNP, troponins, etc.) were not collected as a reference [36, 111-113]. Instead, we relied on the patients' fluid balance (in/out) as a comparator of fluid status, due to its objective character. In the current study, the wearable bioimpedance sensor also showed the expected inverse relation with a patient's fluid balance. For the total study population, a moderate negative correlation was found between changes in fluid balance (in/out) and relative changes in R_{80kHz} from admission to coronary care unit discharge ($r=-0.51$, $p<0.001$). Other research on non-invasive bioimpedance monitoring targeting both lungs found higher correlations [46]. This can be explained by the fact that changes in fluid level happen on the total body level, whereas the thoracic impedance was only measured very locally and only takes into account the basal part of the left lung. Therefore, when using a non-invasive wearable bioimpedance device, the correlation between bioimpedance and fluid balance strongly depends on the location of the excessive fluid and the measurement area of the device. Accordingly, correlations on the individual level can be higher compared to the population level, as was shown in our previous study [44]. Measuring a larger area could improve the correlation, but limits the possibilities to incorporate it in a wearable bioimpedance sensor. On the other hand, when compared to previous research also targeting one side of the thorax, but using invasive thoracic impedance monitoring, the correlation was only slightly different [109]. It is important to bear in mind that when dealing with non-invasive thoracic impedance

measurements, various influencing factors exist. Potential pitfalls include the influence of skin conditions, body composition (i.e. fat percentage, muscle percentage, etc.) and pleural cavity fluid on non-invasive bioimpedance measurements. Also external influences such as body posture and electrode placement can exert an influence. Therefore, to our experience bioimpedance is a measure that should be interpreted in an individualized longitudinal way since absolute bioimpedance values are known to exhibit high individual variability. Individually adjusted thresholds and trends rather than absolute numbers could help in clinical decision making based on bioimpedance measures.

For patients with an increase in R_{80kHz}, the highest change in R_{80kHz} was observed during the first day. This is in accordance with clinical findings from previous research, where it is shown that for acutely decompensated HF patients under diuretic therapy the amount of urinary output is substantially higher during the first 24-hours after admission [114]. Interestingly, for these patients with an increase in R_{80kHz}, a significant survival benefit was observed both for all-cause survival (88% versus 50%, p=0.005) and the composite of all-cause mortality and HF hospitalization (75% versus 25%, p=0.001) at one year of follow-up. Moreover, this difference is already present at 30 days of follow-up. A decrease in R_{80kHz} resulted in a significant hazard ratio of 4.96 (1.82 to 14.37) on the combined endpoint and multivariate analyses, including significantly different baseline characteristics and clinically relevant parameters, revealed no significant influence of these parameters. Effective decongestion is pivotal for good clinical prognosis. Our wearable bioimpedance monitoring device provides an easy to use parameter in this context. The current preliminary results indicate that non-invasive bioimpedance changes early during hospitalization could be used to expose the efficacy of decongestion therapy and improve resource allocation. Accordingly, patients that do not show an improvement in thoracic impedance during the first 48 hours of hospitalization, have a pour clinical outcome and require extra attention.

Furthermore, longitudinal invasive hemodynamic monitoring (i.e. pressure overload) has already shown its clinical relevance by improving HF management [115]. The proposed wearable bioimpedance monitoring device could provide an interesting non-invasive alternative since it enables longitudinal monitoring of fluid volume in an easy, inexpensive and comfortable way. Therefore, besides its in-hospital use as a prognostic parameter, it could be relevant for in-home monitoring for the early detection of volume overload and hence could address the increasing burden of worsening HF that requires hospital admission.

An alternative non-invasive approach which is very promising for fluid monitoring in heart failure was recently proposed by Amir et al. and is based on dielectric sensing technology using a wearable vest [116-118]. Initial animal and clinical studies show very promising results. The only limitation is the fact that it does not allow to distinguish in which lung compartment the fluids accumulate and it was not tested in patients with dominant right-sided heart failure. Furthermore, while bioimpedance measurements are already incorporated in most cardiovascular implantable electronic devices, this is not the fact for the dielectric sensing technology.

STUDY LIMITATIONS

This study should be interpreted in the light of some limitations. Since thoracic impedance measurements were performed on a confined area only covering the basal part of the left lung, changes in bioimpedance measured with the wearable device will therefore only give an approximation of fluid changes that happen on the whole-body level. However, if both lungs would have to be considered, the device loses the advantages of a comfortable miniaturized wearable device. Next, the number of participants is rather small, but comparable in size to other studies that assessed bioimpedance changes in HF patients [45, 46, 109]. Finally, serial echocardiographic parameters and biomarkers were not used as reference measures.

CONCLUSIONS

The current study shows the feasibility of a novel wearable bioimpedance device to track longitudinal changes in fluid status. Early changes in R_{80kHz} are clearly related to clinical outcome both at 30 days and one year of follow-up. Future studies are required to confirm whether bioimpedance monitors could have an added value in providing assistance in diagnostic evaluation, longitudinal prognostication, therapeutic decision making and in-home monitoring for the early detection of volume overload.

CHAPTER 9

Optimal electrode configuration for bioimpedance-based respiration monitoring

De Cannière H, **Smeets CJ**, Lee S, Squillace G, Groenendaal W, Grieten L, Lanssens D, Vandenberk T, Storms V, Thijs IM, Vandervoort PM

Submitted

ABSTRACT

Background: Dyspnea is a hallmark symptom in patients suffering from cardiopulmonary restrictions characterized by an increase in respiratory rate and occasionally a decrease in respiratory volume. Since recently, a rising interest in bioimpedance-based respiration monitoring is observed in the world of wearable healthcare.

Objective: The main objective of this study was to define the optimal electrode configuration for a novel wearable bioimpedance device to measure respiratory parameters at high accuracy by benchmarking against gold standard spirometry.

Methods: A wearable multi-parametric bioimpedance device from imec/Holst Centre (Eindhoven, The Netherlands) was used and benchmarked against a gold standard spirometer. The wearable device measures several physiological signals, i.e. bioimpedance, electrocardiogram and accelerometer data. Four different tetrapolar electrode configurations were tested. For each configuration, healthy subjects (n=10) performed two different protocols, each focusing on different respiratory characteristics (i.e. rate and volume).

Results: Correlation analysis and the level of agreement in measuring respiratory parameters between the wearable device and the spirometer were studied for all four different configurations. A high correlation between both systems was observed for respiratory rates whereas respiratory volumes showed moderate correlation. The configurations covering the largest surface area of the lungs showed the best correlations for both protocols.

Conclusion: Results suggest that by using the proposed optimal electrode configuration, the wearable bioimpedance device is capable of correctly measuring respiratory parameters enabling potential applications in remote disease monitoring.

INTRODUCTION

Dyspnea is a hallmark symptom in patients suffering from cardiopulmonary restrictions characterized by an increase in respiratory rate and occasionally a decrease in respiratory volume. Due to its ability to deduce different health-related parameters, measuring bioimpedance is an upcoming technique that shows a promising future in several healthcare-related applications, including respiratory monitoring.

The electrical principle behind bioimpedance is related to Ohm's law, which describes the connection between voltage drop, current intensity and electrical resistance. Two types of bioimpedance measurements can be distinguished; i.e. single frequency measurements for dynamic parameters (e.g. respiration) and multifrequency for static parameters (e.g. congestion) [119, 120]. The high sampling frequencies of single-frequency bioimpedance measurements enable respiration monitoring (both respiratory rate and volume) [95, 121, 122]. Namely, air enters the lungs during inspiration, causing a decrease in conductivity and therefore an increase in bioimpedance and vice versa.

Previous research focused on finding the ideal electrode placement for bioimpedance based respiratory monitoring. Electrodes positioned on the axillary midline and/or arms, thereby enclosing a large part of the thorax, seemed to be most suitable for this purpose [123-125]. The possibility to incorporate bioimpedance into a wearable sensor, makes it a very promising technique for continuous respiratory monitoring. A wearable bioimpedance device may therefore have an added value for patients suffering from cardiorespiratory restrictions as these are symptoms that progress when the underlying disease advances.

In the current study, a novel wearable bioimpedance device was tested for its ability to correctly measure respiratory parameters. To do so, the device was benchmarked against gold standard spirometry to find the optimal electrode configuration taking into account both signal quality and patient comfort. Such a device could facilitate the follow-up of disease progression.

METHODS

STUDY DESIGN

The current study describes the validation of a wearable bioimpedance device for its ability to accurately track respiration by benchmarking against gold standard spirometry. Healthy subjects were asked to voluntarily participate. Subjects were excluded from the study when suffering from cardiovascular or severe respiratory disorders. The study complied with the Declaration of Helsinki, the local institutional ethics committee approved the protocol, and written informed consent was obtained from all participating subjects.

EXPERIMENTAL PROTOCOLS

Ten subjects were simultaneously equipped with both the wearable bioimpedance device from imec/Holst Centre (Eindhoven, The Netherlands) and a gold standard spirometer (MasterScreen CPX Metabolic Cart, JAEGER®, Würzburg, Germany). The wearable bioimpedance device is capable of measuring several physiological signals, i.e. bioimpedance (sampling rate 1024 Hz, 80 kHz current frequency of 54 μA), electrocardiogram (ECG) (sampling rate = 512 Hz), and accelerometer data (sampling rate = 32 Hz). In total, four different electrode configurations were tested while each subject had to perform two different protocols, each focusing on different respiratory parameters. The first protocol focused on different respiratory rates and patients were asked to perform paced breathing at 10 breaths per minute (bpm), 15 bpm, and 30 bpm respectively. Pacing rhythm was indicated using a digital metronome. The second protocol focused on different respiratory volumes. At first, the subjects had to breathe with high volumes, followed by normal volumes, and finally small volumes at 15 bpm throughout the whole protocol.

ELECTRODE CONFIGURATIONS

Four different electrode configurations were tested to determine the optimal configuration for correctly measuring respiratory parameters (Figure 9.1). The different electrode configurations were selected based on previous studies [44, 123, 124]. The applicability of the electrode configuration into a wearable device and the localization of the lungs in order to ensure a good coverage of the area involved in the breathing maneuver were also taken into account.

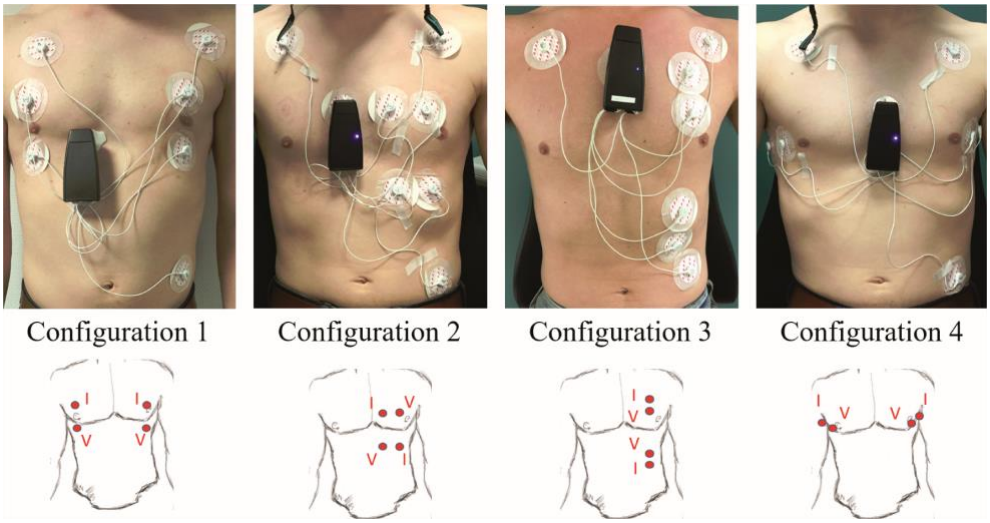

Figure 9.1: Different electrode configurations applied on each subject for each breathing protocol. The same distances between electrodes are used for every subject, except for configuration four that changes according to chest size.

For the bioimpedance electrodes, a tetrapolar electrode configuration was used in order to suppress skin-electrode contact impedance, which is unstable and alters during movement. Two electrodes were used for current injection and two for voltage measuring, making it possible to calculate the representing alterations in tissue conductivity.

STATISTICAL ANALYSIS

Continuous variables are expressed as mean ± standard deviation (SD) if normally distributed or otherwise as median (interquartile range). Normality was assessed by the Shapiro-Wilk statistics. The independent samples student's t-test and Kruskal Wallis test were used as appropriate to define statistical differences between male and female subjects. Respiratory rates and volumes between both devices were analyzed using Pearson correlation and Spearman correlation. Agreement on respiratory rates between both measurement methods was demonstrated using Bland-Altman analysis [126]. For the respiratory volume protocol, Bland-Altman analysis could not be performed as the output concerns two different measurement units (i.e. ohms for bioimpedance and milliliters for respiratory volume). However, determining the strength of correlation was sufficient when studying changes in impedance and volume, e.g. a high change in volume has to be accompanied by a high change in impedance. The significance level for tests was 2-sided with an α of 0.05. All statistical analyses were performed using the Statistical Package for Social Sciences release 23.0 (IBM® SPSS® Inc., Chicago, Illinois, USA).

RESULTS

STUDY POPULATION

10 healthy subjects (6 male, 4 female) performed the complete validation protocol. Baseline characteristics of the study population at the time of inclusion are provided in Table 9.1. The differences between males and females were investigated.

Table 9.1: Baseline characteristics of test subjects, divided into two groups, i.e. males and females.

	Male (n=6)	Female (n=4)	p-value
Age (years)	23.2 ± 2.0	23.6 ± 0.6	0.679
Length (cm)	177.0 ± 2.8	165.3 ± 4.9	0.001**
Weight (kg)	72.8 ± 8.7	58.2 ± 11.2	0.048*
BMI (kg/m2)	23.20 ± 2.3	21.2 ± 3.4	0.295
Chest circumference (cm)	83.0 ± 12.9	71.0 ± 4.7	0.116
Waist circumference (cm)	84.8 ± 10.6	88.5 ± 7.6	0.562

Data are presented as mean ± standard deviation for continuous variables. Categorical variables (gender) are presented as number of patients and percentage. *p<0.05, **p<0.01, ***p<0.001. n: sample size, BMI: Body Mass Index.

RESPIRATORY PARAMETERS

Spearman correlation analysis was performed for both respiratory rate and volume for the entire respiration protocol. An automatic peak detection algorithm was used to calculate the respiratory rates from the bioimpedance signal. Since absolute bioimpedance values are known to exhibit high individual variability, relative bioimpedance values were used to reduce intersubject differences. Therefore, the change in impedance (ΔR) was divided by the mean bioimpedance value measured for each configuration for each subject (R). Afterwards, the correlation between ΔR/R and the change in volume (ΔV) was determined for each electrode configuration (Table 9.2).

Table 9.2: Correlation coefficients between the wearable device and spirometer per electrode configuration for the respiratory rate and volume protocol. Bland-Altman analysis per configuration for the respiratory rate protocol.

	Respiratory rate protocol		Respiratory volume protocol
	Correlation coefficient	Bland-Altman Bias [95% LOA])	Correlation coefficient
CONFIGURATION 1	0.905**	1.26 [-1.17 3.69]	0.784**
CONFIGURATION 2	0.860**	1.31 [-2.39 4.99]	0.558**
CONFIGURATION 3	0.871**	1.30 [-1.97 4.56]	0.801**
CONFIGURATION 4	0.885**	1.25 [-1.24 3.75]	0.820**

*p<0.05, **p<0.01, ***p<0.001. LOA: limits of agreement.

A high positive correlation was obtained for all configurations with respect to respiratory rate, with the highest correlation for configuration 1. Configuration 2 showed a moderate positive correlation for respiratory volumes, whereas the other configurations were characterized by a high positive correlation. In general, higher correlations were observed for the respiratory rate across all configurations, whereas correlations for respiratory volume are more dependent on the electrode configuration.

Next, the correlation and measurement agreement was determined for different respiratory rates and respiratory volumes, for each electrode configuration individually. Whereas normal breathing rates show a moderate to high correlation, correlation reduces with increased respiratory rate. Only configuration two showed a negligible correlation for the highest breathing rate (0.283). Other configurations range from low to moderate positive correlations for the highest breathing rates, with configuration 1 showing the best results over the different breathing rates. Every electrode configuration shows a reduction in correlation with increasing respiratory rate (Table 9.3), as data points are more deviating from the reference line when respiration rate increases (Figure 9.2).

Table 9.3: Correlation coefficients between the wearable device and spirometer for each electrode configuration for the different respiratory rates.

	10 bpm	15 bpm	30 bpm
CONFIGURATION 1	0.670**	**0.645****	**0.526****
CONFIGURATION 2	0.627**	0.474**	0.283**
CONFIGURATION 3	0.601**	0.462**	0.342**
CONFIGURATION 4	**0.723****	0.470**	0.416**

*p<0.05, **p<0.01, ***p<0.001. bpm: breaths per minute.

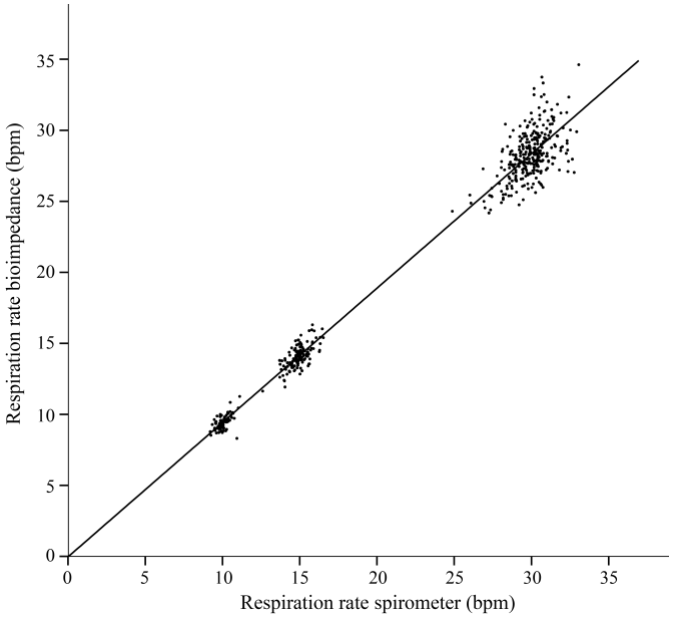

Figure 9.2: Correlation between the wearable device and spirometer for the respiratory rate protocol for configuration 1.

A Bland-Altman analysis was performed to determine the measurement agreement for the different respiratory rates (Table 9.4).

Table 9.4: Bland-Altman analysis per configuration for the respiratory rate protocol.

	10 bpm (Bias [95% LOA])	**15 bpm (Bias [95% LOA])**	**30 bpm (Bias [95% LOA])**
CONFIGURATION 1	**0.59 [-0.09 1.26]**	0.86 [-0.29 2.01]	**1.65 [-1.23 4.52]**
CONFIGURATION 2	0.59 [-0.28 1.45]	0.84 [-0.68 2.36]	1.74 [-2.87 6.35]
CONFIGURATION 3	0.60 [-0.20 1.40]	0.83 [-0.82 2.48]	1.74 [-2.24 5.71]
CONFIGURATION 4	0.57 [-0.24 1.37]	**0.86 [-0.22 1.95]**	1.65 [-1.33 4.64]

*p<0.05, **p<0.01, ***p<0.001. LOA: limits of agreement.

The Bland-Altman analysis shows the bias and 95% limits of agreement between both measurement methods, which both increase with increasing respiratory rates. However, for 10 and 15 bpm, the bias remains below one breathe per minute, whereas it does not cross two breathes per minute for the 30 bpm part. High 95% limits of agreement are seen for the highest respiratory rate, with configuration 2 showing the largest range. The graph shows the Bland-Altman analysis for configuration 4 at a breathing rate of 15 breaths per minute.

The correlation coefficients between the wearable device and the gold standard spirometer for the different respiratory volumes per electrode configuration are shown in Table 9.5.

Table 9.5: Correlation coefficients between the wearable device and spirometer per electrode configuration for the different respiratory volumes.

	High volume	Normal volume	Small volume
CONFIGURATION 1	**0.696****	0.629**	**0.589****
CONFIGURATION 2	0.675**	0.692**	0.399**
CONFIGURATION 3	0.659**	0.595**	0.454**
CONFIGURATION 4	0.594**	**0.704****	0.568**

*p<0.05, **p<0.01, ***p<0.001.

Correlation factors for the different respiratory volumes range from a low to a high positive correlation. Both configuration 1 and 4 show the highest correlation across all volumes.

INTER-SUBJECTIVE DIFFERENCES

Since gender is a demographic parameter that could influence the measured bioimpedance-signal due to the female body composition and hence the correlation coefficients, the correlations for females and males were determined separately. Correlation factors for respiratory rates show a high to very high positive correlation for both males and females across all electrode configurations (Table 9.6). The ability to correctly measure changes in respiratory volumes is gender dependent. Configuration 2 shows a negligible correlation for females when measuring respiratory volume. The other configurations range from a moderate to a high positive correlation between the wearable device and the spirometer for both males and females.

Table 9.6: Spearman correlation coefficients between the wearable device and spirometer taking gender into account when comparing measurement methods per configuration for each protocol separately.

		Respiration rate correlations	Respiration volume correlations
CONFIGURATION 1	Male	**0.902****	0.800**
	Female	**0.911****	0.679**
CONFIGURATION 2	Male	0.859**	0.650**
	Female	0.858**	0.059
CONFIGURATION 3	Male	0.866**	0.818**
	Female	0.877**	0.639**
CONFIGURATION 4	Male	0.863**	**0.802****
	Female	0.919**	**0.853****

*p<0.05, **p<0.01, ***p<0.001.

DISCUSSION

The ability of a wearable device to correctly and accurately measure respiratory parameters shows great application potential in future healthcare [95, 127]. A hallmark symptom of patients suffering from cardiopulmonary diseases are respirational restrictions, characterized by an increase in respiratory rate and accompanied by a reduction in respiration volume. During this study, the optimal electrode configuration for a novel wearable bioimpedance device to accurately measure different respiratory parameters was validated against gold standard spirometry.

Major insights were: (1) Correlation factors for respiratory rates were higher compared to correlation factors for respiratory volumes. (2) Due to influences of torso composition and volume, correlations for respiratory volumes measured by impedance versus spirometer were lower.

For all electrode configurations that were tested, high to very high positive correlations between the wearable device and the spirometer were observed with respect to respiratory rate. Gender did not influence the ability of the wearable device in accurately detecting respiratory rate. It was observed that higher respiratory rates were accompanied by lower correlation factors and limits of agreement. Only configuration 2 transcends the clinically acceptable range of 4 to 6 breaths per minute, as stated by previous research [128]. This can be attributed to the fact that intense thoracic movement due to fast respiration can disturb signal quality, caused by the influence of the diaphragm and liver conductivity characteristics [129, 130]. This is especially the case for configuration 2 and 3 as they are located on a lower position of the midaxillary line.

The correlation factor for respiratory volumes between the wearable device and the spirometer ranges from moderate to high positive correlations, suggesting that the wearable is capable of detecting a change in impedance when a similar change in volume is measured. The lowest correlation was found for configuration 2, for which the electrodes and the bioimpedance signal only cover half of the thorax whereas the spirometer measures the complete lung volume. The position of the electrodes is of importance for the measurement surface covered by the impedance signal [131]. Logic *et al*. [125] and Baker *et al.* [132] concluded that electrodes positioned higher on the midaxillary axis showed a better correlation between impedance and volume changes. Sëppa *et al.* [123] also stated that the lower the electrodes are positioned on the midaxillary axis, the lower the correlation between volume and impedance changes will be. In addition, Hinz *et al.* showed that the level of aerated regions in the lungs affect the impedance signal. Shallow breathing will affect the aerated

regions in the lungs and therefore possibly affect the correlation measured between impedance values and respiratory volumes [133].

Another important aspect is the influence of subject specific characteristics (e.g. body weight or gender) on signal quality [134]. These characteristics can attribute to the low signal quality for certain electrode configurations. The differences in body shape can alter the range of lung volume covered by the impedance signal for certain configurations and can explain the discrepancies between bioimpedance and spirometer outcomes. As such, the female body composition, i.e. fat mass, chest circumference, build can differ substantially from the male body characteristics. Configurations 1, 2, and 3 are subjective to the build of the female and therefore are less suitable, keeping both signal quality and user comfort in mind. Due to these subject specific characteristics it is still not possible to build a conversion factor that allows to determine the absolute value of respiratory volumes based on thoracic bioimpedance. In other words, it is impossible to determine the absolute volume of air that enters and leaves the lungs. When absolute volumes are desired, further research is needed [135].

In conclusion, configuration 1 and configuration 4 appear to generate the optimal bioimpedance signal quality for the measurement of the respiratory parameters. Both the correlation factors and measurement agreement calculated between the wearable device and the spirometer showed the best results for both genders. When considering the user comfort, preference goes out to configuration 4, which is easier to apply in female patients. To conclude, an electrode configuration located on the midaxillary axis at the level of the intercostal line is the most suited configuration taking comfort and signal quality into account.

CONCLUSIONS

The optimal electrode placement is located at the level of the midaxillary axis at intercostal line height. This electrode configuration shows moderate to high positive correlations when compared to gold standard spirometry. On top, it shows a good measurement agreement when assessing both respiratory rate and volume. Since continuous long-term remote monitoring is the intended use of a wearable device, user comfort is of upmost importance. Gender specific characteristics therefore play an important role in determining the optimal electrode configuration. All the above mentioned results support the further development of wearable bioimpedance-based devices for remote monitoring applications, as patients suffering from cardiopulmonary restrictions will benefit from continuous follow-up using wearable technologies. In conclusion, placing the electrodes on the midaxillary axis at intercostal line height is most desirable when considering female subjects.

PART III

REMOTE MONITORING BY NON-INVASIVE PORTABLE DEVICES

CHAPTER 10

A novel intelligent two-way communication system for remote heart failure medication uptitration (the CardioCoach study): a feasibility study

Smeets CJ, Storms V, Vandervoort PM, Dreesen P, Vranken J, Houbrechts M, Goris H, Grieten L, Dendale P

JMIR Cardio

In press

ABSTRACT

Background: European Society of Cardiology (ESC) guidelines for the treatment of heart failure (HF) prescribe uptitration of angiotensin-converting enzyme inhibitors (ACE-I) and β-blockers to the maximum-tolerated, evidence-based dose. Although HF prognosis can drastically improve when correctly implementing these guidelines, studies showed that they are insufficiently implemented in clinical practice.

Objective: The aim of this study was to verify whether supplementing the usual care with the CardioCoach follow-up tool is feasible and safe and whether the tool is more efficient in implementing the guideline recommendations for β-blocker and ACE-I.

Methods: A total of 25 HF patients were randomly assigned to either the usual care group (n=10) or CardioCoach intervention group (n=15) and observed for 6 months. The CardioCoach follow-up tool is a two-way communication platform with decision support algorithms for semi-automatic remote medication uptitration. Remote monitoring sensors automatically transmit patient's blood pressure, heart rate, and weight on a daily basis.

Results: Patient's satisfaction and adherence for medication intake (93%) and vital sign measurements (95%) were excellent. However, the number of technical issues that arose was large, with 831 phone contacts (median 41 [interquartile range, IQR, 32-65]) in total. The semi-automatic remote uptitration was safe, as there were no adverse events and no false positive uptitration proposals. Although no significant differences were found between both groups, a higher number of patients was on guideline-recommended medication dose in both groups compared with previous reports.

Conclusion: The CardioCoach follow-up tool for remote uptitration is feasible and safe and was found to be efficient in facilitating information exchange between care providers, with high patient satisfaction and adherence.

INTRODUCTION

Heart failure (HF) is a major health problem affecting more than 10% in the elderly over the age of 70 years [1-5]. Mortality rates are high, with only 50% of patients surviving up to 5 years after first diagnosis. Hospitalization rates are even higher with 1-year hospitalization rates of approximately 40% and a readmission rate of 30-45% within 6 months after initial admission [6-9]. These high (re)admission rates put a large burden on the current health care system [10-12].

Improvements in treatment strategies have reduced mortality and (re)hospitalization rates. In 2016, the updated guidelines of the European Society of Cardiology (ESC) concerning the diagnosis and treatment of acute and chronic HF with reduced ejection fraction were published [1]. These guidelines prescribe uptitration of angiotensin-converting enzyme inhibitors (ACE-I) and β-blockers to the maximum-tolerated, evidence-based dose in function of a patient's weight, blood pressure, heart beat, and kidney function. There is strong evidence that adherence to guidelines and optimal drug treatment leads to a better clinical outcome and reduced mortality and (re)hospitalizations [1]. Heart failure disease management programs are widely used to facilitate the implementation of guideline recommended treatment strategies [55, 136-139]. Unfortunately, studies have proven that they are still insufficiently implemented in practice [138, 140-142].

The addition of remote monitoring combined with integrated clinical decision support in this aspect could provide added value for both the healthcare provider and the patient. Remote monitoring of vital parameters and other patient information could allow care givers to evaluate and adjust patients' medication schemes remotely according to ESC guidelines [143]. Remote β-blocker uptitration based on patient's self-collected physiologic data transmitted by phone has been previously studied and showed a positive impact on β-blocker use [143-145]. The IN-TOUCH trial was one of the first studies to study the value of a decision support algorithm for medication uptitration in addition to remote monitoring (ie, weight, blood pressure, and electrocardiogram) compared to remote monitoring alone. However, this study lacked a usual care control group and could not show differences in clinical outcome [146, 147]. Kropf et al also developed a remote monitoring strategy with integrated clinical decision support, but the algorithm was only retrospectively analyzed with existing remote monitoring datasets [148]. The aim of Kropf et al was to prospectively study this strategy in a large-scale randomized trial, but unfortunately the trial was stopped and no

results are available. Therefore, the CardioCoach study is the first to study the feasibility of remote monitoring with integrated decision support on HF drug treatment optimization.

The CardioCoach study combines a two-way communication platform with decision support algorithms together with remote monitoring sensors for active medication uptitration. The study will verify whether supplementing the guideline-driven usual care with this two-way communication platform can implement the guideline recommendations for β-blocker and ACE-I more efficiently. This paper focusses on the feasibility of the communication platform for adjusting HF medication remotely and for detecting early deterioration by monitoring blood pressure, heart rate, and weight changes. Patient's vital measurement and therapy adherence were actively encouraged by the smartphone app and were evaluated together with the patient's satisfaction of the CardioCoach tool.

METHODS

STUDY DESIGN

This is a prospective single-center randomized control feasibility trial conducted in a Belgian tertiary care center (Jessa hospital, Hasselt, Belgium) with a specialized HF disease clinic. Newly diagnosed patients with HF and initiation of β-blocker and/or ACE-I therapy or patients with known HF but on suboptimal dosage of β-blocker and/or ACE-I therapy were approached. Upon inclusion, block randomization was used to divide patients in either the usual care control group or the CardioCoach intervention group (clinical trial registration with www.clinicaltrials.gov; identifier NCT03294811). All patients provided written informed consent and were followed for 6 months after study enrolment. The study complies with the Declaration of Helsinki, and the study protocol was approved by the local committee on human research.

USUAL CARE CONTROL GROUP

ESC guidelines on uptitration of β-blocker and/or ACE-I therapy are primarily intended to be used by physicians. Therefore, medication dose adaptions were performed during occasional outpatient visits to the cardiologist or general practitioner. Medication doses were determined based on patient's vital sign measurements, overall well-being, and symptoms. Besides an additional follow-up visit at 3 months, we did not modify the usual care as per standard practice organized in the institution where patients have a scheduled follow-up visit at 6 months.

CARDIOCOACH INTERVENTION GROUP

Patients allocated to the CardioCoach intervention group also had a scheduled follow-up visit at 3 months and 6 months. For these patients, the usual care was supplemented with the CardioCoach follow-up tool to proactively uptitrate β-blocker and ACE-I treatment and improve medication adherence for β-blocker, ACE-I, and diuretic treatment. In terms of diuretic treatment, only medication adherence was monitored because it was not part of the active uptitration protocol. This intervention included a two-way communication platform connected to remote monitoring devices such as a weighing scale and blood pressure monitor to collect vital measurements (ie, weight, blood pressure, and heart rate), in which patients are followed by a technical and clinical call center. Medical follow-up (eg, medication uptitration, alerts on threshold crossing) was done by the clinical call center in the hospital, whereas technical follow-up (eg, missed transmissions, technical issues.) was done by

Remedus (Aartselaar, Belgium). Both call centers were active during working hours; notifications received during the weekend were read on Monday.

THE CARDIOCOACH FOLLOW-UP TOOL FOR SEMI-AUTOMATIC MEDICATION UPTITRATION

The two-way communication platform consisted of a smartphone with the preinstalled CardioCoach app, a blood pressure monitor, weighing scale, and an web-based health management server (Remecare) with a clinical dashboard for the care provider (HF nurse). An overview of the CardioCoach follow-up tool can be found in Figure 10.1. The CardioCoach app was used to trigger the patient to conduct different actions, such as record a vital sign measurement, complete a questionnaire, and confirm medication intake by sending reminders at predefined time points. For each action, a 5-hour time window was set in which the patient could record all necessary data. This time window could be customized for each patient and was made available an hour before and 4 hours after the ideal recording time. All vital sign measurements were transmitted automatically to the CardioCoach app without manual patient input. The patient-specific medication scheme for β-blocker, ACE-I, and diuretic treatment was automatically uploaded to the patients' smartphones every morning to inform them about their actual medication dose for that day. When changes were applied to the medication scheme, the patient was notified via a pop-up message, which he/she had to confirm. In addition, a daily education tip is pushed by the smartphone app to the patient covering different HF disease aspects (eg, tips to manage fluid and salt restriction, exercise,). Screenshots of the CardioCoach app are shown in the Supplementary files, Figure S 10.1.

All information gathered via the CardioCoach smartphone app (ie, vital signs, questionnaires, medication intake) was automatically transmitted to a secured web-based health management server (ie, Remecare) without patient input. On this server, the completeness of patient data and possible deviations of vital signs based on predefined thresholds were verified.

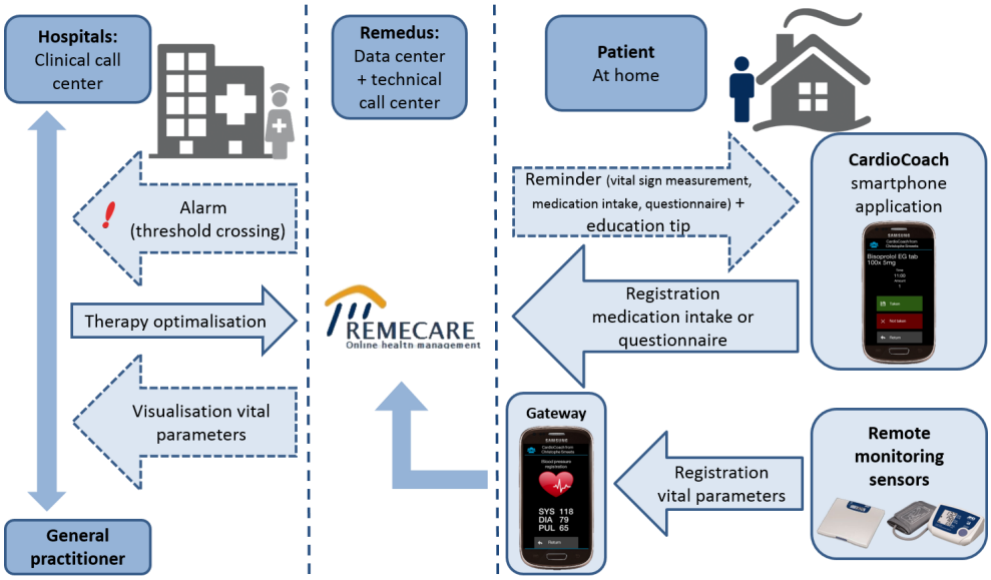

Figure 10.1: Overview of the CardioCoach follow-up tool.

When a patient does not record medication intake or vital sign data or does not complete a questionnaire, a pop-up message was pushed 2 hours after the ideal recording time via the smartphone to inform the patient about the missed registration and stress the importance of this information for the medication uptitration process. If the patient still did not complete the required action 4 hours after the ideal recording time, a *no registration* tag was recorded in the clinical database and the patient was contacted by the technical call center within 12 hours. In case of missed medication intake, the technical call center asked whether the patient forgot to register the medication intake or whether the patient forgot to take the required medication. In case of vital sign thresholds crossings for 3 consecutive days (Table 10.1), an automatic custom-made HF questionnaire was pushed to the patient via the CardioCoach smartphone app to gain insight about his/her general well-being or symptoms related to deviating vital signs, and a message was sent to the clinical call center to review the vital sign data and questionnaire (Supplementary files, Table S 10.1).

Table 10.1: Vital sign thresholds.

Parameter	Thresholds for three consecutive days
Weight	Baseline weight +2kg
Heart rate	<60 bpm or >100bpm
Systolic blood pressure	<90 mmHg or >160mmHg
Diastolic blood pressure	<60 mmHg or >95 mmHg

CARDIOCOACH MEDICATION UPTITRATION CLINICAL DECISION SUPPORT ALGORITHM

In the CardioCoach intervention group, β-blocker and ACE-I medication uptitration was supported by a clinical decision support algorithm, initiated at study inclusion. The algorithm generated a medication uptitration proposal at fixed moments in time during the first 3 months of follow-up, known as the active uptitration phase. Moreover, every 2 weeks, the algorithm alternately generated a medication uptitration proposal for either the β-blocker or ACE-I. At the beginning of week two, the first proposal was generated, which comprised β-blocker uptitration, followed by another proposal for ACE-I uptitration at week 4. In total, there were 6 uptitration proposals during the first 3 months. Before each proposal, the short version of the custom-made HF questionnaire (Supplementary files, Table S 10.1) was pushed to the patient's smartphone to enquire about his/her general health and expose possible medication-induced side effects, which would help in deciding the safety of medication uptitration to the next level. A week before the ACE-I uptitration proposal, the algorithm generated a blood withdrawal request for analysis on kidney function (Figure 10.2). The type of proposal, generated by the algorithm, was generated based on predefined decision trees, taking into account all gathered patient information (vital signs, blood parameters, and questionnaires), which could include the following: (1) medication uptitration to the next level, (2) no uptitration or (3) medication uptitration to the next level only possible after evaluation by the HF nurse due to incomplete data, aberrant vital sign data, or aberrant blood parameters.

Before implementation of the updated medication scheme on the patient's smartphone app, every proposal of the algorithm was reviewed by a dedicated HF nurse. The nurse could either choose to confirm the proposal, to call the patient before taking a decision, to make other changes to the patient's medication scheme or to leave it unchanged or indicate that the optimal medication dose has been reached. During the last 3 months of follow-up (ie, from 3 to 6 months), the active uptitration algorithm was deactivated and was followed by a less intensive follow-up phase during which medication intake and vital sign parameters were still monitored and medication uptitration on the discretion of the HF nurse can still proceed.

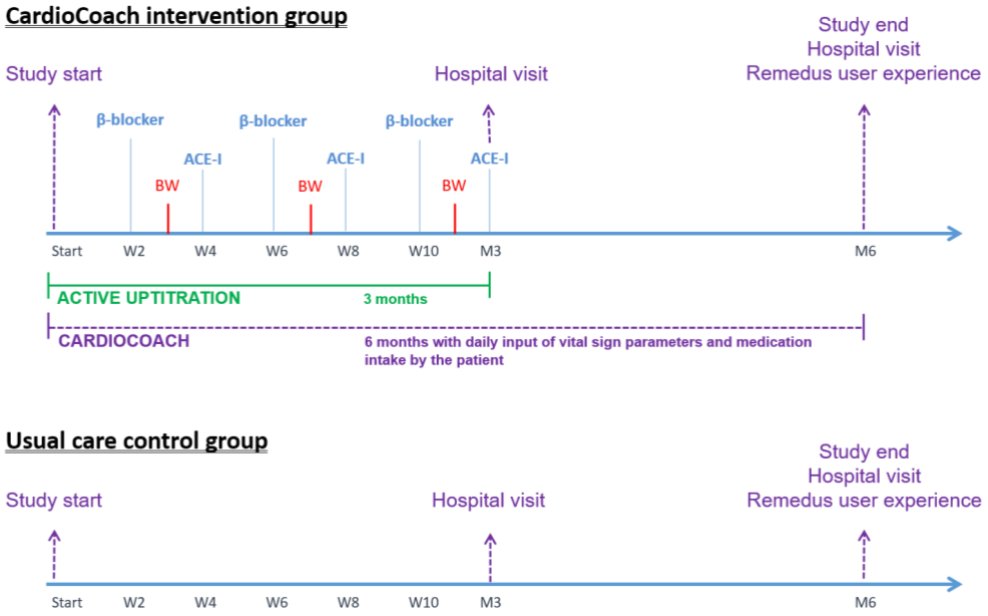

Figure 10.2: Overview of the study protocol for both the CardioCoach intervention group and usual care control group. ACE-I, angiotensin converting enzyme inhibitors; BW, blood withdrawal.

Finally, at 6 months of follow-up, patients from the CardioCoach intervention group were provided with a CardioCoach user experience questionnaire to gain feedback on the use of the CardioCoach smartphone app, the remote monitoring sensors, the contact with HF nurses and technical follow-up team.

OUTCOME MEASUREMENTS

Outcome measures included CardioCoach user experience, (therapeutic) adherence, call center statistics, algorithm performance, and the number of patients on guideline-recommended medication dose for β-blocker and ACE-I (Table 10.2) at both 3 and 6 months of follow-up.

Table 10.2: Max daily dose as recommended by European guidelines.

Active ingredient	Max daily dose (mg)
ACE-I	
Perindopril	10
Enalapril	10
Ramipril	10
Lisinopril	20
Candesartan	16
Losartan	100
β-blocker	
Bisoprolol	10
Nebivolol	5

ACE-I, angiotensin converting enzyme inhibitors.

STATISTICAL ANALYSIS

Demographic and functional characteristics were compared using descriptive statistics. Continuous variables were expressed as mean ± standard deviation if normally distributed, or otherwise as median (interquartile range, IQR). To define statistical differences between both groups, the independent samples student *t* test and Mann-Whitney U test were used for normally and not normally distributed continuous variables, respectively. The chi-square test and Fisher exact test were used accordingly for categorical variables. To define statistical differences between NYHA class, the Kruskal-Wallis test was used. The significance level for tests was two-sided with an alpha of .05. All statistical analyses were performed using the Statistical Package for Social Sciences version 24.0 (IBM SPSS Inc., Chicago, Illinois, USA).

RESULTS

STUDY POPULATION

In total, 25 patients were included in the CardioCoach study. One patient dropped out before 3 months of follow-up and was therefore excluded from analysis. After 3 months of follow-up, 2 more patients dropped out but were still included in the analysis until 3 months of follow-up, because they completed the active medication uptitration phase. The final study population consisted of 24 patients: 14 patients were included in the CardioCoach intervention group and 10 patients were included in the usual care control group. Baseline characteristics of the study population at the time of inclusion are provided in Table 10.3. At the time of study enrollment, no significant between-group differences were observed in clinical characteristics or the use of medications commonly prescribed to patients with HF.

Table 10.3: Baseline characteristics of the study population at the moment of study inclusion (n=24).

Variables	CardioCoach intervention group (n=14)	Usual care control group (n= 10)	*P* value
Male gender	9 (64%)	6 (60%)	1.00
Age, years	63 ± 15	60 ± 15	.55
BMI	28 ± 5	28 ± 5	.88
Heart rate	73 ± 13	73 ± 13	.99
Systolic blood pressure	112 ± 14	127 ± 25	.08
Diastolic blood pressure	75 ± 12	75 ± 12	.98
NYHA functional class (II/III)	6 (43%) / 6 (43%)	4 (40%) / 5 (50%)	.92
Left ventricular ejection fraction, %	28 ± 7	29 ± 7	.84
QRS width, ms	100 (IQR 90-121)	100 (IQR 92-121)	.89
Ischemic cardiomyopathy	4 (29%)	1 (10%)	.36
Dilated cardiomyopathy	5 (36%)	5 (50%)	.68
Risk factors and comorbidities			
Obesity	9 (64%)	3 (30%)	.10
Arterial hypertension	9 (64%)	3 (30%)	.10
Smoking	9 (64%)	9 (90%)	.34
Family history of cardiovascular diseases	7 (50%)	4 (40%)	.70
Hypercholesterolemia	9 (64%)	5 (50%)	.68
Chronic kidney disease	2 (14%)	0 (0%)	.49
Atrial fibrillation	6 (43%)	4 (40%)	1.00
Diabetes	3 (21%)	1 (10%)	.62
Chronic obstructive pulmonary disease	1 (7%)	1 (10%)	1.00
Pro-BNP	559 (IQR118-1278)	262 (IQR 129-467)	.44
eGFR	50 ± 28	65 ± 19	.16
Medication use			
Angiotensin converting enzyme inhibitor	7 (50%)	3 (30%)	.42
β-blocker	7 (50%)	3 (30%)	.42
Spironolactone	1 (7%)	1 (10%)	1.00
Loop diuretic	1 (7%)	2 (20%)	.39
Statin	7 (50%)	3 (30%)	.42
Calcium channel blockers	0 (0%)	1 (10%)	.42
Anti-diabetic medication	1 (7%)	1 (10%)	1.00
Technological experience			
Normal cell phone	8 (57%)	6 (60%)	1.00
Smartphone	3 (21%)	3 (30%)	.67
Computer at home	7 (50%)	4 (40%)	.70
Internet connection at home	2 (14%)	3 (30%)	.62
Tablet at home	7 (50%)	4 (40%)	.70

Continuous data are expressed as mean ± SD if normally distributed and dichotomous data are expressed as n (%). BMI, Body mass index; NYHA, New York Heart Association; BNP, Brain natriuretic peptide; eGFR, Estimated glomerular filtration rate.

CARDIOCOACH MEDICATION UPTITRATION CLINICAL DECISION SUPPORT ALGORITHM

On the basis of gathered data, the CardioCoach algorithm generated 72 medication uptitration proposals in total. In 7% of the cases, the algorithm generated a conclusive proposal, whereas in 93% of cases, the decision was left up to the HF nurse. This was mainly due to aberrant (67%) or incomplete (25%) data. Table 10.4 summarizes the frequency of the different algorithm uptitration proposals.

Table 10.4: Overview of the different algorithm uptitration proposals and their frequency.

	Total (n=72)	β-blocker (n=41)	ACE-I (n=31)
Uptitration to next level	1 (1%)	1 (2%)	0
No uptitration to next level	4 (6%)	3 (7%)	1 (3%)
Uptitration dependent on evaluation heart failure nurse due to incomplete data	18 (25%)	11 (27%)	7 (23%)
Uptitration dependent on evaluation heart failure nurse due to aberrant data	48 (67%)	26 (63%)	22 (71%)
Uptitration dependent on evaluation heart failure nurse due aberrant blood parameters	1 (1%)	0 (0%)	1 (3%)

ACE-I, angiotensin converting enzyme inhibitors.

After each automatic uptitration proposal from the algorithm, the HF nurses in the clinical call center received a notification, which they had to consider. Nurses could respond in different ways to the uptitration proposal (Table 10.5). The algorithm proposal was confirmed by the HF nurse in 69%, and in 35% the patient was contacted for further interrogation before decision. No adverse events or false positive uptitration proposals were reported.

Table 10.5: Overview of the different responses of the heart failure nurses to the algorithm uptitration proposals.

	Total	β-blocker	ACE-I
Confirm algorithm proposal	50 (69%)	29 (71%)	21 (68%)
Patient was contacted before decision was made	25 (35%)	17 (41%)	8 (26%)
Change of other medication	10 (14%)	8 (20%)	2 (6%)
Optimal medication dose reached	25 (36%)	13 (32%)	12 (39%)

THERAPEUTIC ADHERENCE

Overall, therapeutic adherence as confirmed by the patient via the smartphone app (77%) or via the technical call center after contacting the patient (16%) for the 3 drug treatments was 93%, with, respectively, 97% for β-blockers, 95% for ACE-I, and 86% for diuretics. In 1 out of 5 cases, patients did not record medication intake into the CardioCoach smartphone app, and the technical call center had to contact the patients to verify medication intake (Figure 10.3A). In terms of vital sign registration, patient adherence was 95%. In 13% of these cases, technical issues hindered automatic transfer of vital sign data to the online database, and the technical call center had to contact the patient to receive the data, and in 5% no vital sign measurement was recorded (Figure 10.3B).

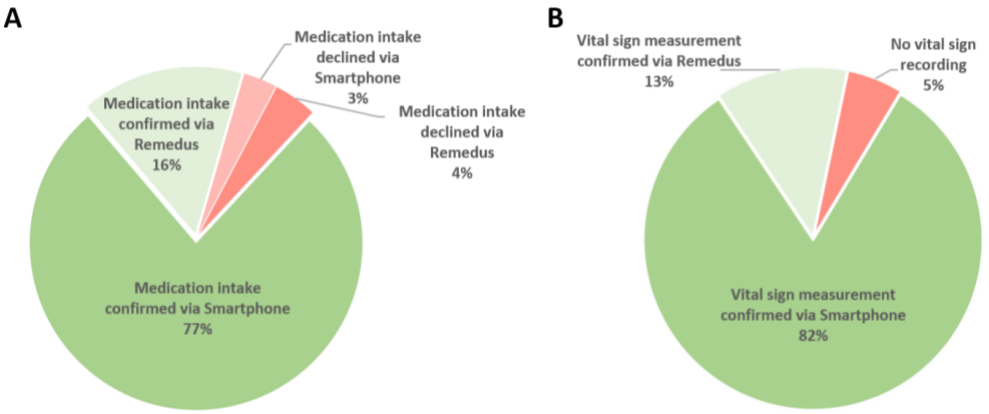

Figure 10.3: Therapeutic adherence for medication intake (A) and vital sign measurement recording (B).

TECHNICAL CALL CENTER STATISTICS

For the 14 CardioCoach patients, the Remedus call center made 831 phone calls in total, with a median of 41 phone calls per patient (IQR 32-65). Phone calls were initiated in case of missed vital sign measurements (n=136), missed medication intake (n=661) (diuretic intake 44%, ACE-I intake 35%, and β-blocker intake 21%), or missing questionnaires (n=34). Due to the limited technical skills of the study participants, technical problems could hardly be solved remotely, and therefore, a device swap was performed in 10 patients: 4 patients had 1 device swap, 5 patients had 2 device swaps, and 1 patient had 3 device swaps.

CARDIOCOACH USER EXPERIENCE

Among the CardioCoach user experience questionnaire, 4 questionnaires were missing: 3 due to early study termination and 1 due to an issue with the web-based questionnaire platform. Detailed results of these questionnaires can be found in the Supplementary files (Table S 10.2). In general, patients were very satisfied, and mentioned the ease of use of the smartphone app and remote monitoring sensors. Daily coaching tips were reviewed as being positive and stimulating. In addition, patients experienced an extra sense of safety, and 50% of patients were eager to continue using the CardioCoach follow-up tool after the study ended. Due to the CardioCoach app, 80% patients reported an increased medication adherence. Patients reported a positive experience in terms of communication with both the technical and clinical call centers. Interestingly, patients were indifferent about the fact that their parameters were being reviewed by an external, home nursing company. Finally, patients did mention a large number of technical issues (eg, connectivity issues, problems with the remote monitoring sensors).

MEDICATION UPTITRATION

No significant differences were observed in the number of patients on guideline-recommended maximum β-blocker dose in the CardioCoach intervention group when compared with the usual care control group at both 3 months (43% vs 40%, $P>.99$) and 6 months (50% vs 40%, $P=.69$) of follow-up (Figure 10.4A). Additionally, in terms of ACE-I uptitration, no significant differences were observed at both 3 months (43% vs 40%, $P>.99$) and 6 months (42% vs 40%, $P>.99$) of follow-up (Figure 10.4B). In addition, there was no difference in terms of time to uptitration to guideline-recommended medication dose. All patients that reached guideline recommended dose, did so before three months of follow-up (except one for β-blockers).

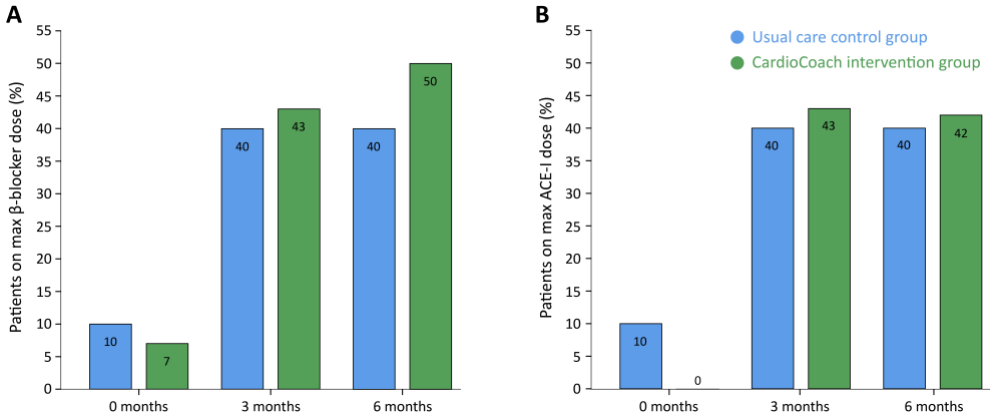

Figure 10.4: The number of patients on max daily dose as recommended by European guidelines for both β-blockers (A) and ACE-I (B). No significant differences were observed between both groups.

DISCUSSION

Since 1997, ESC guidelines for the diagnosis and treatment of acute and chronic HF have recommended the optimization of drug treatment as the first step in patients diagnosed with HF [1, 149]. Unfortunately, these guidelines are insufficiently implemented in clinical practice and many HF patients are still on suboptimal medication dose [138, 140-142]. This paper describes the rationale and feasibility of a novel two-way communication platform with decision support algorithms, in combination with a smartphone app, blood pressure monitor, and weighing scale, intended to support β-blocker and ACE-I uptitration remotely. The success rate of studies monitoring weight, blood pressure, and heart rate to improve clinical outcome is rather low, probably because they are unable to capture the complexity of HF disease progression, which often involves multiple comorbidities [37, 150-154]. However, the benefits of medication uptitration, have only recently been studied and is the objective of this study [143, 148].

The results of this feasibility study with 24 patients, monitored for a period of 6 months, showed a marginal increase in the number of patients on guideline-recommended β-blocker and ACE-I dose when using the CardioCoach remote monitoring follow-up tool compared with usual care. However, in comparison with previous studies, both our intervention and control group consisted of a higher number of patients, who were on guideline-recommended medication dose. Maggioni et al [140] and Heywood et al [141] reported, respectively, 29% and 35% of patients on target dose for ACE-I and 17% and 15% for β-blockers. This suggests that the usual care provided in our institution is superior to the standard care described in literature, and the addition of the CardioCoach follow-up tool can lead to comparable and even slightly better results. Hence, remote monitoring could be a suitable method for increasing the number of HF patients on guideline recommended target dose, especially in centers with less intensive usual care follow-up.

Feedback received from the patients using the CardioCoach follow-up tool revealed overall good patient satisfaction in terms of both the use of the remote monitoring devices and the contact between the patient and technical and clinical call centers. This resulted in excellent overall therapeutic adherence of the patients during the entire study period for medication intake (93%) and vital sign measurements (95%). In spite of the frequent reminders via the smartphone, this shows that the CardioCoach follow-up tool was well accepted by the patients as compared with remote monitoring strategies used in previous studies [155, 156]. Unfortunately, patients did mention many technical issues, which are deduced from the large number of phone calls between the patient and the technical call center of Remedus.

In 1 out of 5 cases, patients were contacted by the technical call center to verify medication intake. In most of these cases, the patients confirmed medication intake, but due to the technical issues, this information was not transmitted to the Remecare platform. Only 7% of cases reported that the patient had not taken his/her medication. This was rarely due to the forgetfulness of the patient, but mostly because of a change in patient's medication scheme outside the CardioCoach environment (eg, by a general practitioner). In terms of vital sign measurements, 13% of the measurements were collected over the phone by the technical call center since technical issues hindered automatic transfer of vital sign data to the Remecare Platform. These technical issues also included issues that arose because of the technophobe elderly study population (eg, problems changing/charging device batteries, reboot smartphone). In 5% of cases, defective remote monitoring sensors made it impossible to record a vital sign measurement. The high number of technical issues clearly demonstrates the need for a separate technical call center to handle these issues, avoid extra work burden for the clinical call center, and ensure complete data for clinical decision making. Although the next generation of seniors will probably be more familiar with technical developments, technical improvements are still necessary to further decrease these issues.

In this study, the algorithm was built with a large safety margin to avoid false positive uptitration proposals, which has led to a low number of conclusive proposal by the algorithm (7%). In addition, every proposal had to be validated by a dedicated HF nurse. In 69% of the cases, the HF nurse confirmed the algorithm proposal. This shows that parameter thresholds can be confined. In this sense, the current feasibility study was very useful for the future development and improvement of an optimal two-way communication system between patients and caregivers. On the basis of feedback from both patients and HF nurses, improvements can be made to the next generation, which will take into account the work efficiency of the HF nurses and enable a customized approach for patients (eg, patient-specific or less confined parameter thresholds, patient-specific uptitration scheme). The CardioCoach follow-up tool is very efficient in facilitating information exchange between the different care providers (ie, HF specialist, HF nurse, general practitioner, home nurse) and enables a safe way for medication uptitration, as there were no adverse events or false positive uptitration proposals reported. The use of the CardioCoach follow-up tool has been shown to be feasible when combined with a technical call center to handle technical issues and reduce the workload of the clinical call center. This study was unable to demonstrate a significant improvement of the CardioCoach follow-up tool on the number of patients on maximum guideline recommended β-blocker and ACE-I dose. Probably, this is related to the fact that patients in the control group were also enrolled in a dedicated HF outpatient

disease management program, where HF medication dosages were being optimized by intensive follow-up by specialized HF nurses and HF specialists. Hence, the CardioCoach follow-up tool might be more suitable in centers with less intensive HF disease management programs.

STUDY LIMITATIONS

This feasibility study should be interpreted in the light of some limitations to place the study findings into a correct context. First, the small sample size and the single-center character may impact its external validity. Therefore, these results should be interpreted as hypothesis generating, and an additional multi-center study is necessary to confirm these results. In this study, the control group received the usual care as per protocols standardized in the institution and received no remote monitoring sensors. This is a general issue in multiple remote monitoring studies, which should be taken into account when interpreting study findings as relevant information from the control group may be missing. An alternative control group could be a group in the same setting (ie, with remote monitoring sensors), but without a physician reviewing the data. Next, technical improvements (eg, Bluetooth connectivity, battery autonomy) are necessary to improve the efficiency of the CardioCoach follow-up tool. Finally, the patient population used to conduct the feasibility study was recruited in a tertiary care center with a specialized HF clinic. Due to the high quality of the usual care provided (reflected by the high number of patients on maximum guideline-recommended medication dose in the usual care group compared with literature) with intensive outpatient follow-up, the institution under study may not have been the optimal choice to demonstrate a potential benefit of the CardioCoach follow-up tool on medication uptitration.

CONCLUSIONS

This study shows the feasibility and safety of a novel two-way communication platform with decision support algorithms in combination with remote monitoring sensors in implementing guideline recommendations concerning β-blocker and ACE-I uptitration. In addition, the CardioCoach follow-up tool was found to be efficient in facilitating information exchange and improving coordination among different care providers. Patients' satisfaction was reported to be high, which has led to excellent adherence rates during a relative long follow-up period of 6 months. Many technical issues arose, clearly indicating the need for a technical call center. A larger multicenter randomized controlled trial needs to be conducted, in centers with minimal usual care follow-up to assess the potential benefits of guideline-recommended medication dose.

Figure S 10.1: Screenshots from the CardioCoach smartphone application with from top to bottom respectively registration of medication intake, weight, blood pressure and heart failure questionnaire.

Table S 10.1: Custom-made heart failure questionnaire pushed to the patient before an uptitration proposal or in case of aberrant vital sign data.

Question	Answer options	Aberrant vital signs	Uptitration
Do you experience any signs of dizziness?	No / Yes, only when standing up or bending / Yes, also when seated	✓	✓
Do you suffer from cold hands or feet?	Yes / No	✓	✓
Are you more fatigue?	Yes / No	✓	✓
Do you suffer from tickling cough?	Yes / No	✓	✓
Are you normally active?	Yes / No	✓	
Which description fits you best?	Dyspnea when performing severe exercise (e.g. one or more stairs) / Dyspnea when performing moderate exercise (e.g. walking or cycling) / Dyspnea when performing a light intensity exercise (e.g. when getting dressed) / Dyspnea at rest	✓	
Do you experience chest pain?	Yes / No	✓	
Do you experience palpitations?	Yes / No	✓	
Do you experience trouble sleeping?	Yes / No	✓	
Do you experience loss of appetite?	Yes / No	✓	
Do you suffer from edema?	No / Edema in feet and lower legs / Edema in upper legs / Edema in upper limbs / Upset stomach	✓	
When applying pressure to the edema, then…	No detectable impression / Indentation visible	✓	
Did you increase salt intake?	Yes / No	✓	
Did you drink more than 1.5l of fluid?	Yes / No	✓	
Did you take any pain killing or anti-inflammatory drugs?	Brufen, voltaren, celebrex, nurofen, apranax, brexine, feldene / Dafalgan, paracetamol, perdolan, aspirin / None of the above	✓	

Table S 10.2: Detailed results of the CardioCoach user experience questionnaire (Part 1).

Question	Answer options	Number
Q1: Did they notify you in time concerning a visit of the Remedus employee to explain the CardioCoach tool?	Yes	9
	No	1
Q2: How did you experience the visits by the Remedus employee?	Good	10
	Neutral	0
	Bad	0
Q3: How did you experience the training session concerning the use of the smartphone application and remote monitoring sensors by Remedus?	Clear	9
	Neutral	1
	Unclear	0
Q4: Is the CardioCoach follow-up tool easy to use?	Yes	5
	No	0
	Yes, but...	5
	No, but...	0
Q5: Did you charge the smartphone every night?	Yes	4
	No	0
	If not, which interval:...	2
Q6: Did you carry the CardioCoach along?	Yes	4
	No, because...	6
Q7: Did you experience any problems with the daily update of the medication scheme (connection problems)?	Yes	10
	No	0
Q8: Was it easy to confirm a medication intake?	Yes	6
	No	0
	Yes, but...	3
	No, but...	1
Q9: Was it easy to understand the questions from the different questionnaires?	Yes	7
	No	0
	Yes, but...	3
	No, but...	0
Q10: Was the heart failure questionnaire complete or were some adverse effects or symptoms missing?	Yes	8
	No, this was missing:	2
Q11: How did you experience the short education tips that were pushed to the smartphone on a daily basis?	Useful	8
	Stimulating	5
	Annoying	1
	Clear	7
	Unclear	0
Q12: Did you take into account the educational tips that appeared in the CardioCoach application?	Yes, sometimes	4
	Yes, always	6
	No	0
Q13: Did you receive reminders because you did not confirm medication intake in time?	Yes	6
	No	4
Q14: Did you receive reminders because you did not record vital sign parameters in time?	Yes	3
	No	7
Q15: De reminders were (more than one answer possible):	Clear	5
	Annoying	1
	Unclear	0
	Stimulating	1
	Other,...	6
Q16: What do you think about the length of the follow-up by the CardioCoach tool (6 months)?:	Too long	1
	Too short	2
	Perfect	7
Q17: Would you like to continue using this technology?	Yes	5
	No	5

Table S 10.3: Detailed results of the CardioCoach user experience questionnaire (Part 2).

Question	Answer options	Number
Q18: Do you have any remarks that we can take into account to improve the devices or smartphone application?	No	6
	Yes,...	4
Q19: Did you experience an improved therapeutic compliance due to the use of the CardioCoach follow-up tool?	Yes	8
	No	2
Q20: Did the technical call center contacted you concerning missed medication intake?	Yes	9
	No	1
Q21: Did the technical call center contacted you concerning missed vital sign measurements?	Yes	5
	No	5
Q22: Are you satisfied with the way you were approached by the technical call center?	Yes	9
	No	0
	Yes, but...	1
	No, but...	0
Q23: How would you describe this type of follow-up?	Describe:...	10
Q24: Do you believe it is an added value that an "external company" helps in the follow-up/monitoring of your heart	Yes	7
	No	3
Q25: Did the technical call center contacted you concerning vital sign recordings?	Yes	7
	No	3
Q26: Are you satisfied with the advices you got from the technical call center?	Yes	8
	No	1
	No, but...	1
Q27: Did you got the advice from the technical call center to contact your treating physician?	Yes	2
	No	8
Q28: Did you take into account the advices that were given to you by the technical call center?	Yes	9
	No, because...	1
Q29: How did you experience the contact with the heart failure nurse?	Pleasant	10
	Unpleasant	0
Q30: Do you think the instructions from the heart failure nurse were clear?	Yes	10
	No	0
	Yes, but...	0
	No, but...	0
Q31: Who was responsible for the periodic blood withdrawals?	General practitioner	9
	Home nurse	1
Q32: Are you satisfied with the way the blood withdrawals were performed?	Yes	9
	No	0
	Yes, but...	1
	No, but...	0

Table S 10.3: Detailed results of the CardioCoach user experience questionnaire (Part 3).

Question	Answer	Explanation
Q4	Yes, but…	Once you become familiar with it, it works. Initially, I had some difficulties knowing how to use the touchscreen.
		Initially, it was difficult since I was not used to work with a smartphone, but afterwards it was easy to use.
		Only if it works, the battery is empty soon causing the smartphone to turn off. Vital sign measurements were not always automatically transmitted. In the beginning, I had to receive a new scale. With the new scale, my weight was different.
		It consumes a lot of energy and I had to plug it in the power source continuously.
		Only if it works. It only worked during the first 2 weeks, afterwards there were a lot of technical issues.
Q5	If not, which interval:…	It consumes a lot of energy and I had to plug it in the power source continuously.
		It consumes a lot of energy and I had to plug it in the power source continuously.
Q6	No, because…	I was told that I was not allowed to do that. In addition, I was afraid that I would break the devices.
		There was no need to since you had to complete everything in the morning and I was not sure whether it would work when I was outside my home environment.
		I was told that I was not allowed to do that.
		This wat not necessary, since I was always at home.
		This wat not necessary.
		This wat not necessary. In addition, I wasn't told to.
Q8	Yes, but…	You sometimes accidentally push the wrong button, and you can not change the answer anymore.
		You sometimes accidentally push the wrong button, and you can not change the answer anymore.
		You sometimes accidentally push the wrong button, and you can not change the answer anymore.
	No, but…	In the evening, it was programmed at 6pm instead of 8pm. I mentioned this, but they did not change it.
Q9	Yes, but…	You could only answer "Yes" to the first question, afterwards you had the possibility to answer "Yes" or "No".
		The answers were Yes or No, there was nothing in between.
		If you answered "No", they did not ask many more questions. In addition, the questions were always the same.
Q10	No, this was missing:…	Headache.
		Chest pain.
Q15	Other,…	This is normal, you have to keep your appointments.
		I did not receive any reminders.
		I did not receive any reminders.
		I did not receive any reminders.
		When the source of the alarm could not be solved, it started to become annoying.
		I did not receive any reminders.
Q18	Yes,…	Increase the autonomy of the battery.
		The phone keys were rather small to input the pin when the smartphone needed a reboot.
		When something went wrong (e.g. device is broken), you had to contact the technical call center yourself. They only contacted you afterwards when they noticed there was a missed transmission.
		It only worked for 14 days, afterwards there were connectivity issues that could not be solved.
Q22	Yes, but…	Due to connectivity issues, I was contacted approximately twice a week by phone to transmit the vital sign parameters. I performed these measurements on a daily basis and noted them in a booklet.
Q23	Describe:…	Excellent, it felt more safe. You were not alone and knew that there was always someone that could immediately help you.
		I would not know how.
		It can be compared with a doctor or general practitioner at a distance, an extension from home to the hospital.
		I would recommend it, it helped me dealing more consciously with my health.
		Good, when you confirmed the medication intake, you were sure you did not forget it.
		It was reassuring. You were not left to your fate.
		Very good.
		This should be available for all patients with cardiac problems, especially during the first six months after diagnosis. Until the highest risk is gone and/or when the patient can monitor himself.
		I was happy that it was registered and monitored. Although, I had the feeling that they did not do much with it. For example, my cardiologist was not aware of my measurement results. You expect more support.
		Very good for patients with cardiac problems, especially the monitoring from the clinical call center.
Q26	No, but…	I did not see them frequently, they did contact me regularly to ask how I was doing.
Q28	No, because…	I can not remember that I received some advice.
Q32	Yes, but…	The blood withdrawals were performed in the hospital at the request of my general practitioner.

GENERAL DISCUSSION AND SUMMARY

GENERAL DISCUSSION

The aim of this PhD thesis was to gain more insights in the use of both invasive and non-invasive remote monitoring technologies in the diagnosis, treatment and follow-up of HF patients, with emphasis on the added value of bioimpedance applications.

PART I – REMOTE MONITORING OF CARDIOVASCULAR IMPLANTABLE ELECTRONIC DEVICES IN HEART FAILURE

The first objective of this thesis was to examine the impact of protocol-driven remote follow-up, in particular bioimpedance monitoring, of CIEDs as part of a HF disease management strategy.

Since the entrance of remote monitoring in CIEDs in 2001, numerous clinical trials have been investigating the added value for both healthcare providers and patients. These studies had variable clinical results, with some studies showing a reduction in HF-related hospitalizations and improved survival, while other studies have shown conflicting results on a possible clinical benefit. A shortcoming in current remote monitoring strategies is the lack of standardization and detailed description concerning alert handling protocols, making it difficult to assess which components of a remote monitoring program contribute to perceived outcome benefits. A better insight and standardization in remote monitoring strategies was therefore urgently needed.

In the first chapter we provided a detailed analysis of all remote monitoring alerts and subsequently triggered interventions from a standardized protocol-driven remote follow-up program of CRT patients. We found that remote monitoring notifications were frequent, with an incidence of approximately 2.5 per patient-year of follow-up, warranting a phone contact with the patient in more than half of all cases. In line with recent findings, where a shift from device monitoring to disease monitoring has been observed, we found that the overwhelming majority of incoming remote monitoring notifications was disease-related. Rhythm-related alerts constituted the majority of incoming disease-related alerts and generated an actual intervention in one out of five cases. Bioimpedance-related alerts were the second most frequent. Due to their potential applicability in HF disease monitoring, these alerts were extensively studied in the second chapter.

In the second chapter, a comprehensive overview of bioimpedance-related remote monitoring notifications is reported. Only a few years after remote monitoring features were

available for CIEDs, bioimpedance algorithms were introduced in this concept. By measuring changes in tissue conductance, these algorithms have the potential to detect changes in patients' intrathoracic fluid status and hence impeding congestion, the major cause for HF-related hospitalizations. We found that the presence of these algorithms led to a significant higher amount of remote monitoring alerts, almost always triggering a phone contact. Remarkably, in three out of four of these cases, providing general HF education was the only action undertaken. This high number of education-only interventions could indicate a high number of alerts where patients do not show alarming symptoms of impeding congestion. Recent improvements in bioimpedance algorithms have led to a significant lower number of alerts, but not concerning the type of triggered interventions. While the low number of actual interventions could imply low added value of bioimpedance alerts, we found some interesting observations in terms of clinical outcome. In our population, baseline characteristics for patients with a CIED with bioimpedance algorithms were unfavorable for clinical outcome compared to those with a CIED without bioimpedance algorithms. We found a significant lower survival rate for patients with a CIED with bioimpedance algorithms, which was driven by these differences in baseline characteristics. Interestingly, despite these important differences in baseline characteristics, no difference in HF-related hospitalizations was observed. We are therefore convinced that the positive impact of repeating HF education in this aspect should not be underestimated. Due to the temporal lag between the onset of congestion symptoms and the actual alert, it is possible that patients are contacted in the early phase of emerging congestion and by repeating general HF education, their perception of disease awareness strengthens, avoiding further worsening of congestion and preventing HF-related hospitalizations.

Furthermore, we experienced that bioimpedance alerts are not only triggered by HF-related thoracic fluid changes, but can also be evoked by several other triggers. Among these are fluid buildup caused by recent illness (e.g. flue or cold), use of medication (i.e. non-steroidal anti-inflammatory drugs, effervescent tablets, etc.), dietary errors (i.e. excessive fluid or salt intake), decrease in daily activity, and so on. Interestingly, normal physiological changes in thoracic fluid content can also trigger a bioimpedance alert. In Chapter 3 and 4, we describe two case reports where we observed physiological thoracic fluid changes in two pregnant women with a CIED that triggered multiple bioimpedance alerts. Most bioimpedance algorithms trigger an alert based on the relation of the raw bioimpedance data to a dynamic reference value, rather than on raw bioimpedance data alone. This could cause the bioimpedance alert to disappear although the raw bioimpedance is still lowered.

From these patients, we learned the importance of how bioimpedance alerts are triggered and interpreted.

Although improvements to bioimpedance algorithms have already been made, future improvements and standardizations in the way bioimpedance is measured, handled and/or interpreted could further increase its clinical relevance. Therefore, in the second part of this thesis, non-invasive bioimpedance measurements were explored to gain more insight in the bioimpedance technique and in wearable bioimpedance applications for HF.

PART II – REMOTE MONITORING BY NON-INVASIVE WEARABLE DEVICES WITH A FOCUS ON BIOIMPEDANCE IN HEART FAILURE

The second objective of this thesis was to explore the application potential of a novel, non-invasive multi-parametric wearable bioimpedance sensor in fluid status monitoring of HF patients.

Wearable bioimpedance measurement tools for fluid monitoring are limited and did not yet find their way into general clinical practice. Only a few examples have been reported in literature, but clinical evidence is scarce. Recently, Holst Centre/imec Netherlands developed a novel, low-power multi-parametric modular sensor platform that allows continuous ECG, bioimpedance and accelerometer recordings. In Part II of this thesis, we validated the ECG and bioimpedance module of this sensor platform to study its applicability in HF. In the first chapter of Part II (Chapter 5), we validated the ECG sensor by benchmarking against a gold standard Holter monitor in patients where a diagnostic ECG showed an atrial fibrillation rhythm and in patients with atrial fibrillation that underwent electrical reconversion to restore normal sinus rhythm. From correlation of RR peak intervals, we concluded that the wearable ECG sensor has the same performance as a medical gold standard Holter system. Using this sensor on its own, however, has little added value for HF disease follow-up but could be a complementary parameter to improve diagnostic positive predictive value.

Therefore, in Chapter 6, we investigated the ability of the bioimpedance sensor to measure thoracic fluid redistribution and accumulation by performing continuous bioimpedance measurements on control patients and patients undergoing a fluid challenge protocol or tilt table test. At the same time, ECG and accelerometer data were recorded. We found that the wearable bioimpedance device was capable of measuring fluid redistributions, changes in fluid status, and subsequent physiological responses. By performing these protocols, we

revealed important new insights in terms of non-invasive bioimpedance measurements. We observed that posture and precise electrode placement have a significant influence on bioimpedance readings and have to be kept in mind when conducting these measurements. The wearable multi-parametric bioimpedance sensor showed the potential to enable longitudinal parameter monitoring and trend analysis in a comfortable way and could provide useful insights for congestive HF and other chronic diseases.

Next, we applied the multi-parameter sensor module in patients admitted to the emergency ward with signs of acute decompensated heart failure and volume overload to follow congestion treatment. In a first pilot study (Chapter 7), we demonstrated that thoracic impedance measurements and a patient's fluid balance (in/out) were strongly correlated. We were even able to measure peripheral edema at the level of the lower limb in a patient with isolated right-sided heart failure. In Chapter 8, a larger feasibility study was performed and the prognostic value of the wearable bioimpedance monitoring device was studied. Patients were divided in two groups according to a positive or negative change in thoracic impedance during hospitalization. Although bioimpedance measurements were conducted under standardized conditions, daily fluid levels and relative bioimpedance changes were only moderately correlated. This observation reveals a limitation of the wearable bioimpedance device. Namely, it only measures bioimpedance across a small area of the thorax and only fluid changes in this area can be detected, whereas changes in fluid levels happen on the total body level. The correlation between bioimpedance and fluid balance thus strongly depends on the location of the excessive fluid and the measurement area of the device. Therefore, correlations on the individual level (as seen in Chapter 7) can be higher compared to the population level. However, despite this moderate correlation, we found that patients who show an improvement (i.e. increase) in thoracic impedance during hospitalization, had a significant better clinical outcome. Early changes in thoracic impedance are clearly related to clinical outcome both at 30 days and one year of follow-up, indicating its use as a prognostic parameter for clinical outcome. This observation could possibly assist in clinical decision making in terms of determining optimal treatment strategies and readiness for discharge. Future studies are required to confirm whether bioimpedance monitors could have an added value in providing assistance in diagnostic evaluation, longitudinal prognostication, therapeutic decision making and in-home monitoring. Therefore, this preliminary work can stimulate further research regarding the use of this wearable multi-parametric bioimpedance device in the management of HF.

In Chapter 9, we studied the ability of the wearable bioimpedance device to monitor respiratory parameters using different electrode configurations. Dyspnea, an increase in respiratory rate and a decrease in respiratory volume, is a hallmark symptom in HF patients. Non-invasive respiration monitoring could aid in the early detection of disease worsening. Higher correlations were found for respiratory rates compared to respiratory volumes. Since the wearable bioimpedance device only takes into account a cross section of the lungs, longitudinal changes can be approached but no absolute volumes. In general, correlations were weaker at higher respiratory rates and lower respiratory volumes. The electrode configuration used in the decompensated HF patients was also able to measure respiratory parameters, but showed lower correlations. The most optimal configuration was found to be at the level of the intercostal line height of the midaxillary axis.

PART III – REMOTE MONITORING IN HEART FAILURE BY NON-INVASIVE PORTABLE DEVICES

The third objective of this thesis was to study the feasibility and safety of a smartphone application in combination with decision support algorithms and remote monitoring sensors to improve efficient implementation of guideline recommended drug therapy in HF.

The success rate of studies monitoring weight, blood pressure and heart rate to improve clinical outcome in HF is low. Probably because these parameters are not able to capture the complexity of HF disease progression which often involves multiple co-morbidities. However, we are convinced that these remote monitoring tools can exert an added value in terms of medication uptitration. In the last chapter of this thesis (Chapter 10), we developed and pilot tested the CardioCoach follow-up tool, a two-way communication platform with decision support algorithms in combination with a smartphone, blood pressure monitor and scale. The tool was tested in HF patients where β-blocker and/or ACE-I therapy was initiated or who were on suboptimal dosage of these drugs. It showed to be feasible and safe and was very efficient in facilitating information exchange between different care actors. Patients satisfaction and adherence rates were high during a relative long follow-up period of six months. Unfortunately, a large number of technical issues was present, indicating the benefit of a technical call center. Although, no significant differences were found between the usual care and intervention group, a higher number of patients was on guideline-recommended medication dose in both groups compared to literature, probably related to the high quality of the usual care. Hence, the CardioCoach follow-up tool might be more suitable in centers with less intensive HF disease management programs.

RELATION WITH CURRENT LITERATURE

Using a standardized approach of protocol-driven remote follow-up in the first chapter of this thesis, we were able to gain novel insights in remote alert handling, especially in the case of bioimpedance alerts. As such, we are one of the first performing an in-depth analysis on remote monitoring notification handling. This research therefore builds further on previous studies since these lack this level of detail. A clear shift from device to a more disease management approach was observed, consistent with prior literature findings. While current literature is still inconclusive about the actual benefit of remote disease monitoring of CIEDs, we found that by structured alert handling excellent survival rates are reached. Although, repeating general HF education was the most frequent triggered intervention, the actual impact is still unclear and could be underestimated. Especially in terms of bioimpedance alerts, repeating HF education could have a beneficial effect on clinical outcome by increasing disease awareness and preventing further deterioration as suggested in this thesis. It became clear that there is not just one remote monitoring approach, but a high variability exists and hence each approach needs to be assessed on its individual merit.

To date, no easy non-invasive fluid monitoring sensor has proven to be effective in assessing longitudinal changes in fluid status and in addition shows a relation with clinical outcome. Due to the close collaboration with imec, we were able to co-develop and validate a novel wearable multi-parametric vital sign sensor in the second part of this thesis. By enabling bioimpedance measurements, this sensor allowed us to gain novel insights in bioimpedance measurements in the field of heart failure. In the future, these insights could be translated and applied in CIEDs to improve the sensitivity and specificity of these alerts. In addition, due to its modular design, this state-of-the-art wearable sensor enables multiple other application domains. The use of non-invasive fluid monitoring approaches, using bioimpedance or other techniques such as dielectric sensing technology should be studied in larger randomized controlled trials as they have the potential to positively impact the detection and treatment of decompensated heart failure.

Finally, we were the first to study the feasibility of a two-way communication platform combined with decision support algorithms and remote monitoring sensors for active medication uptitration. A future randomized controlled trial showing a positive impact on the number of patients on guideline-recommended medication dose and time to reach this dose would be groundbreaking in this field and could reduce mortality and hospitalization rates.

CONCLUSION

It is clear that heart failure patients require close disease follow-up, especially in terms of volume status to predict disease progression. Although remote monitoring of CIEDs is very promising in this context, it does not yet cover the total picture. We found that this is partly due to the high variability in remote monitoring strategies that exists and hence each approach needs to be assessed on its individual merit. Moreover, this type of follow-up does not apply for patients without an implantable device. Therefore, we validated and explored the use of a non-invasive multiparametric remote monitoring sensor in heart failure. We demonstrated that the ECG sensor can be used to detect heart rhythm disorders (e.g. atrial fibrillation) showing the same performance as a medical gold standard Holter monitor. More interestingly, we demonstrated that with adequate posture tracking, the bioimpedance sensor is able to monitor both fluid status and respiratory parameters. In terms of bioimpedance, we were able to gain new insight to improve its use in heart failure. Both invasive and non-invasive bioimpedance seem to work, but also seem to be sensitive to changes in fluid status that are not related with heart failure, which has to be taken into account when interpreting these measurements. We also demonstrated that in the acute setting, it can even contain some prognostic value. In the future, the combination of different parameters and a refinement of bioimpedance algorithms could add up in a stand-alone system to improve diagnostic positive predictive value and enable more targeted solutions. Finally, the addition of remote medication adherence monitoring and uptitration processes can close the loop to obtain a more manageable treatment strategy for heart failure.

LIMITATIONS

The major limitations in the current research are the rather small sample sizes of the different studies and their single-center character, which may impact their external validity. Therefore, our results should be interpreted as rather hypothesis generating. Next, the lack of randomized controlled trials to verify our study findings limits the actual clinical impact and additional multi-center studies are necessary to confirm our current results. Nevertheless, the current research has built an innovative basis for future research.

FUTURE WORK

This PhD thesis was able to unravel challenges and opportunities of bioimpedance measurements in HF by studying both invasive and non-invasive applications. However, the work is far from over, and a lot of interesting pathways have opened up that deserve further exploration in future research endeavors and ongoing collaboration.

Our remote monitoring program for patients with CIEDs is unique in its kind because of the close and personal contact with the patients. This is reflected by the excellent clinical outcomes and standardized alert handling protocols. Therefore, this is the ideal study population to conduct a randomized controlled trial to investigate the impact of remote monitoring. Especially in the case of bioimpedance alerts, where we found a high number of HF education in response to these alerts. A randomized controlled trial would be able to study the actual impact of HF education on clinical outcome. Future studies should also focus on a multi-parameter approach in order to increase the specificity of bioimpedance alerts.

Next, the first generation of imec's wearable bioimpedance device has been applied in several patient populations. During the course of this PhD, input on possible improvements of the non-invasive bioimpedance monitoring device has led to the development of new generation devices with updated and additional features, and even the development of a patch form factor. These new features enable novel application domains, which require further attention. A multi-parameter approach for decompensated HF, including respiratory parameters should be further explored. Currently another PhD project is focusing on cardiopulmonary parameters in HF patients undergoing cardiac rehabilitation. This will definitely shed light to new insights in parameters important in tracking disease progression. Another interesting field that requires further attention is peripheral edema measurement in patients with right-sided HF. Besides HF, many other pathologies are characterized by a disturbed fluid balance and may benefit from bioimpedance measurements. For example, patients with sepsis also frequently develop (peripheral) edema. Next, rehydration measurements in dehydrated patients with a temporary ileostomy should be explored. During this PhD thesis, promising preliminary results were obtained for patients undergoing hemodialysis and a new PhD track will shortly be initiated to further explore this interesting application field. Finally, it has become clear that absolute bioimpedance values have a high inter-individual variability and a lot of external factors influence these recordings. Future studies on non-invasive bioimpedance measurements should therefore focus on defining the actual impact of these influencing factors and how they can be accounted for.

SUMMARY

Heart failure is a prevalent disease with high morbidity and mortality rates and a high number of (re)hospitalizations. The major reason for heart failure (re)hospitalizations is related to congestion or fluid overload. Patients with heart failure benefit from regular follow-up and monitoring of biomedical parameters for optimization of treatment strategies and early detection of disease progression. This can be done by invasive and non-invasive remote monitoring strategies.

In this thesis, we added novel insight to the organization of a structured remote monitoring program for patients with cardiovascular implantable electronic devices, with a focus on the disease management strategies. First, we demonstrated a substantial amount of remote monitoring alerts with the largest amount being disease-related. Frequent phone contacts were triggered by these alerts and in most cases, general heart failure education sufficed. Next, we found that bioimpedance alerts constitute a substantial amount of incoming alerts when turned on during remote follow-up. Although very promising for the early detection of impeding congestion, they did not show an influence on survival outcome. Though, a possible influence on heart failure-related hospitalizations, driven by the high number of heart failure education coupled to bioimpedance alerts, was observed.

Next, we studied the use of non-invasive bioimpedance monitoring devices in congestive heart failure patients. Non-invasive bioimpedance measures correlated well with a patient's fluid balance on the individual level. On the population level, correlations are lower due to the high individual variability and different locations where the excessive fluid is coming from. Interestingly, the wearable bioimpedance device was capable of tracking peripheral edema in the case of a patient with right-sided heart failure. Furthermore, it has become clear that a lot of external factors exert an influence on bioimpedance measures, especially body posture. Most importantly, we observed that patients who do not show an improvement in thoracic impedance have a worse clinical outcome, which indicates its use as a prognostic parameter for clinical outcome.

Finally, we demonstrated that the combination of remote monitoring with decision support algorithms is feasible and safe to use and leads to excellent patient satisfaction and adherence. However, due to the high quality of the usual care in our center, this tool might be more suitable in centers without intensive heart failure disease management programs.

SAMENVATTING

Hartfalen is een veelvoorkomende aandoening die gekenmerkt wordt door een hoge morbiditeit en mortaliteit en een hoog aantal hospitalisaties. De voornaamste oorzaak voor deze hospitalisaties is congestie of volume overbelasting. Hartfalen patiënten hebben daarom baat bij een regelmatige opvolging van hun parameters voor de optimalisatie van de behandeling en tijdige detectie van ziekteprogressie. Om dit mogelijk te maken kan gebruik gemaakt worden van invasieve en niet-invasieve telemonitoring.

In deze thesis hebben we nieuwe inzichten verworven in de organisatie van een gestructureerd telemonitoring programma voor geïmplanteerde cardiale toestellen, met een sterke focus op het ziektebeheer. Eerst toonden we aan dat er een hoog aantal telemonitoring alarmen ontvangen werd, waarvan het merendeel ziekte gerelateerd was. Deze alarmen leidden in de meeste gevallen tot een telefonisch contact met de patiënt, waarbij het meestal volstond hartfaleneducatie te herhalen. Daarnaast bleek dat toestellen, voorzien van bioimpedantie algoritmen, significant meer alarmen genereerden. Hoewel deze veelbelovend zijn in vroegtijdige detectie van congestie, werd er geen voordeel op overleving aangetoond. Wel werd er een mogelijk positief effect gevonden op hartfalen-gerelateerde hospitalisaties door het frequent herhalen van hartfalen educatie.

Daarnaast hebben we de toepassing van een niet-invasief bioimpedantie toestel bestudeerd in een gedecompenseerde hartfalen populatie. We konden aantonen dat deze metingen goed gecorreleerd waren met de vloeistofbalans in individuele patiënten, maar deze correlatie was lager op populatie niveau. Dit is te wijten aan de grote variabiliteit tussen de patiënten en het feit dat het vocht niet altijd afkomstig is van de plaats waar de meting wordt uitgevoerd. Bovendien bleek het mogelijk om naast longoedeem, ook perifeer oedeem te meten. Dit is vooral interessant bij patiënten met geïsoleerd rechter hartfalen. Daarenboven bleken externe factoren een grote invloed uit te oefenen op de bioimpedantie metingen, waarbij vooral de houding van de patiënt van cruciaal belang is. De interessantste bevinding was het feit dat patiënten die geen verbetering vertoonden in thoracale impedantie, gekenmerkt werden door een slechtere klinische uitkomst, waardoor het een interessante prognostische parameter zou kunnen zijn.

Tot slot toonden we aan dat de combinatie van telemonitoring met beslissingsondersteuning efficiënt en veilig is en bovendien leidde tot een uitstekende tevredenheid en therapietrouw van de patiënt. Door de hoge kwaliteit van de standaardzorg in ons studiecentrum, lijkt deze aanpak geschikter als toepassing in centra met minder intensieve hartfalen opvolging.

REFERENCES

1. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2016;37(27):2129-200.
2. Mosterd A, Hoes AW. Clinical epidemiology of heart failure. Heart. 2007;93(9):1137-46.
3. Redfield MM, Jacobsen SJ, Burnett JC, Jr., Mahoney DW, Bailey KR, Rodeheffer RJ. Burden of systolic and diastolic ventricular dysfunction in the community: appreciating the scope of the heart failure epidemic. JAMA. 2003;289(2):194-202.
4. Bleumink GS, Knetsch AM, Sturkenboom MC, Straus SM, Hofman A, Deckers JW, et al. Quantifying the heart failure epidemic: prevalence, incidence rate, lifetime risk and prognosis of heart failure The Rotterdam Study. Eur Heart J. 2004;25(18):1614-9.
5. Ceia F, Fonseca C, Mota T, Morais H, Matias F, de Sousa A, et al. Prevalence of chronic heart failure in Southwestern Europe: the EPICA study. Eur J Heart Fail. 2002;4(4):531-9.
6. Komajda M, Weidinger F, Kerneis M, Cosentino F, Cremonesi A, Ferrari R, et al. EURObservational Research Programme: the Chronic Ischaemic Cardiovascular Disease Registry: Pilot phase (CICD-PILOT). Eur Heart J. 2016;37(2):152-60.
7. Gwadry-Sridhar FH, Flintoft V, Lee DS, Lee H, Guyatt GH. A systematic review and meta-analysis of studies comparing readmission rates and mortality rates in patients with heart failure. Arch Intern Med. 2004;164(21):2315-20.
8. Aranda JM, Jr., Johnson JW, Conti JB. Current trends in heart failure readmission rates: analysis of Medicare data. Clin Cardiol. 2009;32(1):47-52.
9. Krumholz HM, Parent EM, Tu N, Vaccarino V, Wang Y, Radford MJ, et al. Readmission after hospitalization for congestive heart failure among Medicare beneficiaries. Arch Intern Med. 1997;157(1):99-104.
10. Berry C, Murdoch DR, McMurray JJ. Economics of chronic heart failure. Eur J Heart Fail. 2001;3(3):283-91.
11. Lee WC, Chavez YE, Baker T, Luce BR. Economic burden of heart failure: a summary of recent literature. Heart Lung. 2004;33(6):362-71.
12. Stewart S. Financial aspects of heart failure programs of care. Eur J Heart Fail. 2005;7(3):423-8.
13. Ambrosy AP, Pang PS, Khan S, Konstam MA, Fonarow GC, Traver B, et al. Clinical course and predictive value of congestion during hospitalization in patients admitted for worsening signs and symptoms of heart failure with reduced ejection fraction: findings from the EVEREST trial. Eur Heart J. 2013;34(11):835-43.
14. TheTask Force on cardiac p, resynchronization therapy of the European Society of Cardiology . Developed in collaboration with the European Heart Rhythm A, Brignole M, Auricchio A, Baron-Esquivias G, Bordachar P, et al. 2013 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy. Rev Esp Cardiol (Engl Ed). 2014;67(1):58.

15. European Heart Rhythm A, European Society of C, Heart Rhythm S, Heart Failure Society of A, American Society of E, American Heart A, et al. 2012 EHRA/HRS expert consensus statement on cardiac resynchronization therapy in heart failure: implant and follow-up recommendations and management. Europace. 2012;14(9):1236-86.

16. Epstein AE, DiMarco JP, Ellenbogen KA, Estes NA, 3rd, Freedman RA, Gettes LS, et al. 2012 ACCF/AHA/HRS focused update incorporated into the ACCF/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol. 2013;61(3):e6-75.

17. Slotwiner D, Varma N, Akar JG, Annas G, Beardsall M, Fogel RI, et al. HRS Expert Consensus Statement on remote interrogation and monitoring for cardiovascular implantable electronic devices. Heart rhythm : the official journal of the Heart Rhythm Society. 2015;12(7):e69-100.

18. Mullens W, Grimm RA, Verga T, Dresing T, Starling RC, Wilkoff BL, et al. Insights from a cardiac resynchronization optimization clinic as part of a heart failure disease management program. J Am Coll Cardiol. 2009;53(9):765-73.

19. Linde C, Braunschweig F. Cardiac Resynchronization Therapy Follow-up: Role of Remote Monitoring. Card Electrophysiol Clin. 2015;7(4):797-807.

20. Varma N, Piccini JP, Snell J, Fischer A, Dalal N, Mittal S. The Relationship Between Level of Adherence to Automatic Wireless Remote Monitoring and Survival in Pacemaker and Defibrillator Patients. J Am Coll Cardiol. 2015;65(24):2601-10.

21. Lazarus A. Remote, wireless, ambulatory monitoring of implantable pacemakers, cardioverter defibrillators, and cardiac resynchronization therapy systems: analysis of a worldwide database. Pacing and clinical electrophysiology : PACE. 2007;30 Suppl 1:S2-S12.

22. Saxon LA, Hayes DL, Gilliam FR, Heidenreich PA, Day J, Seth M, et al. Long-term outcome after ICD and CRT implantation and influence of remote device follow-up: the ALTITUDE survival study. Circulation. 2010;122(23):2359-67.

23. Crossley GH, Boyle A, Vitense H, Chang Y, Mead RH, Investigators C. The CONNECT (Clinical Evaluation of Remote Notification to Reduce Time to Clinical Decision) trial: the value of wireless remote monitoring with automatic clinician alerts. J Am Coll Cardiol. 2011;57(10):1181-9.

24. Landolina M, Perego GB, Lunati M, Curnis A, Guenzati G, Vicentini A, et al. Remote monitoring reduces healthcare use and improves quality of care in heart failure patients with implantable defibrillators: the evolution of management strategies of heart failure patients with implantable defibrillators (EVOLVO) study. Circulation. 2012;125(24):2985-92.

25. Ladapo JA, Turakhia MP, Ryan MP, Mollenkopf SA, Reynolds MR. Health Care Utilization and Expenditures Associated With Remote Monitoring in Patients With Implantable Cardiac Devices. The American journal of cardiology. 2016;117(9):1455-62.

26. Klersy C, Boriani G, De Silvestri A, Mairesse GH, Braunschweig F, Scotti V, et al. Effect of telemonitoring of cardiac implantable electronic devices on healthcare utilization: a meta-analysis of randomized controlled trials in patients with heart failure. Eur J Heart Fail. 2016;18(2):195-204.

27. Louis AA, Turner T, Gretton M, Baksh A, Cleland JG. A systematic review of telemonitoring for the management of heart failure. Eur J Heart Fail. 2003;5(5):583-90.

28. Hindricks G, Taborsky M, Glikson M, Heinrich U, Schumacher B, Katz A, et al. Implant-based multiparameter telemonitoring of patients with heart failure (IN-TIME): a randomised controlled trial. Lancet. 2014;384(9943):583-90.

29. Boriani G, Da Costa A, Quesada A, Ricci RP, Favale S, Boscolo G, et al. Effects of remote monitoring on clinical outcomes and use of healthcare resources in heart failure patients with biventricular defibrillators: results of the MORE-CARE multicentre randomized controlled trial. Eur J Heart Fail. 2016.

30. Cowie MR, editor REM-HF - Remote monitoring: an evaluation of implantable devices for management of heart failure patients. European Society of Cardiology 2016 Congress; 2016 August 28; Rome, Italy.

31. Tang WH, Tong W. Measuring impedance in congestive heart failure: current options and clinical applications. Am Heart J. 2009;157(3):402-11.

32. Yu CM, Wang L, Chau E, Chan RH, Kong SL, Tang MO, et al. Intrathoracic impedance monitoring in patients with heart failure: correlation with fluid status and feasibility of early warning preceding hospitalization. Circulation. 2005;112(6):841-8.

33. Wang L. Fundamentals of intrathoracic impedance monitoring in heart failure. Am J Cardiol. 2007;99(10A):3G-10G.

34. Vollmann D, Nagele H, Schauerte P, Wiegand U, Butter C, Zanotto G, et al. Clinical utility of intrathoracic impedance monitoring to alert patients with an implanted device of deteriorating chronic heart failure. Eur Heart J. 2007;28(15):1835-40.

35. Ypenburg C, Bax JJ, van der Wall EE, Schalij MJ, van Erven L. Intrathoracic impedance monitoring to predict decompensated heart failure. The American journal of cardiology. 2007;99(4):554-7.

36. Gheorghiade M, Follath F, Ponikowski P, Barsuk JH, Blair JE, Cleland JG, et al. Assessing and grading congestion in acute heart failure: a scientific statement from the acute heart failure committee of the heart failure association of the European Society of Cardiology and endorsed by the European Society of Intensive Care Medicine. Eur J Heart Fail. 2010;12(5):423-33.

37. Abraham WT, Compton S, Haas G, Foreman B, Canby RC, Fishel R, et al. Intrathoracic impedance vs daily weight monitoring for predicting worsening heart failure events: results of the Fluid Accumulation Status Trial (FAST). Congest Heart Fail. 2011;17(2):51-5.

38. van Veldhuisen DJ, Braunschweig F, Conraads V, Ford I, Cowie MR, Jondeau G, et al. Intrathoracic Impedance Monitoring, Audible Patient Alerts, and Outcome in Patients With Heart Failure. Circulation. 2011;124(16):1719-26.

39. Conraads VM, Tavazzi L, Santini M, Oliva F, Gerritse B, Yu CM, et al. Sensitivity and positive predictive value of implantable intrathoracic impedance monitoring as a predictor of heart failure hospitalizations: the SENSE-HF trial. Eur Heart J. 2011;32(18):2266-73.

40. Luthje L, Vollmann D, Seegers J, Sohns C, Hasenfuss G, Zabel M. A randomized study of remote monitoring and fluid monitoring for the management of patients with implanted cardiac arrhythmia devices. Europace. 2015;17(8):1276-81.

41. Bohm M, Drexler H, Oswald H, Rybak K, Bosch R, Butter C, et al. Fluid status telemedicine alerts for heart failure: a randomized controlled trial. Eur Heart J. 2016;37(41):3154-63.

42. Domenichini G, Rahneva T, Diab IG, Dhillon OS, Campbell NG, Finlay MC, et al. The lung impedance monitoring in treatment of chronic heart failure (the LIMIT-CHF study). Europace. 2016;18(3):428-35.

43. Lee S, Polito S, Agell C, Mitra S, Yazicioglu RF, Riistama J, et al., editors. Low-power and Compact-sized Wearable Bio-impedance Monitor with Wireless Connectivity. 15th International Conference on Electrical Bio-Impedance (ICEBI) / 14th Conference on Electrical Impedance Tomography (EIT); 2013 Apr 22-25; Heilbad Heiligenstadt, GERMANY2013.

44. Lee S, Squillace G, Smeets C, Vandecasteele M, Grieten L, de Francisco R, et al. Congestive heart failure patient monitoring using wearable Bio-impedance sensor technology. Conf Proc IEEE Eng Med Biol Soc. 2015;2015:438-41.

45. Gastelurrutia P, Cuba-Gyllensten I, Lupon J, Zamora E, Llibre C, Caballero A, et al. Wearable vest for pulmonary congestion tracking and prognosis in heart failure: A pilot study. Int J Cardiol. 2016;215:77-9.

46. Cuba-Gyllensten I, Gastelurrutia P, Riistama J, Aarts R, Nunez J, Lupon J, et al. A novel wearable vest for tracking pulmonary congestion in acutely decompensated heart failure. Int J Cardiol. 2014;177(1):199-201.

47. Shochat M, Charach G, Meyler S, Meisel S, Weintraub M, Mengeritsky G, et al. Prediction of cardiogenic pulmonary edema onset by monitoring right lung impedance. Intensive Care Med. 2006;32(8):1214-21.

48. Shochat MK, Shotan A, Blondheim DS, Kazatsker M, Dahan I, Asif A, et al. Non-Invasive Lung IMPEDANCE-Guided Preemptive Treatment in Chronic Heart Failure Patients: A Randomized Controlled Trial (IMPEDANCE-HF Trial). J Card Fail. 2016;22(9):713-22.

49. McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Bohm M, Dickstein K, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail. 2012;14(8):803-69.

50. Yancy CW, Jessup M, Bozkurt B, Masoudi FA, Butler J, McBride PE, et al. 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2013.

51. Raatikainen MJ, Arnar DO, Zeppenfeld K, Merino JL, Levya F, Hindriks G, et al. Statistics on the use of cardiac electronic devices and electrophysiological procedures in the European Society of Cardiology countries: 2014 report from the European Heart Rhythm Association. Europace. 2015;17 Suppl 1:i1-75.

52. Hindricks G, Varma N. Remote monitoring and heart failure: monitoring parameters, technology, and workflow. Eur Heart J. 2016;37(41):3164-6.

53. Wilkoff BL, Auricchio A, Brugada J, Cowie M, Ellenbogen KA, Gillis AM, et al. HRS/EHRA Expert Consensus on the Monitoring of Cardiovascular Implantable Electronic Devices (CIEDs): description of techniques, indications, personnel, frequency and ethical considerations: developed in partnership with the Heart Rhythm Society (HRS) and the European Heart Rhythm Association (EHRA); and in collaboration with the American College of Cardiology (ACC), the American Heart Association (AHA), the European Society of Cardiology (ESC), the Heart Failure Association of ESC (HFA), and the Heart Failure Society of America (HFSA). Endorsed by the Heart Rhythm Society, the European Heart Rhythm Association (a registered branch of the ESC), the American College of Cardiology, the American Heart Association. Europace. 2008;10(6):707-25.

54. Verbrugge FH, De Vusser P, Rivero-Ayerza M, Van Herendael H, Rondelez K, Dupont M, et al. Cardiac resynchronization therapy with or without defibrillator: experience from a high-volume Belgian implantation centre. Acta Cardiol. 2013;68(1):37-45.

55. Duchenne J, Verbrugge FH, Dupont M, Vercammen J, Jacobs L, Grieten L, et al. Implementation of transmural disease management in patients admitted with advanced heart failure. Acta Cardiol. 2014;69(2):145-54.

56. Smeets CJP, Verbrugge FH, Vranken J, Van der Auwera J, Mullens W, Dupont M, et al. Protocol-driven remote monitoring of cardiac resynchronization therapy as part of a heart failure disease management strategy. Acta Cardiol. 2017:1-10.

57. Clinicians Practical Guide for Using OptiVol® and Other Trends for Managing Heart Failure Patients. Available from: http://www.medtronic.com/content/dam/medtronic-com-m/mdt/crdm/documents/clinic_pract_gd_optivol.pdf.

58. Sarkar S, Hettrick DA, Koehler J, Rogers T, Grinberg Y, Yu CM, et al. Improved algorithm to detect fluid accumulation via intrathoracic impedance monitoring in heart failure patients with implantable devices. J Card Fail. 2011;17(7):569-76.

59. Mullens W, Oliveira LP, Verga T, Wilkoff BL, Tang WH. Insights from internet-based remote intrathoracic impedance monitoring as part of a heart failure disease management program. Congest Heart Fail. 2010;16(4):159-63.

60. Heist EK, Herre JM, Binkley PF, Van Bakel AB, Porterfield JG, Porterfield LM, et al. Analysis of different device-based intrathoracic impedance vectors for detection of heart failure events (from the Detect Fluid Early from Intrathoracic Impedance Monitoring study). The American journal of cardiology. 2014;114(8):1249-56.

61. Evangelista LS, Dracup K, Doering LV. Treatment-seeking delays in heart failure patients. J Heart Lung Transplant. 2000;19(10):932-8.

62. Yang XW, Hua W, Ding LG, Wang J, Zheng LH, Li CQ, et al. OptiVol fluid index predicts acute decompensation of heart failure with a high rate of unexplained events. J Geriatr Cardiol. 2013;10(3):253-7.

63. Cox DA, Ginde S, Kuhlmann RS, Earing MG. Management of the pregnant woman with Marfan syndrome complicated by ascending aorta dilation. Arch Gynecol Obstet. 2014;290(4):797-802.

64. Curry RA, Gelson E, Swan L, Dob D, Babu-Narayan SV, Gatzoulis MA, et al. Marfan syndrome and pregnancy: maternal and neonatal outcomes. BJOG. 2014;121(5):610-7.

65. Gyselaers W, Tomsin K, Staelens A, Mesens T, Oben J, Molenberghs G. Maternal venous hemodynamics in gestational hypertension and preeclampsia. BMC Pregnancy Childbirth. 2014;14:212.

66. Morris R, Sunesara I, Rush L, Anderson B, Blake PG, Darby M, et al. Maternal hemodynamics by thoracic impedance cardiography for normal pregnancy and the postpartum period. Obstet Gynecol. 2014;123(2 Pt 1):318-24.

67. Tkachenko O, Shchekochikhin D, Schrier RW. Hormones and hemodynamics in pregnancy. Int J Endocrinol Metab. 2014;12(2):e14098.

68. Seth R, Moss AJ, McNitt S, Zareba W, Andrews ML, Qi M, et al. Long QT syndrome and pregnancy. J Am Coll Cardiol. 2007;49(10):1092-8.

69. Gyselaers W, Staelens A, Mesens T, Tomsin K, Oben J, Vonck S, et al. Maternal venous Doppler characteristics are abnormal in pre-eclampsia but not in gestational hypertension. Ultrasound Obstet Gynecol. 2015;45(4):421-6.

70. Andreas M, Kuessel L, Kastl SP, Wirth S, Gruber K, Rhomberg F, et al. Bioimpedance cardiography in pregnancy: A longitudinal cohort study on hemodynamic pattern and outcome. BMC Pregnancy Childbirth. 2016;16(1):128.

71. Tan EK, Tan EL. Alterations in physiology and anatomy during pregnancy. Best Pract Res Clin Obstet Gynaecol. 2013;27(6):791-802.

72. Rosenberg MA, Samuel M, Thosani A, Zimetbaum PJ. Use of a noninvasive continuous monitoring device in the management of atrial fibrillation: a pilot study. Pacing and clinical electrophysiology : PACE. 2013;36(3):328-33.

73. Coyne KS, Paramore C, Grandy S, Mercader M, Reynolds M, Zimetbaum P. Assessing the direct costs of treating nonvalvular atrial fibrillation in the United States. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research. 2006;9(5):348-56.

74. Barrett PM, Komatireddy R, Haaser S, Topol S, Sheard J, Encinas J, et al. Comparison of 24-hour Holter monitoring with 14-day novel adhesive patch electrocardiographic monitoring. The American journal of medicine. 2014;127(1):95 e11-7.

75. Zimetbaum PJ, Josephson ME. The evolving role of ambulatory arrhythmia monitoring in general clinical practice. Annals of internal medicine. 1999;130(10):848-56.

76. Zimetbaum PJ, Kim KY, Josephson ME, Goldberger AL, Cohen DJ. Diagnostic yield and optimal duration of continuous-loop event monitoring for the diagnosis of palpitations. A cost-effectiveness analysis. Annals of internal medicine. 1998;128(11):890-5.

77. Gibson TC, Heitzman MR. Diagnostic efficacy of 24-hour electrocardiographic monitoring for syncope. Am J Cardiol. 1984;53(8):1013-7.

78. Ziegler PD, Koehler JL, Mehra R. Comparison of continuous versus intermittent monitoring of atrial arrhythmias. Heart rhythm : the official journal of the Heart Rhythm Society. 2006;3(12):1445-52.

79. Ritter MA, Kochhauser S, Duning T, Reinke F, Pott C, Dechering DG, et al. Occult atrial fibrillation in cryptogenic stroke: detection by 7-day electrocardiogram versus implantable cardiac monitors. Stroke; a journal of cerebral circulation. 2013;44(5):1449-52.

80. Rothman SA, Laughlin JC, Seltzer J, Walia JS, Baman RI, Siouffi SY, et al. The diagnosis of cardiac arrhythmias: a prospective multi-center randomized study comparing mobile cardiac outpatient telemetry versus standard loop event monitoring. J Cardiovasc Electrophysiol. 2007;18(3):241-7.

81. Bass EB, Curtiss EI, Arena VC, Hanusa BH, Cecchetti A, Karpf M, et al. The duration of Holter monitoring in patients with syncope. Is 24 hours enough? Arch Intern Med. 1990;150(5):1073-8.

82. Krahn AD, Renner SM, Klein GJ, Yee R, Skanes A, Evans EM. The Utility of Holter Monitoring Compared to Loop Recorders in the Evaluation of Syncope and Presyncope. Annals of Noninvasive Electrocardiology. 2000;5(3):284-9.

83. Olson JA, Fouts AM, Padanilam BJ, Prystowsky EN. Utility of mobile cardiac outpatient telemetry for the diagnosis of palpitations, presyncope, syncope, and the assessment of therapy efficacy. Journal of cardiovascular electrophysiology. 2007;18(5):473-7.

84. Kinlay S, Leitch JW, Neil A, Chapman BL, Hardy DB, Fletcher PJ. Cardiac event recorders yield more diagnoses and are more cost-effective than 48-hour Holter monitoring in patients with palpitations. A controlled clinical trial. Annals of internal medicine. 1996;124(1 Pt 1):16-20.

85. Sivakumaran S, Krahn AD, Klein GJ, Finan J, Yee R, Renner S, et al. A prospective randomized comparison of loop recorders versus Holter monitors in patients with syncope or presyncope. The American journal of medicine. 2003;115(1):1-5.

86. Lobodzinski SS. ECG patch monitors for assessment of cardiac rhythm abnormalities. Prog Cardiovasc Dis. 2013;56(2):224-9.

87. Lobodzinski SS, Laks MM. New devices for very long-term ECG monitoring. Cardiology journal. 2012;19(2):210-4.

88. Turakhia MP, Hoang DD, Zimetbaum P, Miller JD, Froelicher VF, Kumar UN, et al. Diagnostic utility of a novel leadless arrhythmia monitoring device. The American journal of cardiology. 2013;112(4):520-4.

89. Buxi D, Berset T, Hijdra M, Tutelaers M, Geng D, Hulzink J, et al., editors. Wireless 3-lead ECG system with on-board digital signal processing for ambulatory monitoring. 2012 IEEE Biomedical Circuits and Systems Conference (BioCAS); 2012 28-30 Nov. 2012.

90. Linker D, inventor; University of Washington, Seattle, WA (US), assignee. Long-term monitoring for detection of atrial fibrillation. United Stated2006.

91. Larburu N, Lopetegi T, Romero I, Ieee. Comparative Study of Algorithms for Atrial Fibrillation Detection. 2011 Computing in Cardiology. 2011:265-8.

92. Stevenson LW, Perloff JK. The limited reliability of physical signs for estimating hemodynamics in chronic heart failure. JAMA. 1989;261(6):884-8.

93. Chakko S, Woska D, Martinez H, de Marchena E, Futterman L, Kessler KM, et al. Clinical, radiographic, and hemodynamic correlations in chronic congestive heart failure: conflicting results may lead to inappropriate care. Am J Med. 1991;90(3):353-9.

94. Stevenson LW. Are hemodynamic goals viable in tailoring heart failure therapy? Hemodynamic goals are relevant. Circulation. 2006;113(7):1020-7; discussion 33.

95. Lee S, Agell C, Polito S, Vullers R, Penders J. A low power and convenient bio-impedance monitor, and its application to respiration monitoring. Proceedings of the 4th Conference on Wireless Health; Baltimore, Maryland. 2534091: ACM; 2013. p. 1-2.

96. Staelens A, Tomsin K, Grieten L, Oben J, Mesens T, Spaanderman M, et al. Impedance cardiography for assessment of gestational hemodynamics: benefits and limitations relative to other techniques. Submitted on March 25th 2013:Expert review on medical devices.

97. Anand IS, Greenberg BH, Fogoros RN, Libbus I, Katra RP, Investigators M. Design of the Multi-Sensor Monitoring in Congestive Heart Failure (MUSIC) Study: Prospective Trial to Assess the Utility of Continuous Wireless Physiologic Monitoring in Heart Failure. Journal of Cardiac Failure. 2011;17(1):11-6.

98. Anand IS, Tang WHW, Greenberg BH, Chakravarthy N, Libbus I, Katra RP, et al. Design and Performance of a Multisensor Heart Failure Monitoring Algorithm: Results From the Multisensor Monitoring in Congestive Heart Failure (MUSIC) Study. Journal of Cardiac Failure. 2012;18(4):289-95.

99. Kyle UG, Bosaeus I, De Lorenzo AD, Deurenberg P, Elia M, Gomez JM, et al. Bioelectrical impedance analysis--part I: review of principles and methods. Clin Nutr. 2004;23(5):1226-43.

100. Nijst P, Martens P, Dupont M, Tang WHW, Mullens W. Intrarenal Flow Alterations During Transition From Euvolemia to Intravascular Volume Expansion in Heart Failure Patients. JACC Heart Fail. 2017;5(9):672-81.

101. Boron WF, Boulpaep EL. In: Schmitt WR, Dudlick M, editors. Medical Physiology. Updated ed. Philadelphia: Elsevier Saunders; 2005. p. 534-57.

102. Boron WF, Boulpaep EL. In: Schmitt WR, Dudlick M, editors. Medical Physiology. Updated ed. Philadelphia: Elsevier Saunders; 2005. p. 814-27.

103. Beckmann L, van Riesen D, Leonhardt S. Optimal electrode placement and frequency range selection for the detection of lung water using bioimpedance spectroscopy. Conf Proc IEEE Eng Med Biol Soc. 2007;2007:2685-8.

104. Adams KF, Jr., Fonarow GC, Emerman CL, LeJemtel TH, Costanzo MR, Abraham WT, et al. Characteristics and outcomes of patients hospitalized for heart failure in the United States: rationale, design, and preliminary observations from the first 100,000 cases in the Acute Decompensated Heart Failure National Registry (ADHERE). Am Heart J. 2005;149(2):209-16.

105. Bourge RC, Abraham WT, Adamson PB, Aaron MF, Aranda JM, Jr., Magalski A, et al. Randomized controlled trial of an implantable continuous hemodynamic monitor in patients with advanced heart failure: the COMPASS-HF study. J Am Coll Cardiol. 2008;51(11):1073-9.

106. Abraham WT, Adamson PB, Bourge RC, Aaron MF, Costanzo MR, Stevenson LW, et al. Wireless pulmonary artery haemodynamic monitoring in chronic heart failure: a randomised controlled trial. Lancet. 2011;377(9766):658-66.

107. Adamson PB, Abraham WT, Bourge RC, Costanzo MR, Hasan A, Yadav C, et al. Wireless pulmonary artery pressure monitoring guides management to reduce decompensation in heart failure with preserved ejection fraction. Circ Heart Fail. 2014;7(6):935-44.

108. Fonarow GC, Committee ASA. The Acute Decompensated Heart Failure National Registry (ADHERE): opportunities to improve care of patients hospitalized with acute decompensated heart failure. Rev Cardiovasc Med. 2003;4 Suppl 7:S21-30.

109. Whellan DJ, Droogan CJ, Fitzpatrick J, Adams S, McCarey MM, Andrel J, et al. Change in intrathoracic impedance measures during acute decompensated heart failure admission: results from the Diagnostic Data for Discharge in Heart Failure Patients (3D-HF) Pilot Study. J Card Fail. 2012;18(2):107-12.

110. Helleputte NV, Konijnenburg M, Kim H, Pettine J, Jee DW, Breeschoten A, et al., editors. A multi-parameter signal-acquisition SoC for connected personal health applications. 2014 IEEE International Solid-State Circuits Conference Digest of Technical Papers (ISSCC); 2014 9-13 Feb. 2014.

111. Donal E, Lund LH, Oger E, Hage C, Persson H, Reynaud A, et al. New echocardiographic predictors of clinical outcome in patients presenting with heart failure and a preserved left ventricular ejection fraction: a subanalysis of the Ka (Karolinska) Ren (Rennes) Study. Eur J Heart Fail. 2015;17(7):680-8.

112. Gromadzinski L, Targonski R. Impact of clinical and echocardiographic parameters assessed during acute decompensation of chronic heart failure on 3-year survival. Kardiol Pol. 2006;64(9):951-6; discussion 7-8.

113. Cleland JGF, Teerlink JR, Davison BA, Shoaib A, Metra M, Senger S, et al. Measurement of troponin and natriuretic peptides shortly after admission in patients with heart failure-does it add useful prognostic information? An analysis of the Value of Endothelin Receptor Inhibition with Tezosentan in Acute heart failure Studies (VERITAS). Eur J Heart Fail. 2017;19(6):739-47.

114. Verbrugge FH, Nijst P, Dupont M, Penders J, Tang WH, Mullens W. Urinary composition during decongestive treatment in heart failure with reduced ejection fraction. Circ Heart Fail. 2014;7(5):766-72.

115. Abraham WT, Adamson PB, Bourge RC, Aaron MF, Costanzo MR, Stevenson LW, et al. Wireless pulmonary artery haemodynamic monitoring in chronic heart failure: a randomised controlled trial. Lancet. 2011;377(9766):658-66.

116. Amir O, Rappaport D, Zafrir B, Abraham WT. A novel approach to monitoring pulmonary congestion in heart failure: initial animal and clinical experiences using remote dielectric sensing technology. Congest Heart Fail. 2013;19(3):149-55.

117. Amir O, Azzam ZS, Gaspar T, Faranesh-Abboud S, Andria N, Burkhoff D, et al. Validation of remote dielectric sensing (ReDS) technology for quantification of lung fluid status: Comparison to high resolution chest computed tomography in patients with and without acute heart failure. Int J Cardiol. 2016;221:841-6.

118. Amir O, Ben-Gal T, Weinstein JM, Schliamser J, Burkhoff D, Abbo A, et al. Evaluation of remote dielectric sensing (ReDS) technology-guided therapy for decreasing heart failure re-hospitalizations. Int J Cardiol. 2017;240:279-84.

119. Jodal L. Eelectrical theory behind the measurement of body fluids with bioimpedance spectroscopy (BIS). Aalborg2008.

120. Vuorela T. Technologies for wearable and portable physiological measurement devices. Tampere: Tampere university of technology; 2011.

121. Staelens A, Tomsin K, Grieten L, Oben J, Mesens T, Spaanderman M, et al. Non-invasive assessment of gestational hemodynamics: benefits and limitations of impedance cardiography versus other techniques. Expert review of medical devices. 2013;10(6):765-79.

122. Seppa VP, Viik J, Hyttinen J. Assessment of pulmonary flow using impedance pneumography. IEEE transactions on bio-medical engineering. 2010;57(9):2277-85.

123. Seppa VP, Hyttinen J, Uitto M, Chrapek W, Viik J. Novel electrode configuration for highly linear impedance pneumography. Biomedizinische Technik Biomedical engineering. 2013;58(1):35-8.

124. Wang HB, Yen CW, Liang JT, Wang Q, Liu GZ, Song R. A robust electrode configuration for bioimpedance measurement of respiration. Journal of healthcare engineering. 2014;5(3):313-27.

125. Logic JL, Maksud MG, Hamilton LH. Factors affecting transthoracic impedance signals used to measure breathing. Journal of Applied Physiology. 1967;22(2):251.

126. Bland JM, Altman DG. Applying the right statistics: analyses of measurement studies. Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology. 2003;22(1):85-93.

127. Vuorela T, Seppä VP, Vanhala J, Hyttinen J. Design and Implementation of a Portable Long-Term Physiological Signal Recorder. IEEE Transactions on Information Technology in Biomedicine. 2010;14(3):718-25.

128. Lim WS, Carty SM, Macfarlane JT, Anthony RE, Christian J, Dakin KS, et al. Respiratory rate measurement in adults--how reliable is it? Respiratory medicine. 2002;96(1):31-3.

129. Baker LE, Geddes LA, Hoff HE, Chaput CJ. Physiological factors underlying transthoracic impedance variations in respiration. J Appl Physiol. 1966;21(5):1491-9.

130. Gabriel S, Lau RW, Gabriel C. The dielectric properties of biological tissues: II. Measurements in the frequency range 10 Hz to 20 GHz. Physics in medicine and biology. 1996;41(11):2251-69.

131. Luo S, Afonso VX, Webster JG, Tompkins WJ. The electrode system in impedance-based ventilation measurement. IEEE transactions on bio-medical engineering. 1992;39(11):1130-41.

132. Baker LE, Geddes LA, Hoff HE. A comparison of linear and non-linear characterizations of impedance spirometry data. Medical & biological engineering. 1966;4(4):371-9.

133. Hinz J, Moerer O, Neumann P, Dudykevych T, Hellige G, Quintel M. Effect of positive end-expiratory-pressure on regional ventilation in patients with acute lung injury evaluated by electrical impedance tomography. European Journal of Anaesthesiology. 2005;22(11):817-25.

134. Balleza M, Fornos J, Calaf N, Feixas T, Gonzalez M, Anton D, et al. [Monitoring of breathing pattern at rest by electrical impedance tomography]. Archivos de bronconeumologia. 2007;43(6):300-3.

135. Houtveen JH, Groot PF, de Geus EJ. Validation of the thoracic impedance derived respiratory signal using multilevel analysis. International journal of psychophysiology : official journal of the International Organization of Psychophysiology. 2006;59(2):97-106.

136. Kasper EK, Gerstenblith G, Hefter G, Van Anden E, Brinker JA, Thiemann DR, et al. A randomized trial of the efficacy of multidisciplinary care in heart failure outpatients at high risk of hospital readmission. J Am Coll Cardiol. 2002;39(3):471-80.

137. Whellan DJ, Gaulden L, Gattis WA, Granger B, Russell SD, Blazing MA, et al. The benefit of implementing a heart failure disease management program. Arch Intern Med. 2001;161(18):2223-8.

138. Albert NM, Fonarow GC, Yancy CW, Curtis AB, Stough WG, Gheorghiade M, et al. Influence of dedicated heart failure clinics on delivery of recommended therapies in outpatient cardiology practices: findings from the Registry to Improve the Use of Evidence-Based Heart Failure Therapies in the Outpatient Setting (IMPROVE HF). Am Heart J. 2010;159(2):238-44.

139. Jaarsma T, Stromberg A. Heart failure clinics in Europe. Prog Cardiovasc Nurs. 2000;15(2):67-8.

140. Maggioni AP, Anker SD, Dahlstrom U, Filippatos G, Ponikowski P, Zannad F, et al. Are hospitalized or ambulatory patients with heart failure treated in accordance with European Society of Cardiology guidelines? Evidence from 12,440 patients of the ESC Heart Failure Long-Term Registry. Eur J Heart Fail. 2013;15(10):1173-84.

141. Heywood JT, Fonarow GC, Yancy CW, Albert NM, Curtis AB, Gheorghiade M, et al. Comparison of medical therapy dosing in outpatients cared for in cardiology practices with heart failure and reduced ejection fraction with and without device therapy: report from IMPROVE HF. Circ Heart Fail. 2010;3(5):596-605.

142. Komajda M, Follath F, Swedberg K, Cleland J, Aguilar JC, Cohen-Solal A, et al. The EuroHeart Failure Survey programme--a survey on the quality of care among patients with heart failure in Europe. Part 2: treatment. Eur Heart J. 2003;24(5):464-74.

143. Antonicelli R, Mazzanti I, Abbatecola AM, Parati G. Impact of home patient telemonitoring on use of beta-blockers in congestive heart failure. Drugs Aging. 2010;27(10):801-5.

144. Moyer-Knox D, Mueller TM, Vuckovic K, Mischke L, Williams RE. Remote titration of carvedilol for heart failure patients by advanced practice nurses. J Card Fail. 2004;10(3):219-24.

145. Spaeder J, Najjar SS, Gerstenblith G, Hefter G, Kern L, Palmer JG, et al. Rapid titration of carvedilol in patients with congestive heart failure: a randomized trial of automated telemedicine versus frequent outpatient clinic visits. Am Heart J. 2006;151(4):844 e1-10.

146. de Vries AE, de Jong RM, van der Wal MH, Jaarsma T, van Dijk RB, Hillege HL. The value of INnovative ICT guided disease management combined with Telemonitoring in OUtpatient clinics for Chronic Heart failure patients. Design and methodology of the IN TOUCH study: a multicenter randomised trial. BMC health services research. 2011;11:167.

147. Kraai I, de Vries A, Vermeulen K, van Deursen V, van der Wal M, de Jong R, et al. The value of telemonitoring and ICT-guided disease management in heart failure: Results from the IN TOUCH study. Int J Med Inform. 2016;85(1):53-60.

148. Kropf M, Modre-Osprian R, Hayn D, Fruhwald F, Schreier G. Telemonitoring in heart failure patients with clinical decision support to optimize medication doses based on guidelines. Conf Proc IEEE Eng Med Biol Soc. 2014;2014:3168-71.

149. The treatment of heart failure. Task Force of the Working Group on Heart Failure of the European Society of Cardiology. Eur Heart J. 1997;18(5):736-53.

150. Lewin J, Ledwidge M, O'Loughlin C, McNally C, McDonald K. Clinical deterioration in established heart failure: what is the value of BNP and weight gain in aiding diagnosis? Eur J Heart Fail. 2005;7(6):953-7.

151. Adamson PB. Pathophysiology of the transition from chronic compensated and acute decompensated heart failure: new insights from continuous monitoring devices. Curr Heart Fail Rep. 2009;6(4):287-92.

152. Zhang J, Goode KM, Cuddihy PE, Cleland JG, Investigators T-H. Predicting hospitalization due to worsening heart failure using daily weight measurement: analysis of the Trans-European Network-Home-Care Management System (TEN-HMS) study. Eur J Heart Fail. 2009;11(4):420-7.

153. Chaudhry SI, Wang Y, Concato J, Gill TM, Krumholz HM. Patterns of weight change preceding hospitalization for heart failure. Circulation. 2007;116(14):1549-54.

154. Dendale P, De Keulenaer G, Troisfontaines P, Weytjens C, Mullens W, Elegeert I, et al. Effect of a telemonitoring-facilitated collaboration between general practitioner and heart failure clinic on mortality and rehospitalization rates in severe heart failure: the TEMA-HF 1 (TElemonitoring in the MAnagement of Heart Failure) study. Eur J Heart Fail. 2012;14(3):333-40.

155. Chaudhry SI, Mattera JA, Curtis JP, Spertus JA, Herrin J, Lin Z, et al. Telemonitoring in Patients with Heart Failure. New England Journal of Medicine. 2010;363(24):2301-9.

156. Koehler F, Winkler S, Schieber M, Sechtem U, Stangl K, Bohm M, et al. Impact of remote telemedical management on mortality and hospitalizations in ambulatory patients with chronic heart failure: the telemedical interventional monitoring in heart failure study. Circulation. 2011;123(17):1873-80.

CURRICULUM VITAE

SMEETS Christophe Jean-Paul

Date of birth: 30 November 1990 (Hasselt, Belgium)

Nationality: Belgian

Address: Joseph Deréstraat 10
3500 Hasselt

E-mail: christophe_smeets90@hotmail.com

EDUCATION

2013-2014	Proficiency in Laboratory Animal Science FELASA C, UHasselt	*Magna cum laude*
2011 – 2013	Master in Biomedical Sciences (MSc) Bioelectronics and nanotechnology, UHasselt	*Magna cum laude*
2011 – 2012	Proficiency in Radiation Protection UHasselt	*Summa cum laude*
2008 – 2011	Bachelor in Biomedical Sciences (BSc) Academic Bachelor, UHasselt	
2002 – 2008	Secondary education Science – Modern Languages, Virga-Jesse College, Hasselt	

PROFESSIONAL EXPERIENCE

2013 – 2017	PhD research, Hasselt University, Ziekenhuis Oost-Limburg

SCIENTIFIC ACHIEVEMENTS

PAPERS PUBLISHED IN INTERNATIONAL PEER-REVIEWED JOURNALS

1. Bertrand PB, Gutermann H, **Smeets CJ**, Van Kerrebroeck C, Verhaert D, Vandervoort P, et al. Functional impact of transmitral gradients at rest and during exercise after restrictive annuloplasty for ischemic mitral regurgitation. The Journal of Thoracic and Cardiovascular Surgery. 2014;148(1):183-7. (IF 4.168)

2. Bertrand PB, Grieten L, **Smeets CJ**, Verbrugge FH, Mullens W, Vrolix M, et al. The figure-of-eight artifact in the echocardiographic assessment of percutaneous disc occluders: impact of imaging depth and device type. Echocardiography. 2015;32(3):557-64. (IF 1.432)

3. Torfs T*, **Smeets CJ***, Geng D, Berset T, Van der Auwera J, Vandervoort P, et al. Clinical validation of a low-power and wearable ECG patch for long term full-disclosure monitoring. Journal of Electrocardiology. 2014. (IF 1.361) **shared first authorship*

4. **Smeets CJ**, Bertrand PB, Spadaccio C, Beran M, Verhaert D, Vandervoort PM, et al. Pulmonary homograft endocarditis and aortic autograft failure after Ross procedure: a double stentless bioprosthesis approach. The Journal of Heart Valve Disease. 2014;23(3):360-3. (IF 0.752)

5. Bertrand PB, Verbrugge FH, Verhaert D, **Smeets CJ**, Grieten L, Mullens W, et al. Mitral valve area during exercise after restrictive mitral valve annuloplasty: importance of diastolic anterior leaflet tethering. Journal of the American College of Cardiology. 2015;65(5):452-61. (IF 17.759)

6. **Smeets CJ***, Lanssens D*, Gyselaers W, Bertrand PB, Grieten L, Vandervoort P. Detection of subclinical transient fluid accumulation during pregnancy in a patient with an implantable cardioverter defibrillator and OptiVol(R) fluid monitoring algorithm. International Journal of Cardiology. 2016;214:163-5. (IF 6.189) **shared first authorship*

7. Bertrand PB, Pettinari M, De Canniere H, Gutermann H, **Smeets CJ**, Verhaert D, et al. Effective orifice Area during exercise in bileaflet mechanical valve prostheses. Journal of the American Society of Echocardiography: official publication of the American Society of Echocardiography. 2016;30(4):404-413. (IF 6.852)

8. Lanssens D, Vandenberk T, **Smeets CJ**, De Canniere H, Molenberghs G, Van Moerbeke A, et al. Remote monitoring of hypertension diseases in pregnancy: a pilot study. JMIR mHealth and uHealth. 2017;5(3):e25. (IF 4.636)

9. **Smeets CJ**, Verbrugge FH, Vranken J, Van der Auwera J, Mullens W, Dupont M, et al. Protocol-driven remote monitoring of cardiac resynchronization therapy as part of a heart failure disease management strategy. Acta Cardiologica. 2017:1-10. (IF 0.808)

10. Vandenberk T, Stans J, Van Schelvergem G, Pelckmans C, **Smeets CJ**, Lanssens D, De Cannière H, Storms V, Thijs IM, Vandervoort P. Clinical Validation of Heart Rate Apps: Mixed-Methods Evaluation Study. 2017;5(8):e129. JMIR Mhealth Uhealth (IF 4.636)

11. **Smeets CJ**, Vranken J, Van der Auwera J, Verbrugge FH, Mullens W, Dupont M, Grieten L, De Cannière H, Lanssens D, Vandenberk T, Storms V, Thijs IM, Vandervoort PM. Bioimpedance alerts from cardiovascular implantable electronic devices: observational study of diagnostic relevance and clinical outcomes. Journal of Medical Internet Research. November 2017, 19(11):e393. (IF 5.175)

12. **Smeets CJ**, Storms V, Vandervoort PM, Dreesen P, Vranken J, Houbrechts M, Goris H, Grieten L, Dendale P. A novel intelligent two-way communication system for remote heart failure medication uptitration (the CardioCoach study): a feasibility study. JMIR Cardio. In press

13. Lanssens D, Vandenberk T, **Smeets CJ**, De Cannière H, Vonck S, Claessens J, Heyrman Y, Vandijck D, Storms V, Thijs IM, Grieten L, Gyselaers W. Cost- analysis of prenatal remote monitoring of women with gestational hypertensive diseases. Journal of Medical Internet Research. (IF 5.175) *In press*

PAPERS AT INTERNATIONAL CONFERENCES, PUBLISHED IN FULL IN PROCEEDINGS

14. Seulki L*, Squillace G*, **Smeets CJ***, Vandecasteele M, Grieten L, de Francisco R, et al. Congestive heart failure patient monitoring using wearable bio-impedance sensor technology. Conf Proc IEEE Eng Med Biol Soc. 2015;2015:438-41. **shared first authorship*

PAPERS IN REVIEW IN INTERNATIONAL PEER-REVIEWED JOURNALS

15. **Smeets CJ**, Lee S, Squillace G, Groenendaal W, Vranken J, De Cannière H, Van Hoof C, Grieten L, Mullens W, Nijst P, Vandervoort PM. Feasibilty and prognostic value of a wearable thoracic impedance sensor in acutely decompensated heart failure with volume overload.

16. **Smeets CJ**, Lee S, Nijst P, De Cannière H, Vandecasteele M, Van Hoof C, Grieten L, Vandervoort PM. A wearable multi-parametric bio-impedance device for monitoring fluid redistribution and accumulation.

17. De Cannière H*, **Smeets CJ***, Lee S, Squillace G, Groenendaal W, Grieten L, Lanssens D, Vandenberk T, Storms V, Thijs IM, Vandervoort PM. Optimal electrode configuration for a wearable bioimpedance-based respiration monitoring device. **shared first authorship*

18. Lanssens D*, **Smeets CJ***, Vandervoort P, Grieten L, Gyselaers W. Intrathoracic Fluid Changes from preconception to postpartum as measured by bio-impedance Monitoring. **shared first authorship*

ABSTRACTS AT (INTER)NATIONAL CONFERENCES

19. **Smeets CJ**, Lee S, Vandervoort P, Penders J, Grieten L. A wearable and low-power bio-impedance monitor as a screening tool for sleep apnea. (Poster, Computing in Cardiology Conference 2013, Zaragoza, Spain).

20. **Smeets CJ**, Lee S, Vandervoort P, Penders J, Grieten L. A wearable and low-power bio-impedance monitor as a screening tool for sleep apnea. (Poster, Biomedica Summit 2014, Maastricht, The Netherlands).

21. Van der Auwera J, **Smeets CJ**, Storms V, Vandervoort P, Grieten L. Telemonitoring for disease management in a tertiary care centre. (Poster, Biomedica Summit 2014, Maastricht, The Netherlands).

22. Drijkoningen L, Lenaerts F, Van der Auwera J, **Smeets CJ**, Storms V, Nuyens D, Vandervoort P, Grieten L. Validation of a smartphone based photoplethysmographic beat detection algorithm for normal and ectopic complexes. (Poster, Biomedica Summit 2014, Maastricht, The Netherlands).

23. Drijkoningen L, Lenaerts F, Van der Auwera J, **Smeets CJ**, Storms V, Nuyens D, Vandervoort P, Grieten L. Validation of a smartphone based photoplethysmographic beat detection algorithm for normal and ectopic complexes. (Poster, Computing in Cardiology Conference 2014, Massachusetts, USA).

24. Van der Auwera J, **Smeets CJ**, Storms V, Vandervoort P, Grieten L. Telemonitoring for disease management in a tertiary care centre: a tool or a treatment? (Poster, 8th Belgian Heart Rhythm Meeting, Brussels, Belgium).

25. Lenaerts F, Drijkoningen L, Van Der Auwera J, **Smeets CJ**, Storms V, Nuyens D, Vandervoort P, Grieten L. Clinical validation of CardiMoni, a smartphone application that detects atrial fibrillation. (Poster, 8th Belgian Heart Rhythm Meeting, Brussels, Belgium).

26. **Smeets CJ**, Lee S, Squillace G, Wentink E, Vandecasteele M, Vandervoort P, Grieten L. A wearable low-power bio-impedance sensor to detect congestion in an in-hospital environment. (Poster, Wireless Health 2014, Bethesda, USA).

27. De Cannière H, **Smeets CJ**, Vandervoort P, Lee S, Squillace G, Vandecasteele M, Grieten L. A wearable bioimpedance device for respiratory monitoring. (Poster, Biomedica Summit 2015, Genk, Belgium).

28. **Smeets CJ**, Van der Auwera J, Vranken J, Mullens W, Dupont M, Verbrugge FH, Grieten L, Vandervoort P. Remote monitoring of cardiac resynchronization therapy patients with a disease management strategy. (Poster, 9th Belgian Heart Rhythm Meeting, Brussels, Belgium).

29. **Smeets CJ**, Van der Auwera J, Vranken J, Mullens W, Dupont M, Verbrugge FH, Grieten L, Vandervoort P. Bioimpedance for fluid monitoring in implantable electronic cardiac devices to detect disease worsening. (Poster, 9th Belgian Heart Rhythm Meeting, Brussels, Belgium).

30. Vranken J, **Smeets CJ**, Lee S, Squillace G, Groenendaal W, Vandervoort P, Grieten L. BIGFOOT study: Bio-impedance fluid monitoring in chronic kidney disease patients treated with hemodialysis. (Poster, Biomedica Summit 2016, Aachen, Germany).

31. **Smeets CJ**, Verbrugge FH, Vranken J, Van der Auwera J, Mullens W, Dupont M, Grieten L, De Cannière H, Lanssens D, Vandenberk T, Storms V, Thijs IM, Vandervoort P. Remote disease monitoring of cardiac resynchronization therapy patients. (Poster, 3rd European Congress on eCardiology and eHealth, Berlin, Germany).

32. **Smeets CJ**, Verbrugge FH, Vranken J, Van der Auwera J, Mullens W, Dupont M, Grieten L, De Cannière H, Lanssens D, Vandenberk T, Storms V, Thijs IM, Vandervoort P. Bioimpedance algorithms in implantable electronic cardiac devices: relevant diagnostics or waste of time? (Poster, ACC.17: 66th Annual Scientific Session & Expo, Washington, USA).

33. De Cannière H, **Smeets CJ**, Groenendaal W, Lee S, Vandervoort P. An Optimal Electrode Configuration to Measure Forced Expirations Using a Wearable Bioimpedance Device. (Computing in Cardiology 2016, Vancouver, Canada).

ORAL PRESENTATIONS

34. **Smeets CJ**, Lee S, Vandervoort P, Penders J, Grieten L. A wearable and low-power bio-impedance monitor as a screening tool for sleep apnea. (Computing in Cardiology Conference 2013, Zaragoza, Spain).

35. **Smeets CJ**, Lee S, Squillace G, Wentink E, Vandecasteele M, Vandervoort P, Grieten L. A wearable low-power bio-impedance sensor to detect congestion in an in-hospital environment. (Wireless Health 2014, Bethesda, USA).

36. **Smeets CJ**, Verbrugge FH, Vranken J, Van der Auwera J, Mullens W, Dupont M, Grieten L, De Cannière H, Lanssens D, Vandenberk T, Storms V, Thijs IM, Vandervoort P. Remote disease monitoring of cardiac resynchronization therapy patients. (Poster, 3rd European Congress on eCardiology and eHealth, Berlin, Germany).

AWARDS

2015 Best Poster Award – 9th Belgian Heart Rhythm Meeting, Brussels, Belgium

2015 Best Poster Award – Biomedica Summit 2015, Genk, Belgium

2015 Second best poster – Wireless Health, Bethesda, USA

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"There is always a reason to smile, find it!"

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www.uhasselt.be
Hasselt University
Martelarenlaan 42 |BE-3500 Hasselt