Novel Concepts for non-invasive telemonitoring in chronic heart failure.

being a Thesis submitted for the Degree of

Doctor of Medicine

by

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Thesis Abstract

Background: The morbidity and mortality from chronic heart failure (HF) remains alarmingly high, in part due to failure to apply substantial disease modifying strategies to halt disease progression. Telemonitoring has been proposed as a potential disease management strategy to deal with the burden posed by HF. While treatment decisions guided by invasive telemonitoring data have shown early promise, it is unclear whether non-invasively derived surrogates of haemodynamics could be reliable enough to guide therapeutic interventions.

Aims: The principal aim of this thesis is to investigate whether non-invasive "smart technologies" could accurately detect and track subtle changes in surrogates of cardiovascular haemodynamics in response to challenges posed by activities of daily living and non-adherence to therapy.

Methodology: A series of prospective clinical studies were conducted in stable patients with chronic heart failure, on optimum tolerated guideline directed therapy for heart failure. Studies were performed under clinically adapted conditions to mimic the patient's own habitat.

Results: Significant systemic haemodynamic perturbations were detected non-invasively with variations in environmental temperature. Additionally, music, which modulates the sympathetic tone, led to modest changes in systemic blood pressure and heart rate, although the changes did not reach statistical significance. Non-adherence to cardiovascular therapy led to striking adverse changes in systemic haemodynamics. Smart technologies demonstrated a remarkable consistency in detecting haemodynamic perturbations.

Conclusion: Non-invasive detection and tracking of changes in haemodynamics is feasible with smart technologies. The results need to be validated in larger multicenter clinical trials, with particular emphasis on using the data to guide therapeutic decisions.

Declaration

This thesis is submitted in accordance with the requirements of the Degree of Doctor of Medicine (MD), University of Hull. The candidate confirms that the work submitted is his own and appropriate credit has been given where references have been made for the work of others.

Statement of originality

This thesis has been prepared by the candidate. Work comprises of two reviews of the relevant literature and original studies (3 prospective studies). The investigative work described in this thesis was performed solely by the candidate, except where clearly described. Appropriate credit has been given where references have been made to the work of others. This thesis has not been submitted for any other academic / professional degree. Publications and academic recognition as a result of work in this thesis are described in the appendices.

Dr Thato Mabote

Publications

Mabote T, Wong K, Cleland JGF. The utility of novel non-invasive technologies for remote hemodynamic monitoring in chronic heart failure
Expert Rev. Cardiovasc. Ther. 12(8), (2014)

Conference extracts

T. Mabote, A. Torabi, R. Antony, A. Shoaib, YA. Agha, R. Dierckx, S. Parsons, P. Pellicori, AL. Clark, JGF. Cleland. Haemodynamic effects of light exercise at different temperatures in chronic heart failure. ESC Heart Failure Association. Lisbon 2013.

T. Mabote, A. Torabi, R. Antony, R. Dierckx, A. Shoaib, S. Parsons, B. Dicken, P. Pellicori, AL. Clark, JGF. Cleland. Non invasive detection of haemodynamic effects of environmental temperature in chronic heart failure. ESC Heart Failure Association. Lisbon 2013.

Thato Mabote, Azam Torabi, Riet Dierckx, Shoaib Ahmad, Sunaina Parsons, Joan Weston, John GF Cleland. Effects of Environmental Temperature on Non-invasive Haemodynamics in patients with heart failure. British Cardiovascular Society. London 2013.

T. Mabote et al. Effect of Music and Noise on Haemodynamics in Patients with Heart Failure.ESC Heart Association Meeting. Belgrade 2012

T. Mabote et al.Effect of Environmental Temperature on Haemodynamics in Patients with Heart Failure.ESC Heart Association Meeting. Belgrade 2012

Poster Presentations

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Table of contents

List of Tables

List of figures

CHAPTER 1

TELEMONITORING FOR HEART FAILURE

1.1 Introduction

Chronic refractory heart failure (HF) is a major health and economic burden. The incidence of this condition is increasing with the ageing of populations around the world. (1, 2) What is more, despite breathtaking advances in pharmacotherapy and device therapy for heart failure, its morbidity and mortality remains frighteningly high, perhaps in part due to failure to effect substantial disease modifying strategies to halt heart failure disease progression. In the National Health Service (NHS), heart failure accounts for a large economic burden, accounting for a million inpatient bed-days, that is 2% of the NHS total and 5% of all emergency hospital admissions. (3) Data from the national heart failure audit for England and Wales show that heart failure related hospitalization still carry an estimated in-hospital mortality of up to 10%. (4, 5) Recurrent hospitalization with HF not only carries a cumulatively increased mortality due to heart failure itself but also due to healthcare associated complications such as venous thromboembolism and nosocomial infections.

Heart failure disease management models are therefore evolving; to attempt to reduce the disease burden, improve self-management of symptoms, improve patient education, improve medication optimization as well as medication uptake.

1.2 Usual care

Traditionally, optimal ambulatory patient care has involved *ad-hoc* visits to the general practitioner for treatment of an individual patient's multiple co-morbid conditions, of which heart failure maybe one of them, and perhaps at best a yearly visit to a hospital specialist for a brief review. Furthermore, patients with heart failure have tended to be managed by non-specialists, a practice which has recently been shown to be associated with an increase in hospital mortality. (5) The traditional model of care has not only

failed to yield a reduction in morbidity and mortality from heart failure as discussed above, but also is largely economically unsustainable.

1.3 Home Telemonitoring

Telehealth involves the remote exchange of physiological data between a patient and healthcare providers as part of the patient's diagnosis and healthcare management. (6, 7) There are several models of telemonitoring that have been trialed
and compared to conventional specialist care. The essence of these modalities is to gather targeted clinical information from heart failure patients in a stable cardiovascular state, managed in a non-hospital setting. The information is then used to optimize individual patient treatment before they decompensate. To this end, structured nurse led telephone support, more sophisticated technology based recording and transmission of patient's heart rate, respiratory rate, weight and blood pressure were the early non invasive modalities studied in direct comparison to usual clinical care. More recently, there has been a trend to attempt to study the impact of telemonitoring surrogate measures of intra thoracic fluid congestion such as bioelectrical impedance using implantable devices as a guide to optimizing heart failure therapy. Furthermore, invasive left atrial pressure monitoring and subsequent guided therapeutic changes to heart failure therapy appear promising. The studies using various telemonitoring modalities are summarized in tables 1 and 2.

The patient's heart failure status is assessed on a regular basis in their home setting. Patient's symptoms and vital signs are measured and remotely transmitted from their home to their healthcare professionals. Early recognition of haemodynamic deterioration from the patient's individual baseline could be detected, prompting timely

modification of the patient's evidence-based care, potentially averting a crisis situation that could culminate in re-hospitalization or death. What's more, a corollary of this disease management strategy could be recruitment of the patient to make them central to their disease management, improved patient education as well as imparting them with confidence to manage their own condition. The fundamental difference of telemonitoring from usual care is heightened monitoring and the opportunity for the healthcare giver to provide timely interventions before patients deteriorate to need hospital admission.

1.4 Strategies to halt heart failure disease progression - where does telemonitoring fit?

Extensive research and landmark advances have been made in the treatment of heart failure in the last three decades. The evidenced- based treatment of heart failure involves combinations of pharmacological therapies to reduce congestion and reduce left ventricular filling pressures with drugs such as diuretics, nitrates and hydrazine, reduce the cardiac workload by reducing the heart rate with drugs such as beta-blockers and selective sinus node I_f channel inhibitor, as well as modulate cardiac remodelling with angiotensin converting enzyme inhibitors and angiotensin receptor blockers. For a select subset of patients on optimal tolerated medical therapy with evidence of dyssynchrony, device cardiac resynchronisation has been shown to decrease morbidity and mortality.(8) Adherence to evidence-based drug therapy is of paramount importance in optimising prognosis in HF patients. (1, 9)

1.5 Medication optimization

There is evidence that treatment optimization in heart failure remains inadequate in large subsets of patients for various reasons such as lack of awareness of guidelines, diminished familiarity with the use of complex therapies in patients with multiple co-morbidities and inadequate resources to manage recurrent reviews of patients with long-term conditions. (10-13) Moreover, adherence to chronic preventive maintenance therapy in patients with long-term conditions such as heart failure remains poor despite the fact that the medication is essential for reducing risks of disease progression, morbidity, and mortality. (14) The reasons for non-adherence are often multifactorial, in part due to side effects but also due to poor education about one's illness and the psychological burden for taking long-term medications. (15, 16)

Home telemonitoring is therefore proposed as a strategy to fill the healthcare vacuum, to provide the 'daily' connection between the individual patients to the healthcare provider. Patient involvement is central to success of the exchange of physiological data, which may in turn provide them with the necessary education and appreciation of the individual treatments that they receive. Furthermore, a great opportunity to study individual patients' baseline parameters and dynamic changes in their condition that may arise with daily life challenges arises, which can then be harnessed in real time to modify therapy.

Figure 1 Telemonitoring model

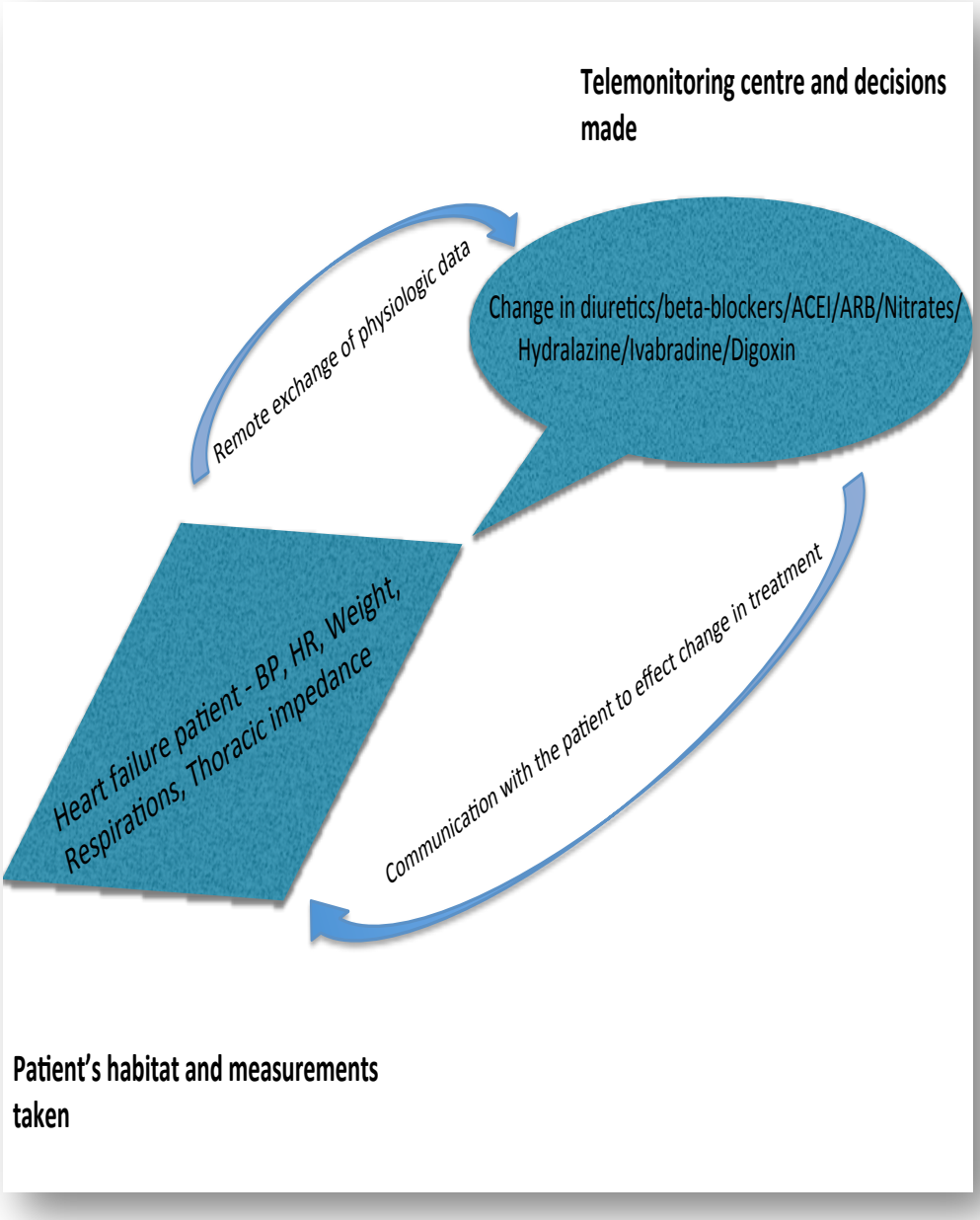


Figure 1 illustrates the telemonitoring model where data is gathered from the patient's home then transferred remotely to a telemonitoring centre for the healthcare giver who studies the changes against the patient's baseline and recommends the necessary changes which are communicated remotely to the patient

1.6 Evidence for and against telemonitoring

The clinical utility of telemonitoring as an adjunct in the management of heart failure has been evaluated in several studies. Whether the strategies investigated translate into clinical benefit remains unproven beyond reasonable doubt. In point of fact, the widespread clinical applicability of remote heart failure monitoring has not been adopted and recommended in clinical practice guidelines such as the European Society of Cardiology (ESC) Heart Failure (17) or the American College of Cardiology Foundation (ACCF) / American Heart Association (AHA) joint guidelines(18). Two comprehensive systematic reviews and meta-analyses of several observational cohort studies and randomized control trials (19, 20) initially raised optimism that the weight of evidence may favour telemonitoring.

1.6.1 Meta-analyses of telemonitoring in heart failure

A meta-analyses to assess the effect of remote patient monitoring of heart failure on the outcome of chronic heart failure patients by Klersy and colleagues (20) reported promising results. In total, meta-analyses of the results of 20 randomised controlled clinical trials (n = 6258) and 12 Cohort Studies (n = 2354), showed that when remote patient monitoring of heart failure was compared with usual care, there was significant reductions in mortality and hospitalization rates. The significant protective clinical effect was seen in both cohort studies and randomized clinical studies. Subsequently, Inglis and colleagues' Cochrane Review (19) in 2011 compared structured telephone interview and remote telemonitoring to standard care. The study comprised a total of 8323 patients; of which16 studies evaluated structured telephone support (comprising 5613 patients) and 11 studies evaluated telemonitoring (comprising 2710 patients). Overall there was a 30% reduction in all-cause mortality with telemonitoring while no significant trends were found with structured telephone support. In addition, both

interventions were associated with reduced heart failure related hospitalisations. Considerations made during the critical appraisal of the Cochrane review include observations that there is likely to have been substantial heterogeneity in the protocols of the studies included. More importantly, following the conclusion and dissemination of the results of the Cochrane review, two very large well conducted randomized controlled trials (21, 22) were published, contradicting the astounding mortality and rehospitalisation benefits ascribed to remote telemonitoring.

1.6.2 Home and Remote Monitoring of Heart failure clinical trials

The clinical trials which reported a positive clinical benefit of home and remote monitoring of heart failure are; The Weight Monitoring in Heart failure (WHARF) trial (23), the HOME-HF trial (24) and The Trans-European Network-Home Care ManagementSystem (TEN-HMS) study (25). The WHARF trial, which was a multicenter randomized control study, recruited 280 subjects with severely reduced left ventricular ejection fraction (≤ 35%) and symptomatic heart failure (New York Heart Association functional class 3 and 4), and used an electronic weight and symptom monitoring system, in conjunction with heart failure program care compared to heart failure program care alone, to assess for reductions in heart failure hospitalisation. Overall, after 6 months followed-up, there was no beneficial effect on rehospitalisation rates but a substantial reduction in the secondary endpoint of mortality. In another large randomized clinical trial, the Trans-European Network-Home Care Management System (TEN-HMS), study standard usual care was compared to home based telemonitoring services or nurse based telephone support. In this study that enrolled 426 participants, patients randomly assigned to receive usual care had higher one-year mortality than patients assigned to receive nurse telephone support or home based telemonitoring services. The Home-HF trial, which was a relatively smaller study (n =

182), sought to evaluate whether daily home telemonitoring of symptoms, weight, blood pressure, heart rate and blood oxygen saturation compared to conventional specialist care had an impact on days alive and out of hospital in recently discharged typical elderly heart failure from three centres. Although there was no difference between home telemonitoring and conventional specialist care, there was a net benefit in having fewer unplanned hospital visits with home telemonitoring.

In contrast, the studies that reported a net neutral benefit from home telemonitoring compared to conventional care include; The Home or Hospital in Heart failure (HHH) study (26), the telemonitoring in heart failure (TELE-HF) study (22) and the Telemedical Interventional Monitoring in Heart Failure (TIM-HF) trial (21). First, the HHH study, which was a European Community-funded, multinational, randomized controlled clinical trial, recruited 461 participants with moderate to severe heart failure symptoms, to assess the feasibility of a home telemonitoring system to monitor clinical and physiological parameters. Following a 12-month follow-up period, its efficacy when compared with conventional expert care in reducing adverse cardiac events (heart failure hospitalisation or cardiac death) in heart failure patients was not significant. Similarly, in 'The telemonitoring for heart failure' (TELE-HF) trial, which was a large randomized controlled study of 826 patients recently hospitalised for heart failure, randomly allocated to daily telemonitoring by means of an automated voice interactive system collecting clinical information on weight and symptoms, and compared with 827 patients on conventional specialist care, telemonitoring did not improve on all-cause readmissions or all-cause mortality between the study cohorts. Finally, (TIM-HF) study aimed to evaluate the impact of telemonitoring on mortality in 710 ambulatory patients with chronic heart failure. 354 participants with NYHA class II–III HF, LVEF ≤35%, and a history of cardiac decompensation were randomized to management guided by

home telemonitoring while 356 participants were randomized to usual care. Overall, home telemonitoring did not confer a significant difference on all-cause mortality or the composite of cardiovascular mortality and heart failure hospitalization between the groups.

With the conflicting evidence discussed above taken into consideration, the real world impact of telemonitoring on readmissions, consults, home visits, quality of life and economic endpoints is currently being assessed in a United Kingdom based prospective multicenter randomized clinical trial, the Implementation of Telemonitoring in Chronic Heart or Lung Failure (TELECRAFT) trial. (27) In this study, the factors that influence how patients integrate telemonitoring into their daily routines as well as how healthcare professionals use telemonitoring to aid decision- making will be explored.

1.6.3 Remote Impedance monitoring using complex pacing devices

Advanced heart failure device therapy is now part of the mainstay of the management of chronic heart failure. Cardiac resynchronization therapy with defibrillator or pacing capability (CRT – D or P) and implantable cardioverter defibrillator devices (ICD) are have now been adopted and recommended in clinical practice guidelines such as the European Society of Cardiology (ESC) Heart Failure (17) or the American College of Cardiology Foundation (ACCF) / American Heart Association (AHA) joint guidelines(18). What's more, CRT and ICD devices are capable of monitoring intrathoracic bioelectrical impedance, which has been shown to correlate well with pulmonary fluid congestion and predict heart failure decompensation before any clinically detectable symptoms. (28, 29) The clinical applicability of monitoring intra thoracic fluid congestion status with implantable biventricular defibrillator devices was studied in a small case control study of two homogeneous groups comprising 27 participants in each arm, who had an indication for device therapy for heart failure. (30) One cohort had devices capable of monitoring intra thoracic fluid accumulation and alert healthcare professionals while the other group did not. Following about 1 year follow up period, the investigators concluded that it was feasible to use implantable cardiac devices to detect and monitor intrathoracic fluid accumulation 'in the real world' leading to early institution of therapy and resultant significant reductions in heart failure hospitalization. Similar significant trends towards early detection and reductions in heart failure hospitalization were replicated in another study of 532 heart failure patients with implantable cardioverter defibrillators (31) In the Program to Access and Review Trending Information and Evaluate Correlation to Symptoms in Patients With Heart Failure (PARTNERS HF) trial, which was a prospective, multicenter observational study in patients with implantable cardioverter-defibrillators, (32) a combined HF

device diagnostic algorithm which include impedance data identified those at risk of heart failure decompensation. In another multicenter randomized trial, the evolution of management strategies of heart failure patients with implantable defibrillators (EVOLVO), (33) involving 200 patients, remote monitoring resulted in a net benefit of less unplanned hospital visits and reduced healthcare costs when compared with conventional care.

However, despite the early promising results from the randomized controlled studies discussed above, there have been clinical questions raised in further clinical studies about the generalizability of the 'real world' clinical applicability of impedance monitoring for the early detection of acute on chronic heart failure decompensation. First, the Sensitivity of the InSync Sentry OptiVol feature for the prediction of Heart Failure (SENSE-HF) Study, (34) which enrolled 501 patients reported a disappointing sensitivity of 20.7% and positive predictive accuracy of only 4.7% for admission with decompensating heart failure. What's more, the Diagnostic Outcome Trial in heart failure (DOT-HF), (35) which was a large prospective randomized controlled study powered to assess the impact of monitoring intrathoracic impedance on morbidity and mortality in patients with chronic heart failure, did not only not improve outcome but also surprisingly increased heart failure hospitalizations and outpatient visits in heart failure patients, perhaps related to a high false alarm rate.

With the abovementioned cautions in mind, there have been further studies to attempt to cement the role of remote monitoring and early detection of heart failure decompensation using complex pacing devices on morbidity and mortality in patients with chronic heart failure. To this end, the Implant-based multiparameter telemonitoring of patients with heart failure (IN-TIME) study, (36) which was a prospective

international multicenter randomised control trial, enrolled 664 patients with a recent dual-chamber ICD or CRT-D implant and symptomatic chronic heart failure. The participants were on optimal tolerated medical therapy, with left ventricular ejection fraction of no more than 35% and not in permanent atrial fibrillation. The primary outcome was a composite clinical score combining all-cause death, overnight hospital admission for heart failure, change in NYHA class, and change in patient global self-assessment, for the intention-to-treat population. Complex heart failure device based telemonitoring of rhythmic and technical parameters had a significantly beneficial effect on the composite clinical score and all-cause mortality in the telemonitoring group versus the control group. There are other clinical trials in the pipeline that are due to report in the next few years. One such trial is the United Kingdom based REM-HF, (37) which is a multicentre, randomized, non-blinded, parallel trial which has randomized 1650 patients and is expected to complete in early 2016. The study is designed to provide important data on the cost-effectiveness and effect on morbidity and mortality impact, of remote monitoring-driven management of implanted cardiac devices.

1.6.4 Implantable haemodynamic monitoring devices for heart failure

Therapeutically targeting acute on chronically raised left ventricular filling pressures that commonly accompany acute decompensated heart failure (38) is a promising and emerging field. Intracardiac pressures directly reflect the patient's congestion status, which in turn provides valuable actionable information to guide targeted changes in the pharmacological therapy in chronic heart failure. Continuous invasive measurement of right ventricular pressures, (39) left atrial pressures (40) and pulmonary artery pressure (41) using smart sensor technology in implantable devices is safe and feasible in patients with advanced heart failure. Clinical management of patients with heart failure guided by invasively derived right ventricular pressures in a feasibility study (39) resulted in less hospitalization. Furthermore, left atrial pressure guided management was found to improve haemodynamics, symptoms of cardiac failure and clinical outcomes in patients with advanced heart failure in HOMEOSTASIS (Haemodynamically Guided Home Self-Therapy in Severe heart failure Patients), which was a prospective, observational study. (42) The reported beneficial effects conferred by left atrial pressure guided therapy are being further investigated in the Left Atrial Pressure Monitoring to Optimize Heart Failure Therapy Study (LAPTOP-HF) clinical trial (43), which is a prospective, multicenter, randomized, controlled clinical trial which aims to enroll up to 730 ambulatory patients with advanced heart failure. The safety and clinical effectiveness of a physician-directed patient self-management therapeutic strategy based on left atrial pressure measured twice daily by means of an implantable sensor will be compared with a control group receiving usual conventional therapy. Finally, the clinical utility of wireless pulmonary artery pressure guided management of chronic heart failure has been studied in the landmark CHAMPION (CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in

NYHA Class III heart failure Patients) trial. (44) This was prospective randomised controlled clinical trial in 550 stable but advanced heart failure patients, who were implanted with an implantable continuous haemodynamic monitoring device in the pulmonary artery. The participants were either randomly assigned to pulmonary artery pressure guided therapy or conventional care. Following a 6month follow up period, the pulmonary artery pressure guided therapy cohort had a 39% reduction in heart-failure-related hospitalisation compared with the control group.

Despite the improved heart failure management and beneficial gains in reducing heart failure hospitalisation, there have been other neutral clinical studies that have cast some doubt on the gains reported. The Chronicle Offers Management to Patients with Advanced Signs and Symptoms of heart failure (COMPASS) trial, (45) a prospective multicentre randomised controlled study enrolled 274 subjects with moderate to severe heart failure symptoms, and implanted a continuous haemodynamic monitor with a pressure sensor situated at the tip located in the right ventricular outflow tract, capable of measuring systolic and diastolic right ventricular pressures as well as estimated diastolic pulmonary artery pressure. Overall, integration of right ventricular implantable continuous haemodynamic monitor derived pressures into patient management did not reduce heart failure related events compared with conventional care. A further cautionary tail to inform future developments in the implantable haemodynamic monitors became evident in the Reducing Decompensation Events Utilising Intracardiac Pressures in Patients with Chronic HF (REDUCE-HF) trial, (46) which was another prospective randomized multicenter trial that enrolled 400 out of the planned 1300 participants with a previous heart failure hospitalization, living with mild to moderate heart failure symptoms who also had an indication for an implantable cardioverter-defibrillator. A combination implantable continuous haemodynamic sensor-ICD was

implanted and patients were randomly allocated to a treatment cohort in which hemodynamic information was used or a control group in which no hemodynamic information was available. Unfortunately the trial was terminated early due to implantable haemodynamic monitor lead failures.

Table 1 Studies favouring telemonitoring in heart failure

Study, year	N	Key inclusion criteria	Key findings
Meta-Analysis			
Klersy et al., (20) 2009	8612	Meta-analysis of 20 RCTs (n = 6258) and 12 Cohort Studies (n = 2354)	Reduced risk of all-cause mortality and HF-related hospitalizations. Improved quality of life and reduced costs
Inglis et al., (19) 2011	8323	Meta-analysis of 25 RCTs (n = 8323)	Reduced risk of all-cause mortality and HF-related hospitalizations. Improved quality of life and reduced costs
Home and remote telemonitoring			
WHARF, (23) 2003	280	NYHA III - IV + HF hospitalisation	No effect on re-hospitalization. Reduced mortality
HOME-HF, (24) 2009	184	NYHA II – IV + HF hospitalisation	No effect on mortality. Fewer unplanned HF- related hospitalizations
TEN-HMS, (25) 2005	426	HF symptoms + HF hospitalisation	No effect on re-hospitalization. Reduced 1 year mortality by NTS and RTM compared to usual care
Impedance monitoring using ICD or CRT-D			
Maines et al (30)	54	NYHA II - IV + EF 24%	HF hospitalizations reduced
PARTNERS-HF, (32) 2010	694	NYHA III - IV + EF - 35%	Combined diagnostic HF algorithm identified patients at risk for ADHF
OptiVol CRT, (31) 2009	532	NYHA II-III + EF <35%	Reduced hospitalization in the intervention group
EVOLVO, (33) 2012	200	LVSD or LVEF <35%	Reduced healthcare costs
IN-TIME, (36) 2014	664	NYHA II – III + EF ≤ 35%. Not in permanent AF	composite clinical score and reduced all-cause mortality
Implantable haemodynamic monitors			
Permanent RV IHM system (39)	32	NYHA III - IV	RV pressure increases preceded hospitalizations
HOMEOSTASIS, (42) 2010	40	NYHA III - IV + previous HF hospitalization	Increased event free survival, lower LAP
CHAMPION, (44) 2011	550	NYHA III + previous HF hospitalization	Reduced and shorter HF hospitalizations, lowered PAP, more medication changes in intervention group

Table 2 Studies showing neutral results for telemonitoring in heart failure

Study, year	N	Key inclusion criteria	Key findings
Home and remote telemonitoring			
HHH study, (26) 2009	461	NYHA II - IV + HF hospitalisation	Negative
TELE-HF, (22) 2010	1653	HF hospitalisation	Negative
TIM-HF, (21) 2011	710	NYHA II - III + HF hospitalisation	Negative
Impedance monitoring (ICD or CRT-D)			
DOT-HF, (35) 2011	335	NYHA II - IV+EF - 35%+ previous HF hospitalisation	Negative. More hospitalisations in intervention group
Implantable haemodynamic monitors			
COMPASS, (45) 2008	274	NYHA III - IV + previous HF hospitalisation	Non-significant reduction of HF events. Safety endpoints met
REDUCE-HF, (46) 2011	400	NYHA II - III + previous HF hospitalisation + ICD indication	Ended prematurely for lead problems. No effects on HF events

ADHF, acute decompensated heart failure; CRT, cardiac resynchronisation therapy device; EF, ejection fraction; HF, heart failure; ICD, cardioverter defibrillator; IHM, implantable haemodynamic monitors; LAP, left atrial pressure; NTS, nurse telephone support; NYHA, New York Heart Association (functional class); PA, pulmonary artery; PAP, pulmonary artery pressure; RCT, randomised controlled trial; RTM, remote telemonitoring; RV.

1.7 Discussion

Telemonitoring serves as an adjunct to our current armament of programmes to help manage the increasing disease burden in the setting of constraints in resources. Whether remote monitoring provides the best direction in managing ambulatory patients with heart failure remains under investigation. Two large systematic reviews of evidence and meta-analysis of data have been performed, both positively pointing to the potential benefits of telemonitoring in heart failure. (19, 20) These studies showed that telemonitoring is associated with a reduced risk of all-cause mortality and HF-related hospitalizations. There are also additional benefits of improved quality of life, reduced costs of management as well as improved prescribing of guideline directed therapy among heart failure patients enrolled into telemonitoring programmes.

Several landmark multicenter randomized clinical trials support the effects of home and remote telemonitoring in heart failure using non-invasive devices. Although there were no significant reductions in hospitalization in the WHARF and TEN-HMS studies, there was a significant reduction in mortality in the intervention arm. (25, 47) On the contrary, in HOME-HF, there was no significant reduction in mortality in the intervention arm, but fewer unplanned heart failure related hospitalizations with home telemonitoring. (24) However, home telemonitoring strategy did provide overall clinical benefit over and above usual care in terms of reducing the risk of death, HF-related hospitalizations and improving quality of life in other randomized controlled clinical studies. (21, 22, 48) The conflicting results suggest that a one-size fit all model of telemonitoring would fail to recognize the significant variability among individual heart failure patients and their unique response to treatment. While its difficult to pinpoint the exact reason for lack of benefit in some studies while in others there is positive clinical benefit, heterogeneity among the study cohorts in different randomized controlled

clinical trials may account for the conflicting results observed. Intuitively, the patients are likely to benefit the most from telemonitoring are those who have been recently discharged from hospital who may still be in NHYA functional class III dyspnoea or worse. In addition, patients not on maximal tolerated medical therapy are similarly at higher risk of decompensation and re-admission to hospital. To this end, careful selection of the 'sickest' patients into clinical trials, who may not yet be on optimal medical therapy, will likely yield more cost effective benefit than selecting more 'fit' patients. The findings from the United Kingdom based 'Implementation of Telemonitoring in Chronic Heart or Lung Failure' (TELECRAFT) trial, (27) on the factors that influence how patients integrate telemonitoring into their daily routines as well as how healthcare professionals use telemonitoring to aid decision- making will be provide further insight on the real world general applicability of home telemonitoring.

Sophisticated methods of telemonitoring in heart failure that involve invasive monitoring either with implantable cardiac monitors or devices, to monitor impedance and cardiac haemodynamics, have received much attention in the last few years. Briefly, bioelectrical impedance is inversely correlated with pulmonary capillary wedge pressure (49) and correlates with natriuretic peptide levels and mitral E-wave deceleration time. (50) What is more, intrathoracic impedance change monitoring has been shown to be superior to acute weight changes in predicting the risk of worsening heart failure events, (51) but surprisingly low sensitivity and positive predictive value for predicting heart failure decompensation in another randomized controlled study. (34) Clinical studies of the utility of intrathoracic bioimpedance monitoring, have similarly yielded conflicting evidence. Device based impedance monitoring and intervention may lead to reduced heart failure hospitalization (31) and reduced healthcare usage costs. (33) Furthermore, device based heart failure decompensation diagnostic algorithms identify those with a

heightened risk of HF hospitalization. (32) The potential benefits of invasive telemonitoring have to be carefully balanced against risk of increased healthcare usage due to false alarms and device related complications. (35, 46)

The use of implantable haemodynamic monitoring devices holds substantial promise to improve real-time detection of clinical changes in cardiac filling pressures, which are chronically raised in chronic heart failure and increase before heart failure hospitalization. (38, 52) Wireless pulmonary artery pressure (44) and left atrial pressure (42) guided therapy compared to standard usual care may lead to improved utilization of heart failure therapy, improve symptoms and outcomes in advanced heart failure. Pressure guided changes to heart failure therapy however failed to reduce total heart failure related events in one study. (45)

1.8 Conclusions and future considerations

Telemonitoring as a heart failure disease management model is rapidly evolving, to attempt to modify the adverse trajectory of the disease burden. The model seems inevitable as standard usual care, with guideline directed strategies still presides over dreadful disease morbidity and mortality. The advent of smart technologies heralds an era when non-invasive detection of worsening elevated left ventricular filling pressures, a hallmark of acute heart failure decompensation, maybe within reach. Intuitively, remote monitoring of data pointing to decline in an individual patient's haemodynamic profile and baseline bio-impedance profile, could aid physicians' clinical assessment of congestion and volume status. Ultimately, this would translate into effective adjustments of medical therapy, perhaps keeping left ventricular filling pressures within range and probably altering the natural history of the disease.

Further studies are ongoing at present; to further investigate the utility of pressure guided therapy in chronic heart failure, with special emphasis on patient self - management algorithms. (53) Non-invasive measurements of bio-electrical impedance, using wearable vests is currently being investigated for use in the ambulatory setting. (54) It seems feasible that once validated in large randomised controlled trials, this modality may be used to gather information useful for early detection of heart failure decompensation. Finally, heart rate variability, a measure of cardiac autonomic nervous tone, can be measured by cardiac resynchronization devices and used to predict groups at risk of adverse outcomes. (55) This may yet represent another modality to be harnessed and incorporated into smart decompensation algorithms to aid early detection. (32)

Chapter 2

Research questions and specific aims of the doctorate thesis

2.1 Is there a rationale to investigate non-invasive haemodynamic telemonitoring models?

The current telemonitoring models have investigated using structured telephone support, remote telemonitoring using voice interactive systems, implantable continuous haemodynamic monitors as well as haemodynamic monitoring using advanced heart failure devices. The above telemonitoring models are detailed in Chapter 1 of this thesis. The bulk of the data discussed in chapter 1 would seem to suggest that invasive monitoring of intra cardiac pressures to guide heart failure treatment might be better when compared to easily acquired traditional parameters such as weight, blood pressure and heart rate, measures that not only respond late to subtle changes in lung congestion but often only become perturbed at the point before a heart failure decompensation. What's more, the majority of patients in heart failure do not quality for device therapy. How should these patients' be remotely monitored? The status quo provides limited information to personalize and adapt medication therapy for heart failure.

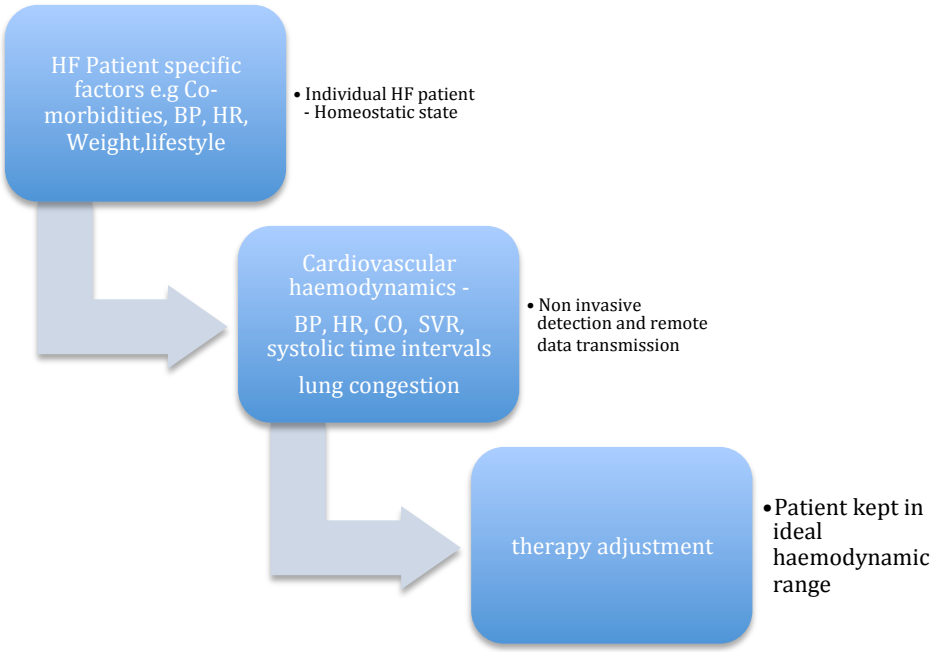
Given the important ramifications that the increasing burden of managing chronic diseases such as heart failure has on the delivery of care, clinical outcomes, as well as health care spending, a viable non-invasive approach to telemonitoring of intra cardiac pressures to guide heart failure treatment seems necessary, as telemonitoring (TM) is now being proposed as a potential solution to deal with the increasing prevalence of chronic disease among an ageing population, (6, 56) with potential benefits to reduce mortality, (19) improve symptoms and reduce the need for hospitalization. (25) The principal question addressed in this thesis is whether there are ideal innovative technologies for remote haemodynamic monitoring which may remotely monitor estimates of cardiovascular haemodynamics which correlate well with left ventricular filling pressures, which may enable earlier detection of heart failure decompensation, and ultimately be adapted for home telemonitoring in chronic heart failure. Which

estimates of cardiovascular haemodynamics can be reliably detected non-invasively? An important consideration which is considered is that various telemonitoring modalities are bedeviled by high false positive rates, (35) which lead to increased anxiety among patients and healthcare professionals alike, and may contribute to increased use of healthcare resources and increased failure rates among the remotely monitored patients. The research thesis addresses this critical problem by investigating whether non-invasive sensors purporting to measure non-invasive cardiac haemodynamic parameters can detect subtle changes in cardiac haemodynamics, which may result from activities of daily living such as change in posture, emotional stress and missing drug therapy. A corollary of this research may be to help establish a simple way of monitoring patient's haemodynamic status that might aid a 'health maintenance' strategy in which the physician strives to therapeutically keep the patient in an ideal range haemodynamic zone. Furthermore, the approach may recruit the patient to become a central 'partner' in their individual disease management through frequent self-monitoring and improved interaction with health professionals. (57, 58)

2.2 Health Maintenance Strategy for the management of heart failure

An approach to remote telemonitoring that employs the 'health maintenance' strategy which was investigated in the heartcycle programme (58, 59), has been promoted by investigators in the last decade. (60, 61) The Heartcycle programme was an integrated, European Commision funded initiative to investigate and develop smart technological solutions which provide multi-parametric monitoring and analysis of vital signs, as well as provide algorithms to interpret data and services to facilitate the remote management of both heart failure patients and coronary heart disease patients at home. Enabling patients to measure their haemodynamic status on a regular basis in their own home with transmission of information to an expert system and clinician overview, could transform the way that care for heart failure is given. In this concept, non-invasive surrogate measures of the cardiovascular function and lung congestion such as bioelectrical impedance, systolic time intervals, pulse wave characteristics, Cardiac index (CI) and Systemic Vascular Resistance (SVR), which are well established clinical measures, are used to develop medication adaptation algorithms as well as proposals for medication adjustment, (62). This strategy aims to attempt to maintain cardiovascular function in an ideal steady-state range. Rather than trying to detect something going seriously wrong and fixing it, a health maintenance strategy declares an ideal range of values and adjusts treatment to try to maintain the patient in a safe envelope. (58)

Figure 2 Non Invasive telemonitoring concept



Abbreviations: BP; blood pressure, HR; heart rate, CO; cardiac output, SVR; systemic vascular resistance

The strategy is advantageous for several reasons which include motivating patients to be more centrally involved in their care and thereby improving their engagement, as well as improving proposals for daily adjustments of some medications, such as diuretics. Furthermore, maintaining cardiovascular function in an ideal range may have favourable effects on the natural history of disease compared with crisis management, and may positively influence adverse outcomes, such as pulmonary hypertension, atrial fibrillation, and sudden death. (61)

2.3 Cardiac haemodynamics – the physiological basis for haemodynamic monitoring in chronic pump failure

Fundamentally, the hallmark of symptomatic heart failure is decreased cardiac output. The determinants of cardiac output are predominantly the heart rate and stroke volume. The stroke volume is in turn determined by the interplay between preload, afterload, and cardiac contractility. Haemodynamic changes in chronic heart failure (CHF) often comprise a sympathetically mediated increased heart rate and decreased stroke volume. Additionally, the preload is often increased, while the afterload, which is the systemic vascular resistance to the flow of blood, will often be increased. Myocardial contractility will often be decreased.

Figure 3 Haemodynamics of heart failure

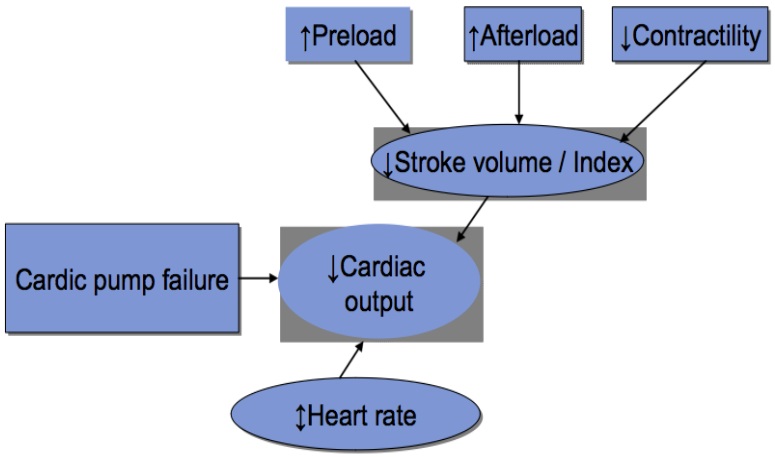


Figure 3 illustrates cardiac haemodynamic changes in symptomatic heart failure which are decreased cardiac output, decreased stroke volume, increased or decreased heart rate, increased preload, increased afterload as well as decreased myocardial contractility.

2.4 Decompensating Heart Failure haemodynamics

Abnormal left ventricular loading conditions leading to pulmonary congestion usually precede heart failure hospitalisation. (63, 64) Weight, a traditionally monitored variable in heart failure, poorly correlates with increase in pulmonary pressure and worsening symptoms of acute HF. (65, 66) An interplay between reduced capacitance in the venous system leading to increased preload, increased arterial stiffness and resistance and subsequent increased afterload is thought to drive intrathoracic fluid accumulation. (67, 68) Conceptually, continuous monitoring of fluid status in HF patients would therefore aid identification of volume overload, thus providing an opportunity to intervene at an early stage and possibly avert hospital admission for acute decompensated HF.

2.5 Health Maintenance Haemodynamics

This concept leans on continually restoring haemodynamic homeostasis in a patient with congestive HF. Maintenance of cardiovascular function in an ideal range steady-state would aim to balance the preload, afterload and improve cardiac contractility as illustrated in figure 4 below.

Figure 4 Illustration of ideal range haemodynamics in heart failure - parameters to measure and potential therapeutic strategy.

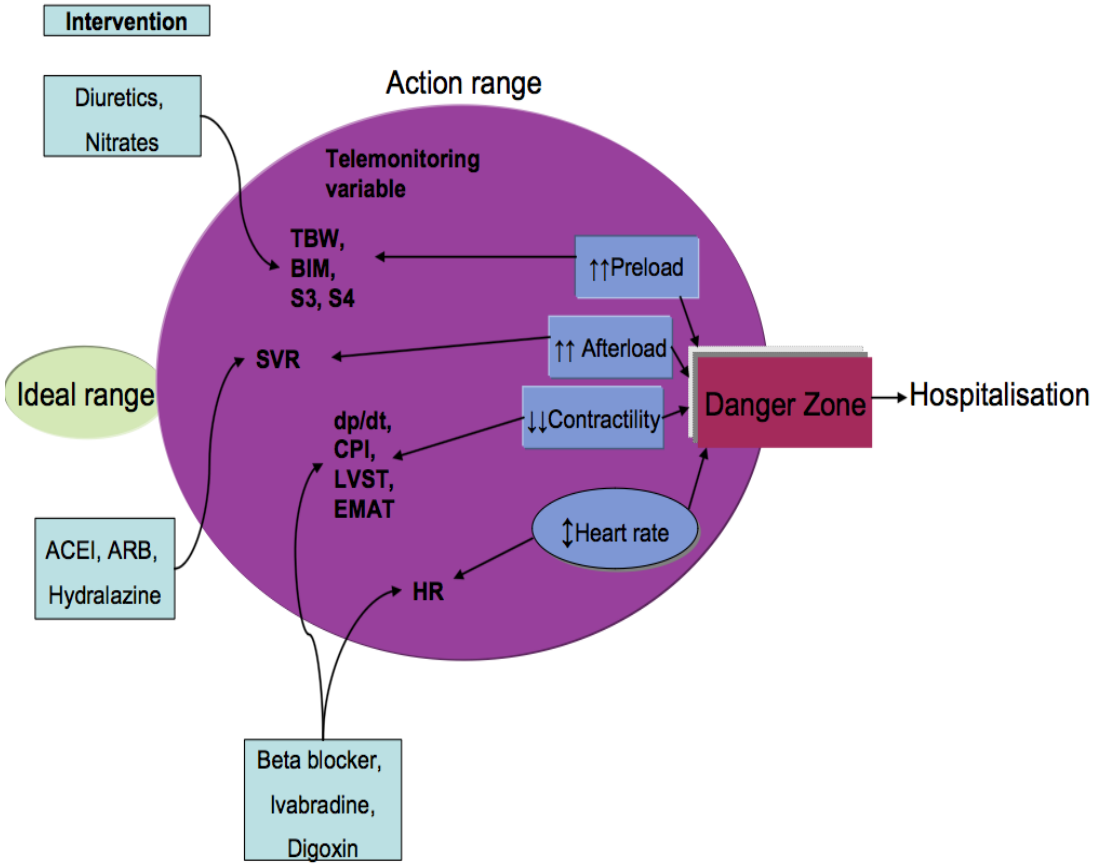


Figure 4 illustrates the underlying reason for the health maintenance strategy and the possible actionable measurements which can be taken from the decompensating heart failure patient. The possible interventions which a clinician could undertake are shown. Within the action range phase, telemonitoring of TBW; total body water, BIM; bio-impedance, S3; third heart sound, S4; fourth heart sound, SVR; systemic vascular resistance, CPI; cardiac power index, LVST; left ventricular systolic time, EMAT; electromechanical activation time, dt/pt; left ventricular contractility could be undertaken. Then treatments with diuretics, ACEI; angiotension converting enzyme inhibitor, ARB; angiotension receptor blocker, Nitrates etc could be instituted to prevent deterioration to the danger zone.

2.6 Novel sensors for the remote monitoring in heart failure

The ideal novel sensor for remote haemodynamic monitoring should be simple to use, especially given that the majority of heart failure patients are elderly. Furthermore it should have been tested under robust clinical conditions and shown not only to accurately detect haemodynamic pertubations consummate with decompensating pump failure but also to detect and track subtle changes, even with changes in patients' activities of daily living. Such modalities include non-invasive devices for measuring cardiac haemodynamics using impedance cardiography, finger plethysmography, phonocardiography as well as thoracic impedance vests. In the MyHeart observational clinical trial, (69)148 heart failure patients were monitored daily for up to 1 year using a novel telemonitoring sensor system recording symptoms questionnaires, body weight and blood pressure, nocturnal respiratory and heart rate as well as thorax bioimpedance. In this study, nocturnal respiratory rate and thoracic congestion derived by means of a bioimpedance vest showed the highest predictive value for heart failure decompensation. We will now review how these modalities may be useful for remote haemodynamic monitoring of patients with heart failure.

2.7 Impedance Cardiography

Thoracic electrical BIM is inversely proportional to lung congestion. It is a validated non-invasive method that measures cardiac haemodynamic parameters, (70, 71) including in the ambulatory setting. (72) Briefly, impedance cardiography uses low-amplitude, high-frequency alternating signal to determine changes in electrical impedance, cardiac ejection and the velocity of blood flow within the aorta, (73) from which stroke volume, cardiac output, systemic vascular resistance and total body water

can be derived. Whole body BIM monitoring using a Non-Invasive Cardiac System (NICaS) has been used to estimate cardiovascular function in an outpatient CHF population, providing good predictive information of readmissions with CHF. (74) The PREDICT study, (75) which was also an outpatient clinic based study, further consolidated the findings that when performed regularly in stable patients with HF with a recent clinical decompensation, impedance cardiography can identify patients at increased risk of recurrent decompensation.

2.8 Spectroscopic bioimpedance

Bioimpedance spectroscopy has emerged as a potential method to detect subtle changes in thoracic fluid content heart failure patients. (54, 76) A feasibility study using the BIM sensor for home TM has been conducted, where it was shown to predict episodes of hospitalisation for worsening HF. (69) Multimodal assessments of CHF patients with natriuretic peptides, BIM and clinical evaluation have been shown to identify those with thoracic congestion and more adverse prognosis. (77) This modality of lung congestion monitoring holds great promise in providing ‘snap-shot’ measurements, which may be easily performed at home on a daily basis, to provide crucial information about patients at risk of ‘danger zone congestion status.’ Such information could then be remotely transferred to the healthcare provider who would in turn swiftly optimize therapy and thereby prevent a ‘crisis’ hospitalisation.

2.9 Finger Plethysmography

Non-invasive haemodynamic monitoring using pressure pulse contour analysis has been validated in patients with advanced HF. (78) In this method, continuous beat-to-beat cardiac output, blood pressure, and systemic vascular resistance are determined from the pulsatile systolic area of the blood pressure curve. (79, 80) This method is promising but remains to be tested in the ambulatory setting.

2.10 Pulse wave characteristics

Peripheral arterial tonometry using ankle-brachial sphygmomanometers combined with finger-toe plethysmography (Enverdis) enable easy, noninvasive determination of vascular dysfunction. Disordered pulse wave amplitude is linked to endothelial dysfunction which is present in patients with early asymptomatic (81) as well as symptomatic (82) HF. Endothelial dysfunction, increased oxidative stress, and baroreceptor dysfunction contribute to the pathophysiology of CHF. (83, 84) Moreover, patients with impaired endothelial function are at increased risk for cardiovascular events and death. (84) Pulse-wave characteristics such as aortic pulse wave velocity (PWV), augmentation index (AIx) and mean arterial pressure (MAP) can therefore be determined noninvasively to aid identification of high risk groups which can be aggressively treated both non-pharmacologically with exercise and advice to stop smoking, as well as pharmacologically with blood pressure reduction using angiotensin converting enzyme inhibitors and statin therapy- measures which are known to positively influence endothelial function. This method is likely more suitable for snap-shot assessments in outpatient clinics and general practice to provide simple non-invasive markers of vascular dysfunction.

2.11 PhonoCardiography

Acoustic Cardiography enables detection of normal and abnormal heart sounds and simultaneously correlates the timing of those heart sounds in every cardiac cycle to the onset of the P wave and QRS complex on the electrocardiogram (ECG). (85) Parameters determined using this modality include the strength of the third heart sound (S3) graded from 0 to 10, the strength of the fourth heart sound (S4), electromechanical activation time (EMAT, interval from Q wave to the first heart sound) and systolic dysfunction index (SDI, a combination of EMAT/RR, S3 score, QRS duration and QR interval). S3 Strength >5 has been shown to correlate with left ventricular end-diastolic pressure (LVEDP) >15mmHg. (86, 87) Diastolic heart sounds provide diagnostic and prognostic information in HF. The third heart sound has been shown to be independently associated with adverse outcomes, including progression of HF. (88) In addition, an S4 is associated with increased LV stiffness and also elevated LVEDP. (89) Systolic time intervals are validated indicators of HF. (90, 91) In patients suffering from HF with reduced ejection fraction, electromechanical activation time is prolonged whilst LV contractility (dP/dt) is low. Overall these highly specific measures have been found to improve diagnostic accuracy for decompensated HF and LV dysfunction. (92, 93) Ambulatory acoustic cardiography holds promise as it provides an assessment of the electro-mechanical performance of the heart. There could be a role for use in heart failure follow-up in the home setting to aid optimization of therapy.

2.12 Summary:

Intrathoracic fluid congestion, changes in LV filling pressures and reduced cardiac function are common pathophysiologic events that occur prior to heart failure hospitalisations. Interestingly these events may occur with little changes in traditionally monitored variables such as weight, heart rate and blood pressure. Conceptually, enabling patients to measure estimates of their haemodynamic status on a regular basis in their own home with transmission of information to an expert system and clinician overview could transform the way that care for heart failure is given. An added advantage of the strategy is that patients are likely to become more empowered and thus become more proactive in managing their disease.

An ideal innovative telemonitoring sensor should be simple and easy to use in the home scenario, inexpensive and easily operated by patients who can then perform daily checks themselves. Furthermore it should acquire vital cardiac signals simultaneously and extract prognostic cardiac information that can then be intelligently transferred to an expert system with clinician overview. With such technology in mind, telemonitoring could be transformed from a concept of 'crisis detection and management' strategy to a 'health maintenance' strategy.

Monitoring intrathoracic impedance, abnormal diastolic heart sounds and systolic time intervals, have clearly been shown to correlate with early signals of heart failure decompensation. Conceptually therefore, novel innovative sensors employing this technology could be useful in maintaining individual patients in an ideal range of haemodynamic status. Further studies to assess the impact of the health maintenance strategy in heart failure on morbidity and mortality as well as the economic benefits are required.

Chapter 3

Research Methodology

3.1 Research Hypothesis

We hypothesized that non-invasive "smart technologies" can reliably and accurately detect and track subtle changes in surrogates of cardiovascular haemodynamics in response to challenges posed by activities of daily living and non-adherence to therapy.

3.2 Methodology

To test the validity of our research proposal, a series of prospective clinical studies were designed and conducted in stable patients with chronic heart failure, on maximal tolerated guideline directed therapy for heart failure. Studies were performed under clinically adapted conditions to mimic the patient's own habitat.

3.3 Temperature (Study 1)

The choice of temperature as a variable to use to assess whether non-invasive devices can detect the changes that it induces on cardiac parameters is relevant. First, alterations in temperature are a universal phenomenon, experienced by both healthy people and those with chronic medical conditions such as heart failure. As telemonitoring devices are deployed in the patient's own habitat, it is important that the impact of patient daily activity and the 'real world' changes that they often encounter are considered when interpreting telemonitoring data. The temperatures chosen for the study purposes were 19^0C and 28^0C. These temperatures were chosen as they are common temperatures, which patients can encounter in the United Kingdom. We did not consider more extreme temperatures, as there is evidence that elderly patients with heart failure and other co-morbidities have impaired responses to temperature, which may contribute to higher morbidity and mortality. (94, 95) The impact of temperature on the haemodynamics detected by non invasive devices was studied on two separate study days which were allocated in random order as 'cold day' and 'warm day'.

3.4 Music (Study 2)

Music is also universally available from various media sources and is easily accessible to elderly patients with heart failure. There is some evidence that different types of music may exert different effects on the cardiovascular system(96), and autonomic nervous system. Acute auditory exposure to heavy metal musical auditory stimulation has been found to decrease the sympathetic and parasympathetic modulation on the heart, while auditory exposure to classical baroque music has been reported to reduce sympathetic regulation on the heart. (97) To this end, we selected a heavy metal rock track as 'irritating music' and a classical type track as 'soothing music'. We did not specifically look to assess whether heart failure patients develop tolerance to irritating music over time but rather concentrated on the acute auditory exposure to elicit a cardiovascular response. The impact of acute auditory music exposure on the cardiovascular haemodynamics detected by non invasive devices was at 19^0C, which is the usual ambient temperature that heart failure patients in the United Kingdom would be exposed at home. Two consecutive 45minute episodes of acute auditory exposure to either 'heavy metals or irritating music' or 'classical or soothing music' were studied in the same patient, with a twenty minute interval in between the music episodes, during which focused echocardiography was performed to obtain the echocardiographic data to correspond to the first music session.

3.4 Non-adherence (Study 3)

Patients with chronic medical conditions including congestive heart failure are commonly 'burdened' with taking multiple pharmacological agents. Missing drug therapies is a common occurrence, whether intentional (true non-adherence), planned such as missing diuretics when attending hospital for tests or truly forgotten perhaps due to other co-morbidities such as cognitive impairment. Notably, cardiovascular medication nonadherence is associated with an increased risk of mortality and re-

hospitalization, (98-100) may be responsible for up to twenty percent of readmissions with acute decompensated heart failure, (101, 102) making it an important target for quality improvement. (103) We chose a 'supervised' guideline directed heart failure therapy holiday for 48hrs to attempt to mimic 'real world' non-adherence. A 48 hour drug holiday may not be sufficient for all drugs such as angiotensin converting enzyme inhibitors , angiotensin receptor blocker (104) to be completely removed from the systemic circulation while beta blockers are like to be nearly cleared from the systemic circulation by 48hours. (105) The mainstay of the study however was to mimic short term day to day drug holidays as opposed to total clearance of the drugs from the systemic circulation.

3.5 Dynamic physiological manouvres

Various physiological manouvres were incorporated into the daily protocol during the measurement taken during the non-adherence study. The manouvres were chosen in part because of the central aim of the thesis assess activities of daily living which are likely to be common among heart failure patients. Furthermore, our work sought to establish whether the potentially subtle changes in parameters such as bioimpedance, induced by postural changes could be reliably detected and tracked by the bioimpedance vests. Intuitively, different body positions are likely to change the venous return, aided by the gratitational force and therefore influence the preload. Straight leg raising has been a subject of interest, especially in the intensive care setting where its clinical value lies in predicting fluid responsiveness. (106) Straight leg raising increases systemic venous return, preload and relative lung congestion. Similarly, the supine position is likely to allow more blood from the peripheral vascular bed to the heart and lead to relatively more pulmonary congestion. The increased venous return and subsequent pulmonary congestion form the basis for orthopnoea, a classical symptom common in patients with predominantly left ventricular failure. The sitting and standing positions

on the other hand may induce a fall in the central blood volume, subsequently reducing central venous and right atrial mean pressure, (107, 108) leading to less pulmonary congestion. The valsalva maneuver similarly decreases thoracic blood volume (109, 110) and systemic blood pressure.

3.6 Subjects and study design

Study 1 (temperature) and (study 2) were single centre, observational cross over studies involving 18 patients. Twelve of the subjects were males in stable congestive heart failure (NYHA ≥ II) aged between 46 and 90 years (mean, 72 ± 13 years). 6 patients (5 male and 1 woman) enrolled had treated hypertension aged between 51 and 75 years (mean, 67 ± 9yrs). The mean left ventricular ejection fraction was 32 ± 12% in the congestive cardiac failure cohort and 57 ± 5% in the HTN group. Study 3 (Non-adherence) was also a single centre, controlled clinical study which enrolled 30 patients. Twenty patients (16 males) were in stable congestive heart failure (NYHA ≥ II), aged between 45 and 88 years (mean, 69.95±10.72 yrs) while10 patients (3 women) had hypertension (HTN), aged between 46 and 78 years (mean, 67.90±7.86yrs). Patients with heart failure were randomly assigned to attend for cardiovascular measurements on three separate days, which were at least 72 hours apart: baseline, day with heart failure medication taken, day with heart failure medication omitted for 48 hours. For patients with hypertension (HTN), measurements were made at baseline and on the days when medication was omitted. The baseline study day was a short introductory day to fit the bioimpedance vest and improve the patient's familiarity with the study protocol.

3.7 Inclusion Criteria

Patients were included into the congestive heart failure group if: (i) they had a history of CHF > 3months (ii) they were treated with a loop diuretic, at least 40mg of furosemide or 1mg of bumetanide (iii) they were treated with beta-blockers and ACE inhibitors (or

angiotensin receptor blockers) for at least 6 weeks (iv) either LVEF <35% or NT-proBNP >400 pg/mL recorded within previous year (v) willing and able to give informed consent. Exclusion Criteria for the CHF group were: (i) patients with breathlessness at rest or on mild exertion (ii) patients with an admission for worsening heart failure in the previous 6 weeks (iii) patients who have required an increase in diuretic therapy in the previous 6 weeks. Patients in the HTN cohort were hypertensives treated with any conventional agent but with no objective evidence of heart failure. Patients were recruited from the heart failure out patient clinics. All patients gave signed informed consent. The study was performed at the academic cardiology department of the University of Hull, and the study protocol approved by the local Ethics Committee and conducted according to the Declaration of Helsinki.

3.8 Experimental Protocol

The protocols for study days for the temperature, music and non-adherence controlled studies are presented as schematic diagrams labeled as figures 5, 6 and 7.

Figure 5 Music Protocol

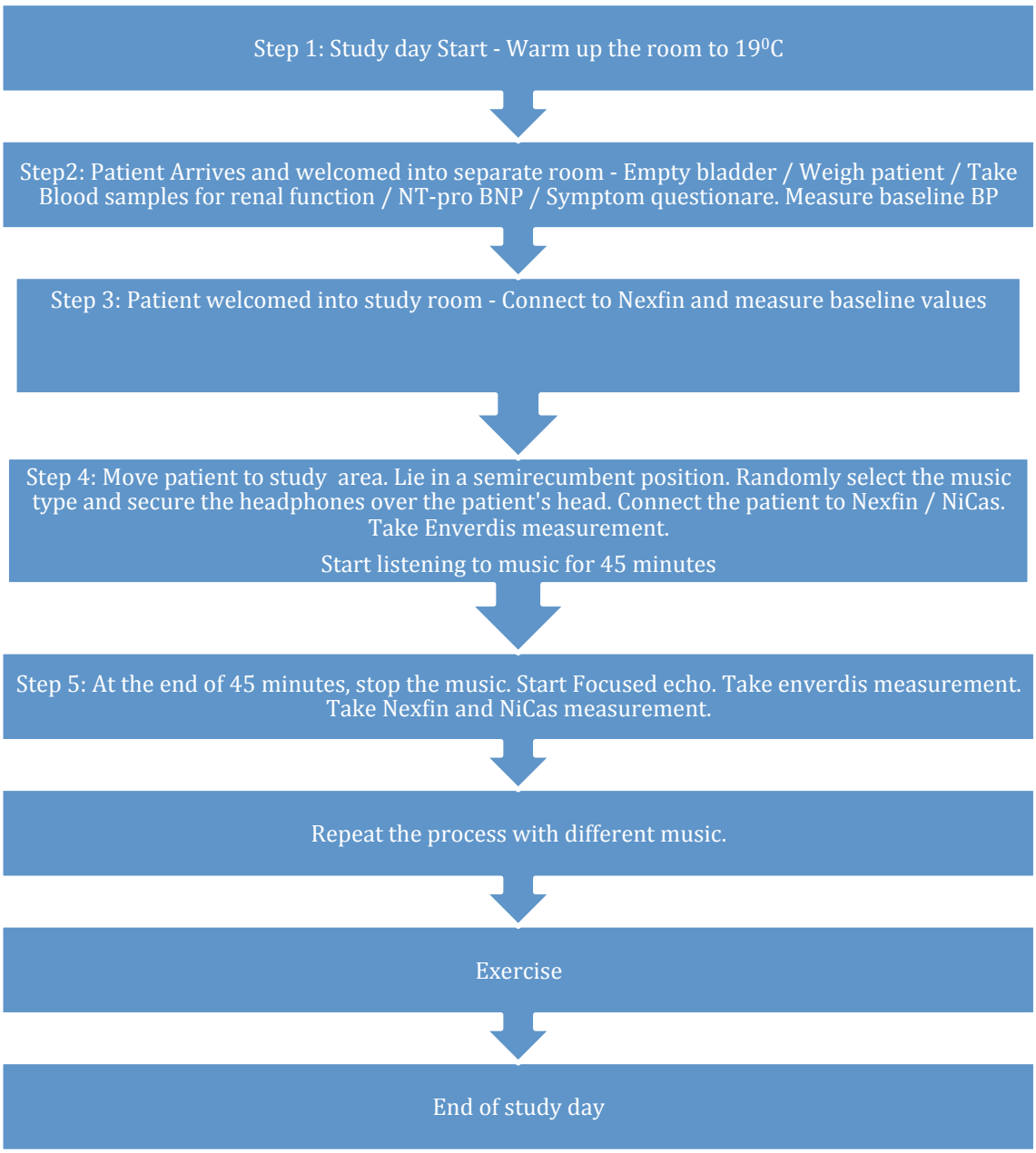


Figure 6 Temperature Protocol

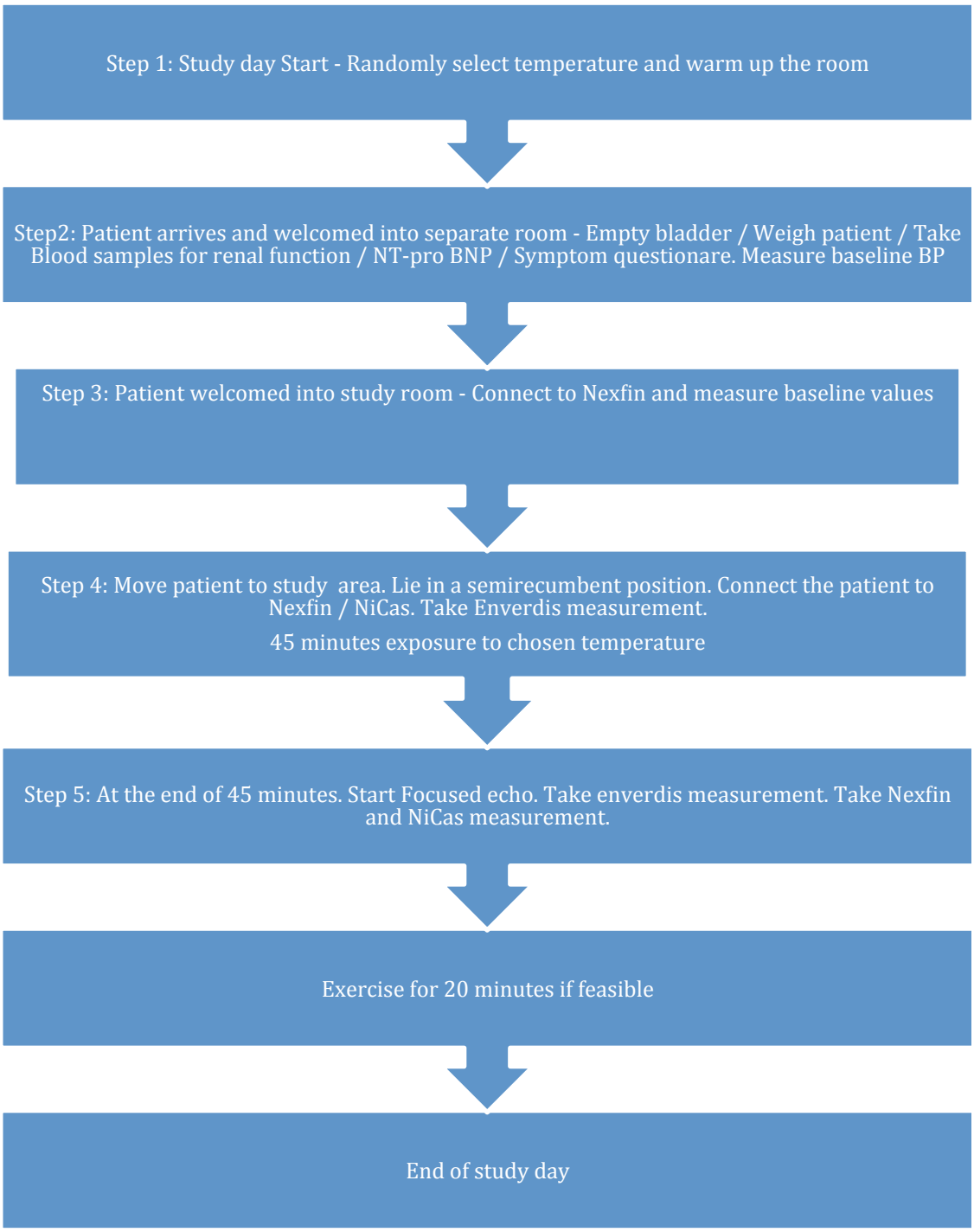
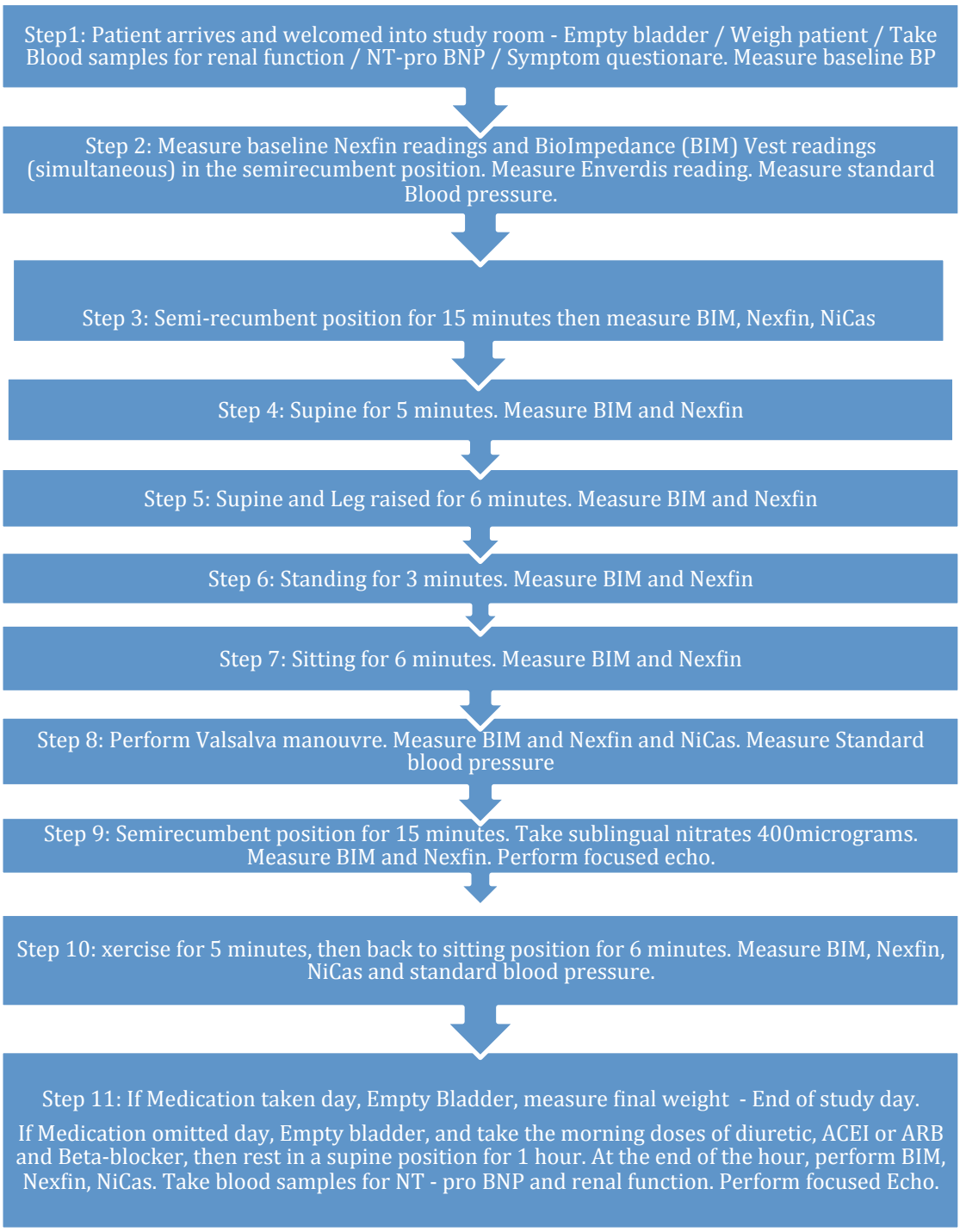


Figure 7 Non-Adherence Study protocol



On each study day, patients were asked to take a similar light breakfast with their usual medication but to avoid strong coffee or tea and not take more than 500mls of liquid. At baseline, each patient was asked to empty their bladder. Tanita scales were then used to measure baseline weight, total body water and distribution, bioelectrical impedance, fat and muscle mass distribution. Breathlessness, fatigue and emotional function of daily living were explored with the aid of the European quality of life questionnaire. After a short clinical examination and blood sampling, baseline measurements were performed. Blood pressure and heart rate were recorded with a validated automatic blood pressure (BP) device (GE DINAMAP V100).

3.9 Temperature control

Cardiovascular function was measured non-invasively on separate days at cool (19ºC) and warm (28ºC) room temperatures in the supine position and during light exercise. Room temperature was thermostatically controlled with an air conditioner (MR SLIM MITSUBISHI ELECTRICAL Model PKA – RP35GAL). A wall mounted analogue thermometer (Brannan 12/407 Thermometer Max-Min Slimline) was used to record the actual room temperature. Patients were randomly assigned to start with a warm or cool study day

3.10 Impedance Cardiography

Global blood flow (Cardiac Index, CI - the global blood flow per minute, and Stroke Index, SI - the global blood flow per beat), respiration and a host of cardiodynamic parameters were assessed noninvasively using the NICaS™ apparatus. This technology uses whole body bio-impedance and the Tsoglin-Frinerman formula for non-invasive determination of CI.(78, 111) Bioimpedance cardiography uses a low-amplitude, high-frequency alternating signal to calculate impedance of the flow of electricity through the chest. The instantaneous changes in electrical impedance and various other parameters are measured, from which stroke volume, cardiac output, cardiac index, and other haemodynamic parameters, including systemic vascular resistance, can be calculated.

3.11 Finger Plethysmography

After calibration, continuous measurements of BP, CI, systemic vascular resistance (SVR) were obtained at baseline in resting supine position for 5 minutes using a finger-tip, volume-clamp (Nexfin, Bmeye, Netherlands). Following acclimatisation, intermittent continuous recordings were made at 45 minute intervals after echocardiographic assessment. Finally, continuous measurements were made during exercise, at constant load of 25 watts, on a bicycle ergometer (ERGOLINE GmbH) for 20 minutes, which is equivalent to 4-7 METS. This level of exercise was chosen to simulate a 6-minute walk test commonly used to evaluate patients with heart failure.

3.12 Pulse wave characteristics

Following a 45 minute period of acclimatization, ankle-brachial sphygmomanometers combined with finger-toe plethysmography (Enverdis) were used to measure pulse-wave characteristics such as aortic pulse wave velocity (PWV) and augmentation index (AIx) in the supine position.

3.13 Echocardiography

Detailed echocardiographic assessment of ventricular function, valve integrity, and regional wall motion abnormalities was performed by experienced sonographers using a Philips Vivid E9 machine and a 3.5MHz probe. In addition to the qualitative examination of the cardiac chambers and valves, further measurements made via the standard parasternal and apical views included the following: LV end-diastolic and end-systolic volumes (LVEDV and LVESV) using biplane modified Simpson's rule, from which stroke volume (SV) and ejection fraction (EF) were calculated. From the apical four chamber view, peak mitral inflow E and A velocity waves on pulse-wave Doppler, E/A ratio, E-wave deceleration time, isovolumetric relaxation time, and colour M-mode mitral inflow velocity of propagation were measured. The systolic s' and diastolic e' and a' peak velocities were obtained by tissue-Doppler imaging (TDI) at both the septal and lateral mitral origins on four-chamber apical view, and the e'/a' ratio and LV filling index E/e' ratio were calculated as per British Society of Echocardiography guidelines. (112). Peak systolic tricuspid insufficiency gradient was also measured from the apical four-chamber view. Stroke volume (SV) and cardiac output (CO) (113, 114) were calculated using left ventricular outflow tract diameter (LVOTd) and doppler derived velocity time integral (VTI).

$SV = \pi /4 \times (LVOTd)^2 \times LVOT\ VTI$

$CO = SV \times heart\ rate$

Stroke Index (SI) and Cardiac index (CI) were then respectively calculated by dividing SV and CO by the body surface area (BSA).

$SI = SV/BSA$

$CI = CO/BSA$

3.14 Statistical analysis

The change in Nexfin™ derived systolic BP was defined as a primary endpoint using the patient as their own control. An average of about 300 individual systolic BP measurements was taken. The power calculation was based upon results of earlier studies in our laboratory. Assuming a standard deviation of 3mmHg then 10 patients were assumed to be needed to have 90% power with $P \leq 0.05$ to show a 5mmHg difference in blood pressure. The data were checked for normal distribution and most data were considered normally distributed. Therefore, data were expressed as mean ± standard deviation (SD). Data were analysed by paired Student's t-test. Statistical significance was defined as p value ≤ 0.05. Bland - Altman plots (115) were constructed to assess for agreement between echocardiographically derived stroke index (SI) and cardiac index (CI) versus Nexfin and NiCas derived SI and CI. Statistical analysis has been performed using SPSS 19.0 (SPSS Inc., Chicago, IL, USA).

Student's T-test: The studies reported in the thesis were essentially small pilot studies. In this regard, the student's T-Test, which is considered robust in handling small data sets (116) was preferred to compare variables.

Significance: A p-value of 0.05 or less was accepted as significant leading to rejecting the Null hypothesis. (117)The Null hypothesis was assumed to be that there is no change in measured variables e.g. no change in systolic blood pressure between colder and warmer temperature settings in patients with heart failure or controls.

Normality: Data were rigorously inspected for normal distribution to guide the appropriate use of statistical tests. (118) A visual inspection of the data using quarntile quarntile plots (Q-Q plots), Gausian distribution was used to gain perspective of data normality. A one sample Kolmogorov-Smirnov test was also used to test whether residuals were normally distributed.

Agreement between measurement methods: Bland-Altman plots(115) were constructed to check for congruency in measurement methods e.g whether measurement of cardiac index with Nexfin device agreed with measurements with either echocardiography or NiCas device.

Chapter 4

Effect of Environmental Temperature on Haemodynamics in Patients with Heart Failure

4.1 Abstract

Aims: To investigate the effects of environmental temperature on haemodynamics and measures of congestion, using non-invasive devices that might be adapted for remote patient monitoring, in patients with heart failure and control subjects

Methods and results: Patients with a clinical diagnosis of heart failure due to left ventricular systolic dysfunction, receiving loop diuretics and a control group with hypertension but no heart failure were enrolled. Cardiovascular function was measured non invasively on separate days at cool (19ºC) and warm (28ºC) room temperatures in the supine position and during light exercise using: - Electrical bio-impedance (NICas), finger plethysmography (Nexfin, Bmeye, Netherlands) and ankle-brachial sphygmomanometers combined with finger-toe plethysmography (Enverdis). A rise in temperature induced vasodilation, resulting in a fall in systolic blood pressure (135 ± 28 mmHg at 19^{o}C vs 120 ± 27 mmHg at 28^{o}C, p = 0.05). Conversely, vasoconstriction at lower temperatures resulted in significantly higher systemic vascular resistance (2096 ± 632 dyn•s/cm^5 at 19^0C vs 1685 ± 456 dyn•s/cm^5 at 28^0C p = 0.003), aortic PWV (7.5 ± 1.7 m/s at 19^0C vs 6.6 ± 1.7 m/s at 28^0C p = 0.02) and augmentation index (35 ± 15% at 19^0C vs 25 ± 16% at 28^0C p = 0.01). Total body impedance was lower at 28^0C (406 ± 67 ohms at 19^0C vs 374 ± 67 ohms at 28^0C p = 0.002). There was no change in the left ventricular ejection fraction (39 ± 15 % at 19^0C vs 40 ± 17 % at 28^0C p = 0.594)

Conclusions: Changes in environmental temperature have marked effects on haemodynamics which can be detected non-invasively with telemonitoring devices. Local environmental conditions should be taken into account as they may be important for interpretation of data. Control of environmental temperature should be

explored as a potential adjunct to therapy in patients with heart failure. Longer term studies are required to assess effects on fluid balance.

Key words: Heart failure• Haemodynamics•Bio-impedance•Blood pressure•Cardiac index. Pulse wave velocity•Systemic vacular resistance•Augmentation index.

4.2 Introduction

Despite monumental advances in the treatment of congestive heart failure (CHF) over the last two decades, early detection of impending CHF decompensation remains elusive.(119) CHF remains one of the most common reasons for emergency medical admission, readmission and hospital bed-days occupancy.(120) Rehospitalisation for worsening congestive heart failure (CHF) predicts adverse prognosis, especially in the elderly, and is often initiated by intrathoracic fluid overload leading to symptomatic pulmonary congestion.(64, 121, 122) Early clinical detection of intrathoracic fluid congestion is therefore of paramount importance. Risk-prediction models based on clinical signs and radiological features of CHF are unreliable in accurately predicting intrathoracic fluid accumulation.(123-126) Moreover, traditionally monitored variables such as weight gain seem unreliable at predicting impending CHF decompensation and hospitalisation.(65, 66) Consequently, telemonitoring is in rapid evolution and appears to be moving towards more technically sophisticated novel strategies to more precisely assess and monitor fluid status in HF.(23, 25, 127) In recent developments, monitoring total body electrical impedance, systemic vascular resistance and cardiac index in conjunction with traditionally monitored variables such as weight and CHF specific symptoms as a surrogate for fluid status, has gathered pace and appears to hold promise in improving early detection of which patients are likely to be readmitted with decompensated CHF, with the potential to intervene early.(78, 128)

To date, the impact that environmental temperature might have on haemodynamic recordings obtained via novel telemonitoring technologies has not been examined. Additionally, we found no evidence that local measurement of environmental conditions is usually considered during interpretation of data although this may be important. It was thus the aim of this study to investigate the effects of environmental temperature on haemodynamics and measures of congestion, using non-invasive devices that might be adapted for remote patient monitoring, in patients with heart failure and control subjects.

Methods: (Please refer to the methodology section)

4.3 Results:

4.3.1 Clinical characteristics

Baseline characteristics and medications of the study population are shown in Table 6. The control group had a significantly higher BP, normal EF and lower NT pro BNP. Risk factor distribution was largely different between the groups: history of arterial hypertension (CHF 5/12 and Control 6/6), dyslipidaemia (CHF 8/12, Control 4/6), Diabetes (CHF 4/12, Control 3/6). The control group was mainly treated with ACEI/ARB and statins for risk factor control and primary prevention while the CHF group was on pharmacotherapeutic agents for heart failure as recommended by the European Society of Cardiology guidelines. According to the protocol, all patients in the CHF group were treated with a loop diuretic. Patients remained clinically stable during the study with no HF decompensation.

Table 3 Baseline patient characteristics, co-morbidities and medications

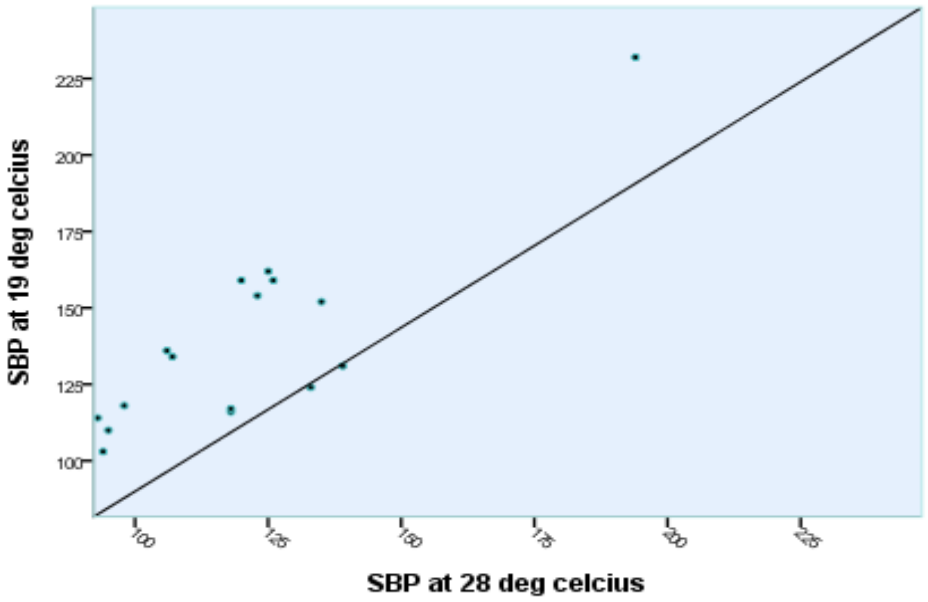
	CHF (n = 12) n = 12	HTN (n = 6) n = 6
Demographics		
Age, years	72 ± 13	67 ± 9
Men n (%)	12 (100)	5 (83)
NYHA, II/III	10 / 2	NA
HR, bpm	62 ± 9.3	61 ± 12
Systolic BP, mmHg	118 ± 25	145 ± 23
NT pro BNP, (IQR)	1207 (431 – 3506)	103 (48 – 178)
LVEF, %	32 ± 12	57 ± 5
Co-morbidities		
IHD, n(%)	10 (83)	0 (0)
DM, n(%)	4 (33)	3 (50)
AF, n(%)	2 (17)	0 (0)
HTN, n(%)	5 (42)	6 (100)
Dyslipidaemia, n(%)	8 (67)	4 (67)
Medications		
Loop diuretics, n (%)	12 (100)	0 (0)
ACEIs / ARBs, n(%)	11 (92)	6 (100)
Beta-blockers , n(%)	12 (100)	1 (17)
Aldosterone Antagonist, n (%)	7 (58)	1 (17)
Statins, n (%)	8 (67)	4 (67)

NYHA, New York Heart Association; IQR, inter quartile range; HR, heart rate; bpm, beats per minute; NT pro BNP; LVEF, left ventricular ejection fraction; AF, atrial fibrillation

4.3.2 Systolic blood pressure

Continuous Systolic BP measurement by finger-tip, volume-clamp finger plethysmography was significantly lower at 28^0C in overall population (135 ± 28 mmHg at 19^oC vs 120 ± 27 mmHg at 28^oC, p = 0.05). Similar changes in systolic BP were consistently observed for the heart failure cohort (125 ± 23 mmHg at 19^oC vs 111 ± 28 at 28^oC mmHg) as well as the control group (157 ± 25 mmHg at 19^0C vs 137 ± 15 mmHg at 28^0C). Individual systolic BP data points of the overall population are displayed in figure 8 below.

Figure 8 Shows the relationship between systolic BP at 19^0C and 28^0C



Line is line of identity (x = y = 1). Data points are above the identity line if the systolic blood pressure is increased by cold conditions.

4.3.3 Congestion variables

Total body impedance data is shown in Table 4 below. The body weight was constant. The extracellular water (ECW) and total body water (TBW) tended to increase with a rise in temperature to 28^0C. Conversely bio-electrical impedance and plasma haematocrit were significantly lower at 28^0C.

Table 4 Congestion variables at 19^0C and 28^0C in the overall population

	19^0C	***28^0C***	***p-value***
Tanita (bio-impedance)			
Weight (kg)	79.7 ± 17.9	79.9 ± 18.2	**0.20**
TBW, (kg)	40.0 ± 10.4	41.1 ± 8.2	**0.23**
ECW (kg)	17.7 ± 2.8	18.1 ± 2.8	**0.006**
NiCas			
Bio-impedance R, (ohms)	406 ± 67	374 ± 67	**0.002**
Laboratory			
Log NT pro BNP	2.69 ± 0.72	2.71 ± 0.78	**0.927**
Haematocrit	**0.406 ± 0.039**	**0.385 ± 0.041**	**0.003**

Congestion variables in the heart failure cohort followed the trends denoted in Table 4 with no significant change in weight (78.4 ± 20.0 at 19^0C vs 78.8 ± 20.5 at 28^0C) and total body water (TBW = 41.4 ± 12.9 kg at 19^0C vs 42.1 ± 9.5 kg at 28^0C). Extra cellular water (ECW) was higher at 28^0C (18.0 ± 3.2 kg vs 18.4 ± 3.4 kg). Similarly, Nicas derived bio-impedance was lower at higher temperature (418 ± 68 ohms at 19^OC vs 379 ± 75 ohms at 28^OC).

The control group had lower bio-impedance (382 ± 64 ohms at 19^0C vs 365 ± 59 ohms at 28^0C), extracellular water (ECW = 17.3 ± 2.4 kg at 19^OC vs 17.9 ± 2.3 kg at 28^OC) and total body water (TBW = 38.0 ± 6.3 kg at 19^OC vs 39.8 ± 6.5 kg

at 28^{O}C) but similar trends as in the overall population. No significant change in weight was observed (81.3 ± 16.5 kg at 19^{O}C vs 81.5 ± 16.4 kg at 28^{O}C).

4.3.4 Cardiac haemodynamics

Table 5 below shows continuous measures of global blood flow measured by finger plethysmography and total body bio-electrical impedance in the overall population. The cardiac index (CI) did not differ significantly between the cold and hot environment. Bio-impedance was significantly lower at 28^{o}C. LVEF tended to be higher at 28^{0}C while the tricuspid annular planar excursion (TAPSE) remained unchanged. Left atrial volume index (LAVI) and left ventricular filling index (E/E') tended to be lower at 28^{0}C although the changes did not achieve significance.

Table 5 Measures of continuous global blood flow by finger plethysmography and total body bio-electrical impedance in the overall population

	19^{o}C	28^{o}C	p-value
Nexfin			
CI (L/min/m^2)	2.2 ± 0.8	2.3 ± 0.6	0.51
NiCas			
CI (L/min/m^2)	2.3 ± 0.4	2.4 ± 0.5	0.59
CPI (w/m^2)	0.49 ± 0.10	0.49 ± 0.11	0.92
Echocardiographic data			
LVEF (%)	39 ± 15	40 ± 17	0.594
LVEDD (mm)	6.1 ± 0.9	6.2 ± 1.0	0.253
LAVI (ml/kg/m^2)	45 ± 23	42 ± 20	0.116
E/E'	13 ± 6	12 ± 3	0.628
TAPSE (mm)	18 ± 4	18 ± 4	0.302

Cohort analysis showed haemodynamic trends similar to those of the overall population as follows: Within the heart failure group – bio-impedance derived CI

(2.4 ± 0.5 L/min/m^2 at 19^0C vs 2.5 ± 0.5 L/min/m^2 at 28^0C)and cardiac power index (CPI = 0.48 ± 0.10 w/m^2 at 19^0C vs 0.50 ± 0.13 w/m^2 at 28^0C) did not change significantly, as did plethysmography derived CI (2.2 ± 0.9 L/min/m^2 at 19^0C vs 2.2 ± 0.5 L/min/m^2 at 28^0C). Similarly, within the control group – plethysmography derived CI (2.4 ± 0.7 L/min/m^2 at 19^0C vs 2.5 ± 0.7 at 28^0C L/min/m^2), bio-impedance derived CI (2.2 ± 0.4 L/min/m^2 vs 2.3 ± 0.4 L/min/m^2) and CPI 0.53 ± 0.10 w/m^2 vs 0.51 ± 0.10 w/m^2 did not change to achieve significance.

Table 6 shows the echocardiogaphic data of the heart failure and control groups. The left ventricular end diastolic diameter (LVEDD) and left atrial volume index (LAVI) were bigger in the heart failure cohort. Left ventricular filling index (E/E′ ratio) was higher in the heart failure population.

Table 6 Electrocardiographic data of the heart failure and control groups

Echocardiographic data	19⁰C	28⁰C
Heart Failure		
LVEF (%)	32 ± 12	32 ± 13
LVEDD (mm)	6.7 ± 0.9	6.8 ± 1.0
LAVI (ml/kg/m^2)	53 ± 2.5	48 ± 2.3
E/E'	14 ± 7	13 ± 4
TAPSE (mm)	17 ± 0.5	17 ± 0.5
Control		
LVEF (%)	55 ± 2	57 ± 7
LVEDD (mm)	5 ± 0.4	5 ± 0.5
LAVI (ml/kg/m^2)	30 ± 4	30 ± 2
E/E'	11 ± 1	11 ± 2
TAPSE (mm)	20 ± 3	20 ± 3

4.3.5 Pulsatile haemodynamics

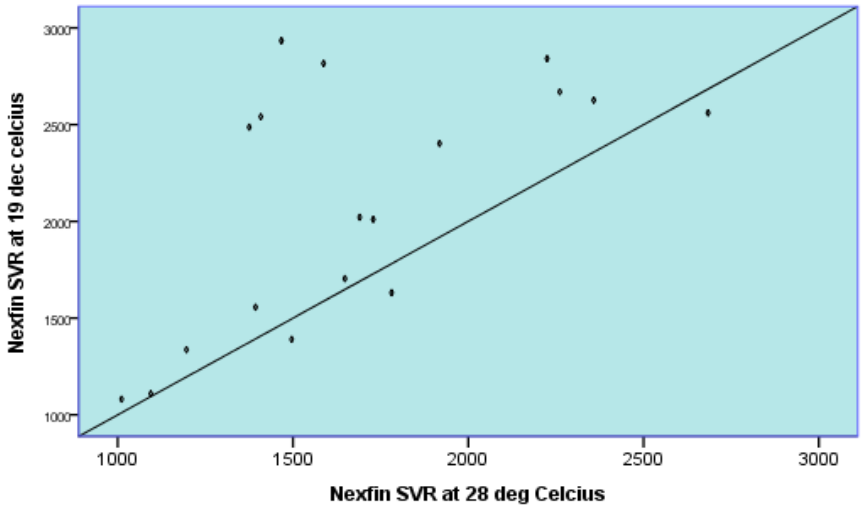
Table 7 displays vascular physiologic characteristics of the overall population. A rise in temperature was associated with significant reductions in systemic vascular resistance (SVR), aortic pulse wave velocity (PWV) and augmentation index (Aix).

Table 7 Vascular physiologic characteristics of the overall population

	19°C	28°C	p-value
Enverdis			
Aortic PWV (m/s)	7.5 ± 1.7	6.6 ± 1.7	0.02
Aortic Aix (%)	35 ± 15	25 ± 16	0.01
Nexfin			
SVR (dyn·s/cm^5)	2096 ± 632	1685 ± 456	0.003

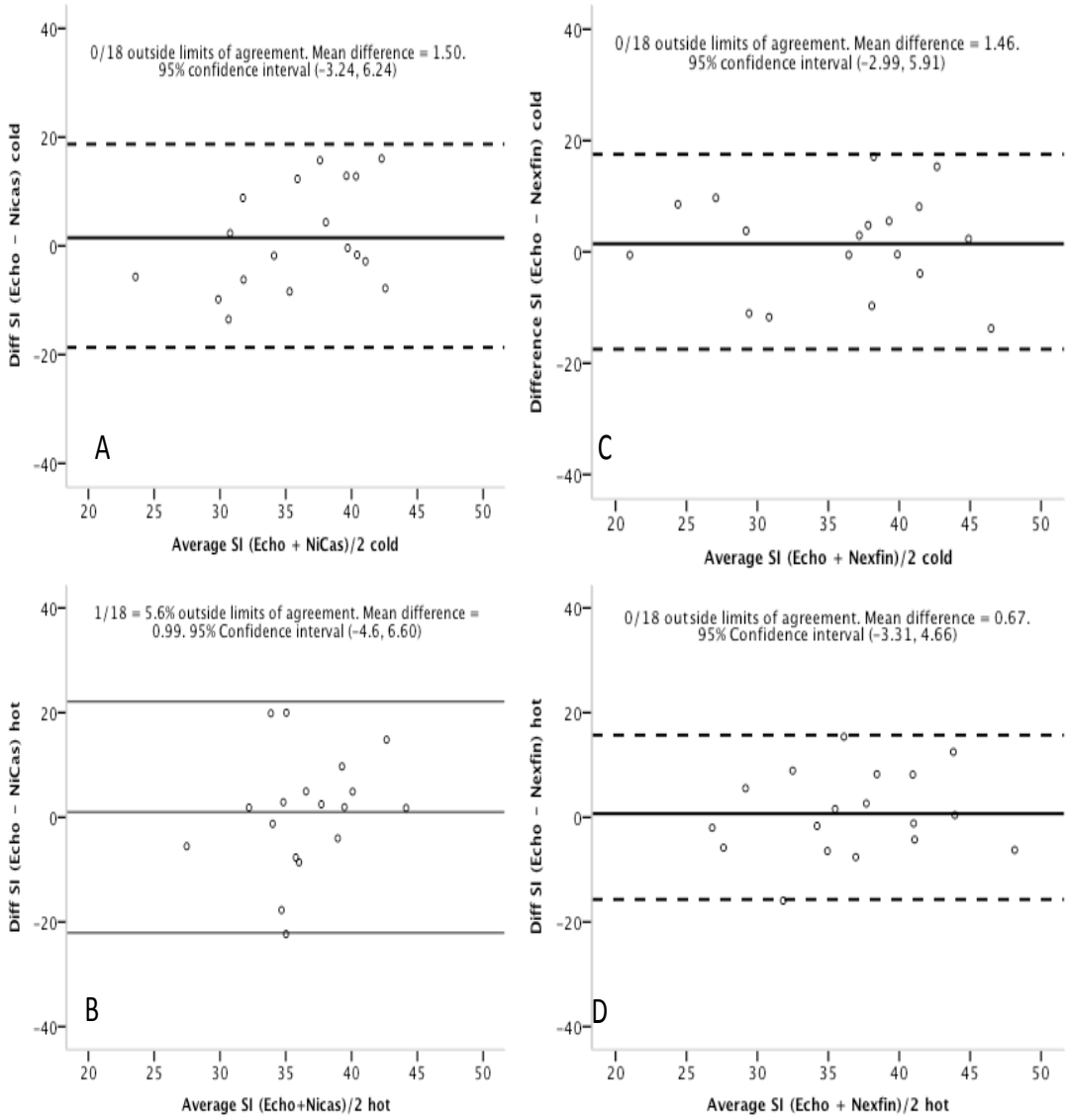
Analysis of the heart failure cohort data showed similar trends as follows;- Aortic PWV 7.4 ± 1.8 m/s at 19^{0}C vs 6.2 ± 1.6 m/s at 28^{O}C, Aix 34 ± 15% at 19^{O}C vs 21 ± 14% at 28^{O}C and Nexfin derived SVR 2071 ± 641 dyn·s/cm^5 at 19^{0}C vs 1673 ± 465 dyn·s/cm^5 at 28^{0}C. The control group had higher baseline SVR, PWV and Aix than the heart failure group but similar trends as in table 4 above with Nexfin derived SVR 2143 ± 672 at 19^{0}C dyn·s/cm^5 vs 1707 ± 480 dyn·s/cm^5 at 28^{0}C, aortic PWV 8.2 ± 1.8 m/s at 19^{0}C vs 7.5 ± 1.6 m/s at 28^{0}C and aortic Aix 41 ± 20 % at 19^{0}C vs 33 ± 12 % at 28^{0}C.

Figure 9 Shows the relationship between SVR at 19^0C vs 28^0C



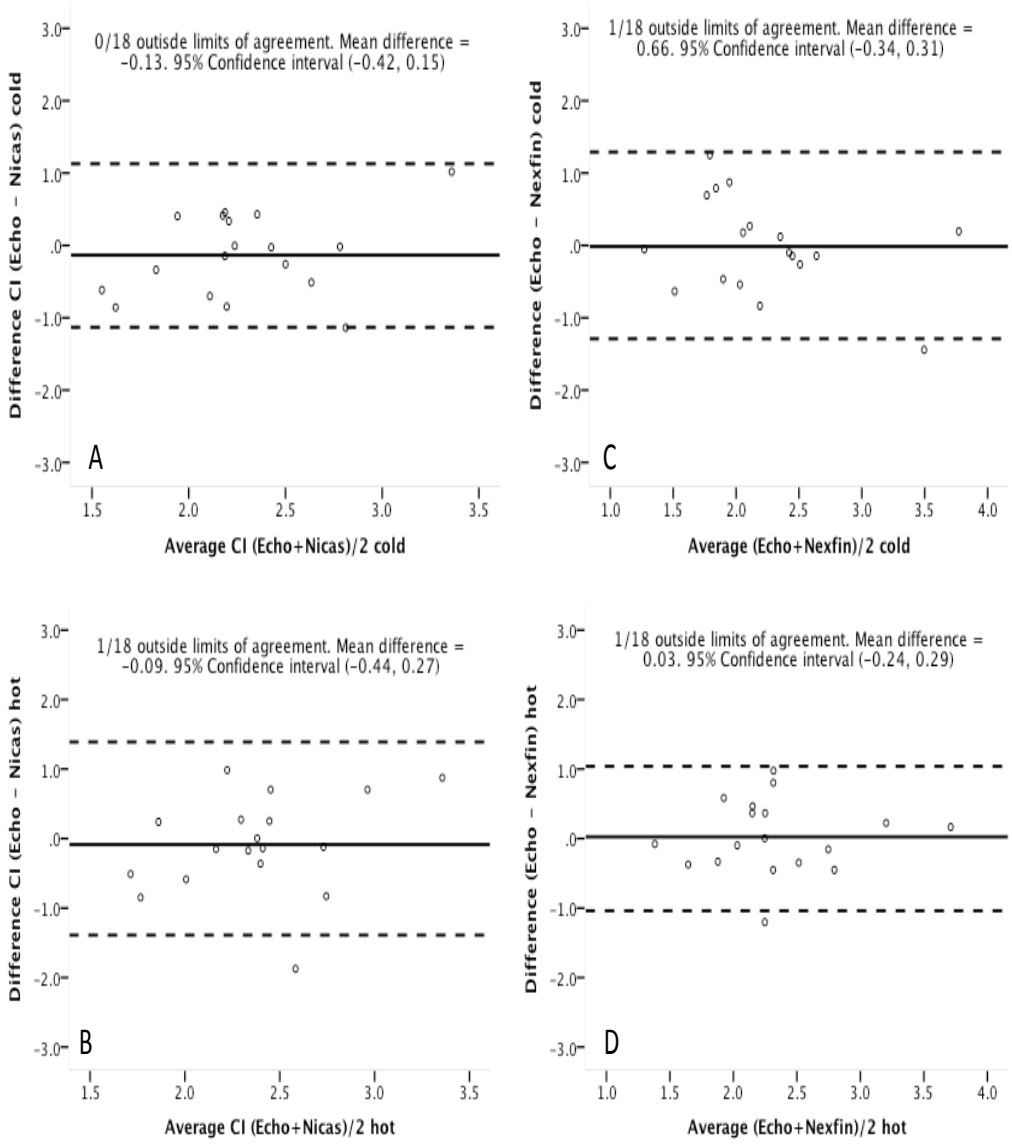
Line is line of identity (x = y = 1). Data points are above the identity line if the SVR is increased by cold conditions.

Figure 10 Bland and Altman plots comparing Stroke Index (SI) measurements using doppler echocardiography (gold standard) versus NiCaS and Nexfin devices



(a) Bland and Altman plot to compare echocardiography derived SI and NiCas derived SI measured at 19^0C, (b) Bland and Altman plot to compare echocardiography derived SI and NiCas derived SI measured at 28^0C. (c) Bland and Altman plot to compare echocardiography derived SI and Nexfin derived SI measured at 19^0C. (d) Bland and Altman plot to compare echocardiography derived SI and Nexfin derived SI measured at 28^0C. Lower level of agreement (LLA) = Mean – 2SD and upper level of agreement (ULA) = mean + 2SD marked by dotted lines.

Figure 11 Bland and Altman plots comparing Cardiac Index (CI) measurements using doppler echocardiography (gold standard) versus NiCaS and Nexfin devices



(a) Bland and Altman plot to compare echocardiography derived CI and NiCas derived CI measured at 19^0C, (b) Bland and Altman plot to compare echocardiography derived CI and NiCas derived CI measured at 28^0C. (c) Bland and Altman plot to compare echocardiography derived CI and Nexfin derived CI measured at 19^0C. (d) Bland and Altman plot to compare echocardiography derived CI and Nexfin derived CI measured at 28^0C. Lower level of agreement (LLA) = Mean – 2SD and upper level of agreement (ULA) = mean + 2SD marked by dotted lines.

4.4 Discussion:

The results of the present observational study demonstrate that changes in environmental temperature have marked effects on haemodynamics, particularly systolic blood pressure, systemic vascular resistance and aortic augmentation index. The mechanism of haemodynamic perturbation with altering temperature conditions has been a subject of historical interest. Our findings are congruous with previous studies which show that physiological changes in response to altering temperature conditions are attributable to either vasoconstriction or vasodilatation.(129, 130) The acute haemodynamic effects of warm-water and sauna bathing and the potential benefits of thermal vasodilation therapy were evaluated by Tei and colleagues in 34 patients with CHF, concluding that haemodynamics improve after warm-water or sauna bathing in patients with chronic CHF. In their study, cardiac index and stroke index increased markedly from the control level due to the reduction in cardiac preload and afterload.(131) In addition, we observed lower total body electrical bioimpedance at higher temperature conditions, a finding suggestive of lower intra-thoracic fluid congestion. Caution should be exercised in interpreting this finding as changes in cutaneous impedance of the skin in response to temperature may erroneously increase predicted total body water and underpredict fat mass.(132) Conversely, cold temperatures make hypertension worse and trigger cardiovascular complications such as CHF.(133) Increased sympathetic system activity manifest by increased urinary and plasma catecholamines and subsequent rise in BP during the winter season has been observed.(134) Furthermore, it has been postulated that lower environmental temperature may exert a direct effect on the heart (135) or have an indirect effect via changes in blood pressure.(136) In our study, we observed a mean rise of systolic blood pressure of 15mmHg in cooler conditions. In Britain, winter blood pressures exceed summer blood pressures by around 5 mmHg.(137) Sustained blood pressure differences

of this order have been associated with a 21% increase in coronary heart disease events.(138)

Another important observation from the study is that there is no statistically significant difference in echocardiographic measurements between 19^0C and 28^0C. This observation further underscores the validity of echocardiography as a non-invasive tool for the assessment of left atrial volume, left ventricular volumes, ejection fraction as well as indices of left ventricular relaxation.

Finally, there was congruency between Nexfin and NiCas derived SI and CI with echocardiographically derived SI and CI, which strongly correlates with thermodilution derived SI and CI. (113, 114) This finding may serve to provide reassurance that the non-invasive methods of measuring cardiohaemodynamics are comparable with established methods.

4.5 Limitations:

The observations reported in the study pertain to measurements at either 19^0C or 28^0C only. The investigators would therefore caution against generalising the results to measurements at other temperatures, such as more extreme temperatures.

4.6 Conclusion

Changes in environmental temperature may have marked effects on haemodynamics recorded by non-invasive devices used for telemonitoring. Changes in temperature affect bio-impedance but whether this reflects true changes in the content or distribution of body water is uncertain. The physiological perturbation of haemodynamics and vascular resistance in response to varying temperature conditions can be reliably detected and tracked non-invasively with telemonitoring devices. The data and

observations described here underscore the need to consider establishing different normal ranges according to the season of the year when non invasively assessing haemodynamics, at least in certain parts of the world. In view of the seasonal variation in haemodynamics, local measurement of environmental temperature should in general be routinely factored in, as it may be important for interpretation of telemonitoring data. Awareness of this phenomenon will result in more personalized, tailored remote monitoring of CHF patients. Finally, control of environmental temperature should be explored as a potential adjunct to therapy in patients with heart failure. However, the potential benefits of reduced vascular resistance and increased cardiac output might be offset by fluid retention under some circumstances. Longer term studies are required to assess effects on fluid balance.

Chapter 5

Effect of Music and Noise on Haemodynamics in Patients with Heart Failure

5.1 Abstract

Aims: To investigate the effects of irritating noise and music on haemodynamics and measures of congestion using non-invasive devices that might be adapted for remote patient monitoring in patients with heart failure and in control subjects.

Methods and results: Patients with a clinical diagnosis of heart failure, receiving loop diuretics and with objective evidence of cardiac dysfunction and a control group with hypertension but no heart failure were studied. Patients were studied in the supine position, at a room temperature of 19^0C, either under quiet conditions, or with soothing music or listening to loud and irritating noise through headphones for 45 minute periods on separate study days, approximately two hours after intake of usual daily medication. Cardiovascular function was measured non invasively in the supine position and during light exercise using: - Electrical bio-impedance (NICas), finger plethysmography (Nexfin, Bmeye, Netherlands) and ankle-brachial sphygmomanometers combined with finger-toe plethysmography (Enverdis).

Systolic blood pressure tended to rise with irritating music although the change did not reach statistical significance (SBP 129 ± 29 mmHg during soothing music vs 135 ± 28 mmHg during irritating music, p = 0.19). Similarly we did not observe a significant change in the cardiac index (2.2 ± 0.6 L/min/m^2 during soothing music vs 2.3 ± 1.6 L/min/m^2 during irritating music, p = 0.10). Central aortic augmentation index, a sensitive marker of arterial stiffness trended to be higher during irritating noise although the change did not reach statistical significance (Aix 34 ± 16 % during soothing music vs 40 ± 15 % during irritating music). Pulse wave velocity similarly increased during irritating noise (PWV 7.3 ± 1.9 m/s during soothing music vs 8.0 ± 1.7 m/s during irritating music). The change in the

cardiac power index similarly did not reach significance (CPI 0.46 ± 0.08 w/m^2 during soothing music vs 0.50 ± 0.13 w/m^2 during irritating music, p = 0.32).

Conclusions: Environmental noise appears to have only a modest effect on haemodynamic variables obtained by non-invasive monitoring devices. Any effect of noise pollution on haemodynamics might be more related to the patients emotional response to it rather than noise itself.

Key words: Heart failure• Haemodynamics•Bio-impedance•Blood pressure•Cardiac index. Pulse wave velocity•Systemic vacular resistance•Augmentation index.

5.2 Introduction

There are concerted efforts worldwide to deal with the increasing prevalence of chronic disease among an ageing population, employing novel telemonitoring (TM) techniques. (56) What is more, there is some evidence that home TM of patients with heart failure (HF) can reduce mortality, improve symptoms and reduce the need for hospitalisation. (19, 25, 57) Consequently, there is growing interest in the use of non-invasive devices for remote monitoring of cardiovascular function, using more technically sophisticated novel strategies to more precisely assess and monitor fluid status in HF. (47, 127) Monitoring total body electrical impedance, systemic vascular resistance and cardiac index as well as traditionally monitored variables such as weight and congestive HF specific symptoms as a surrogate for fluid status is likely to improve early detection of patients at risk of decompensated congestive HF, with the potential to intervene early. (78, 128) As part of the clinical calibration of novel devices for home telemonitoring, there needs to be systematic investigation of the ability of the devices to closely and accurately track physiological changes which may inadvertently result from environmental influences.

Blood pressure (BP) and heart rate (HR) are closely controlled by sympathetic nervous system (139) which in turn can be influenced by environmental changes in noise levels. Environmental factors causing stress or relaxation may affect haemodynamic parameters. (140-142) The impact that environmental factors causing stress or relaxation might have on haemodynamic recordings obtained via novel telemonitoring technologies has not been examined. It was thus the aim of this study to investigate the effects of environmental noise on haemodynamics, using non-invasive devices that might be adapted for remote patient monitoring, in patients with heart failure and control subjects.

Methods: (Please refer to the methodology section)

5.3 Results:

5.3.1 Clinical characteristics

Baseline characteristics and medications of the study population are shown in Table 8. The control group had a significantly higher BP, normal EF and lower NT pro BNP. Risk factor distribution was largely different between the groups: history of arterial hypertension (CHF 5/12 and Control 6/6), dyslipidaemia (CHF 8/12, Control 4/6), Diabetes (CHF 4/12, Control 3/6). The control group was mainly treated with angiotensin converting enzyme inhibitor (ACEI) /angiotensin receptor blocker (ARB) and statins for risk factor control and primary prevention while the CHF group was on pharmacotherapeutic agents for heart failure as recommended by the European Society of Cardiology guidelines. According to the protocol, all patients in the CHF group were treated with a loop diuretic. Patients remained clinically stable during the study with no HF decompensation.

Table 8 Baseline patient characteristics, co-morbidities and medications

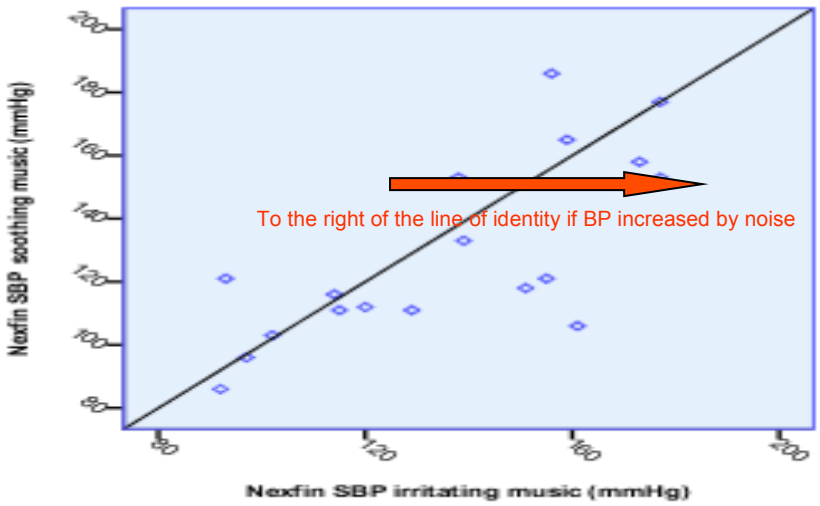
	CHF (n = 12)	HTN (n = 6)
Demographics		
Age, years	72 ± 13	67 ± 9
Men n (%)	12 (100)	5 (83)
NYHA, II/III	10 / 2	NA
HR, bpm	62 ± 9.3	61 ± 12
Systolic BP, mmHg	118 ± 25	145 ± 23
NT pro BNP, (IQR)	1207 (431 – 3506)	103 (48 – 178)
LVEF, %	33 ± 11	55 ± 5
Co-morbidities		
IHD, n(%)	10 (83)	0 (0)
DM, n(%)	4 (33)	3 (50)
AF, n(%)	2 (17)	0 (0)
HTN, n(%)	5 (42)	6 (100)
Dyslipidaemia, n(%)	8 (67)	4 (67)
Medications		
Loop diuretics, n (%)	12 (100)	0 (0)
ACEIs / ARBs, n(%)	11 (92)	6 (100)
Beta-blockers , n(%)	12 (100)	1 (17)
Aldosterone	7 (58)	1 (17)
Statins, n (%)	8 (67)	4 (67)

NYHA, New York Heart Association; IQR, inter quartile range; HR, heart rate; bpm, beats per minute; NT pro BNP, N-amino terminal pro-brain natriuretic peptide; LVEF, left ventricular ejection fraction; AF, atrial fibrillation; ACEI, (angiotensin converting enzyme inhibitor); ARB, angiotensin receptor blocker; HTN, hypertension; IHD, ischaemic heart disease; DM, diabetes mellitus

5.3.2 Systolic blood pressure

In overall population, continuous systolic BP measured by finger-tip, volume-clamp finger plethysmography was lower during soothing music although the change did not reach significance (SBP 129 ± 29 mmHg during soothing music vs 135 ± 28 mmHg during irritating music, p = 0.19). A similar trend in systolic BP was observed in the heart failure cohort (119 ± 27 mmHg *vs* 129 ± 30mmHg) but not in the control group (150 ± 22 mmHg *vs* 150 ± 24 mmHg). Individual systolic BP data points of the overall population are displayed in figure 12 below.

Figure 12 Shows the relationship between systolic BP during soothing music vs irritating music



Line is line of identity. Data points are to the right of the line of identity if BP increased by noise.

5.3.3 Cardiac haemodynamics

The cardiac index (CI) did not differ significantly between soothing and noisy background noise. LVEF remained unchanged.

Table 9 Measures of continuous global blood flow derived by finger plethysmography and total bio-electrical impedance in the overall population

	Soothing noise	Irritating	p-value
Nexfin			
CI (L/min/m^2)	2.2 ± 0.6	2.3 ± 1.6	0.10
NiCas			
CI (L/min/m^2)	2.2 ± 0.2	2.3 ± 0.5	0.32
CPI (w/m^2)	0.49 ± 0.10	0.49 ± 0.11	0.92
Echocardiographic data			
LVEF (%)	39 ± 15	40 ± 17	0.594

Cohort analysis showed haemodynamic trends similar to those of the overall population as follows: Within the heart failure group – bio-impedance derived CI (2.2 ± 0.4 L/min/m^2 during soothing music vs 2.4 ± 0.4 L/min/m^2 during irritating music)and cardiac power index (CPI = 0.46 ± 0.08 w/m^2 during soothing music vs 0.48 ± 0.10 w/m^2 during irritating music) did not change significantly, neither did plethysmography derived CI (2.1 ± 0.5 L/min/m^2 during soothing music vs 2.2 ± 0.7 L/min/m^2 during irritating music). Similarly, within the control group – plethysmography derived CI (2.3 ± 0.7 L/min/m^2 during soothing music vs 2.5 ± 0.7 L/min/m^2 during irritating music), bio-impedance derived CI (2.2 ± 0.4 L/min/m^2 during soothing music vs 2.3 ± 0.8 L/min/m^2 during irritating music) and CPI 0.51 ± 0.10 w/m^2 vs 0.54 ± 0.18 w/m^2 did not change to achieve significance.

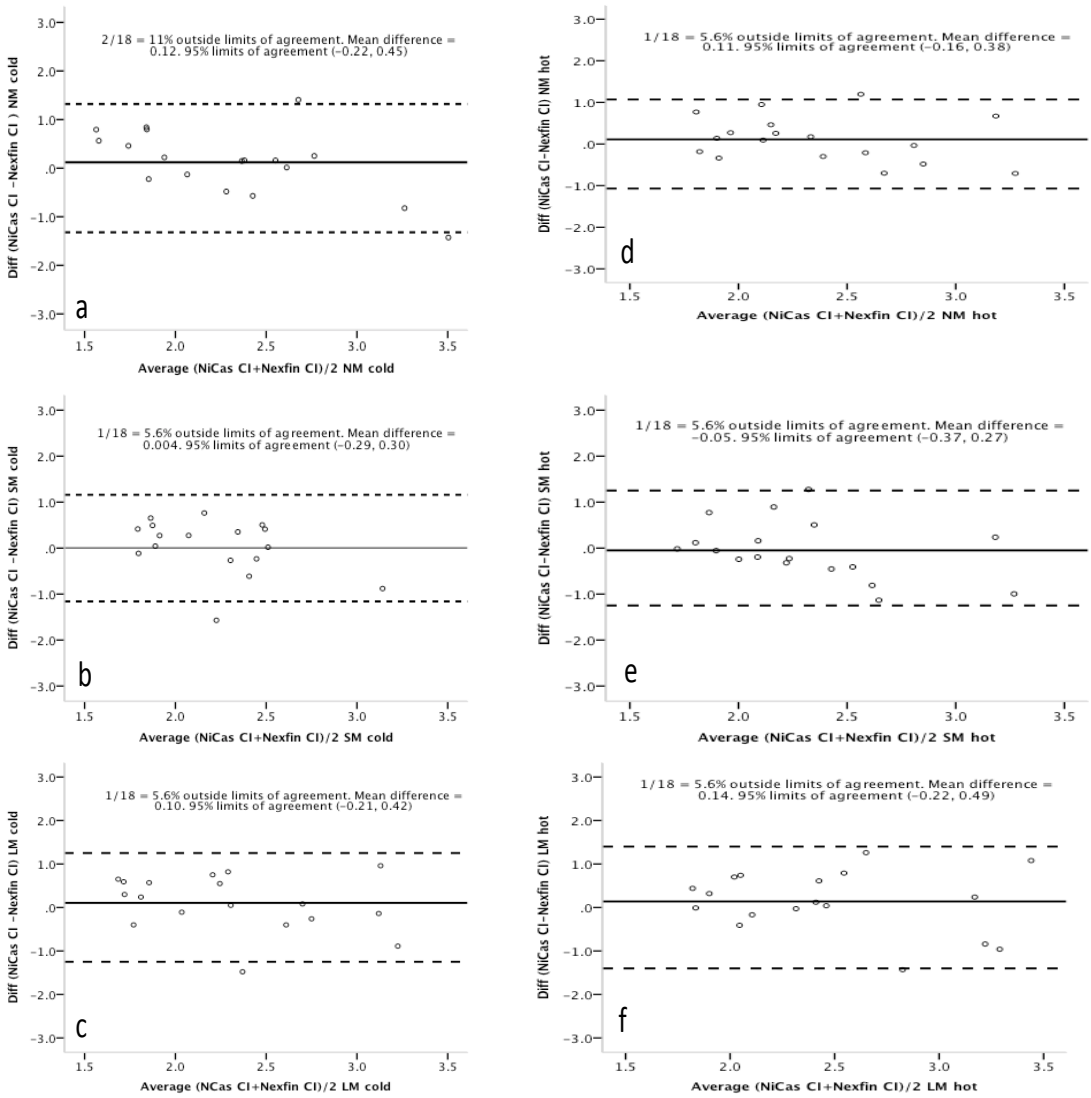
5.3.4 Pulsatile haemodynamics

Central aortic augmentation index, a sensitive marker of arterial stiffness trended to be higher during irritating noise although the change did not reach significance. Pulse wave velocity similarly increased during irritating noise. Conversely, the systemic vascular resistance was lower during irritating noise.

Table 10 Vascular physiologic characteristics of the overall population

	Soothing noise	**Irritating noise**	**p-value**
Enverdis			
Aortic PWV (m/s)	7.3 ± 1.9	8.0 ± 1.7	0.63
Aortic Aix (%)	Aix 34 ± 16	40 ± 15	0.26
Nexfin			
SVR(dyn·s/cm^5)	2035 ± 586	1985 ± 597	0.49

Figure 13 Bland-Altman plots comparing cardiac index (CI) measurements using NiCaS and Nexfin devices



(a) Bland-Altman plot to compare NiCas derived CI and Nexfin derived CI measured at 19^0C during no music (NM), (b) Bland-Altman plot to compare NiCas derived CI and Nexfin derived CI measured at 19^0C during soft music (SM). (c) Bland and Altman plot to compare NiCas derived CI and Nexfin derived CI measured at 19^0C during loud music (LM). (d) Bland and Altman plot to compare NiCas derived CI and Nexfin derived CI measured at 28^0C during NM. (e) Bland and Altman plot to compare NiCas derived CI and Nexfin derived CI measured at 28^0C during SM. (f) Bland and Altman plot to compare NiCas derived CI and Nexfin derived CI measured at 28^0C during LM. Lower level of agreement (LLA) = Mean – 2SD and upper level of agreement (ULA) = mean + 2SD marked by dotted lines.

5.4 Discussion:

In this observational study, changes in environmental noise appear to have only a modest effect on haemodynamic variables obtained by non-invasive monitoring devices. There is statistical agreement in the cardiac index measured by NiCas and Nexfin devices. Our results provide new insights into the ability of novel non-invasive TM devices to accurately track haemodynamic modulations induced by environmental noise. The observed haemodynamic pertubations are congruous with previous studies which show that environmental factors causing stress or relaxation may affect haemodynamic parameters. (140-142) Physiological changes in response to soothing music are thought to closely mimic the same 10 second rhythm which matches the innate cardiovascular rhythm of the human body, called Mayer waves (140) hence their ability to reduce blood pressure and heart rate. Conversely, mental stress has been found to elicit increases in blood pressure, heart rate, cardiac output, and skeletal muscle blood flow while decreasing renal and splanchnic blood flow. Additionally forearm vascular resistance decreases. (143, 144) These responses are thought to be mediated through the autonomic nervous system and endocrine system, (143) presumably to restrict blood flow to visceral capillary beds and to redirect blood to systems of the body that respond to stressful stimuli, such as the heart, brain, and skeletal muscle.

There could be clinical applications for the effect seen on the blood pressure and heart rate of people listening to soothing music. (138) Harnessing the potential cardiovascular benefits that result from clinical applications that build on the 10 s rhythm of Mayer waves which is seen in music, to modulate blood pressure may confer favourable cardiovascular outcomes. (138)

5.5 Limitations

Our study should be viewed in the context of its limitations. This was a single-centre study with a relatively small sample size. We did not assess the impact of repeated exposure to similar noise levels over a sustained period of time although this was expected based on our study design. We do not however believe that the lack of repeated exposure will have significantly altered the results as the physiologic oscillations in baroreceptor and chemoreceptor reflex control systems is not based on repeated exposure. (145, 146)

5.6 Conclusion

Changes in environmental noise have may have modest effects on haemodynamics. The physiological perturbation of cardiac function in response to varying noise conditions can be detected non-invasively with telemonitoring devices. The data and observations described here underscore the need to consider environmental factors such as noise when non invasively assessing haemodynamics. Awareness of this phenomenon will result in more personalized, tailored remote monitoring of CHF patients. Finally, research into effects of novel therapies with haemodynamic effects as endpoints should also take into account the potential confounding effects of environmental factors.

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Competing Interests: None

Chapter 6

The impact of non-adherence on cardiovascular haemodynamics in heart failure

6.1 Abstract

Aims: To investigate the effects of non-adherence on haemodynamics and measures of congestion using non-invasive devices that might be adapted for remote patient monitoring in patients with heart failure and in control subjects.

Methods: Patients with a clinical diagnosis of heart failure, receiving loop diuretics and with objective evidence of cardiac dysfunction and a control group with hypertension but no heart failure were studied. Cardiovascular function was measured non invasively using: - Electrical bio-impedance (NICas), finger plethysmography (Nexfin, Bmeye, Netherlands) and ankle-brachial sphygmomanometers combined with finger-toe plethysmography (Enverdis), in the semi-recumbent, supine, supine with legs raised to 45^0, sitting and standing positions.

Results: Medication omission for 48 hours resulted in a decrease in bio-electrical impedance by –12.5±2.9 %. The systolic blood pressure increased by 2.5mmHg while the heart rate increased by 2.3 beats per minute. Bio-electrical impedance values were generally lower in the upright torso body positions.

Conclusions: Non invasive devices can reliably detect changes in heart rate, blood pressure and bioimpedance. Larger scale studies are required to confirm the findings of this pilot study.

6.2 Introduction

Cardiovascular medication nonadherence is associated with an increased risk of mortality and re-hospitalization. (98-100) Nonadherence to medication may be responsible for up to twenty percent of readmissions with acute decompensated heart failure, (101, 102) making it an important target for quality improvement. (103) The predictors of poor adherence can be classified into 5 broad domains: socioeconomic status, type of healthcare system, prescribed therapy, condition being treated, and individual patient-related factors. (103, 147, 148)

Medication adherence comprises of four components: (1) taking adherence (taking the prescribed medicines each day); (2) dosing adherence (taking the correct number of doses each day); (3) timing adherence (taking doses within ±2 hours of the time prescribed); and (4) avoiding drug holidays (eg, >48 hours between doses). (149) Whilst there are concerted efforts to improve guideline adherence by treating physicians, (1, 9, 10, 12) gaps still exist in our knowledge, of how best to improve nonadherence to evidence based cardiovascular therapies. To this end, telemonitoring has been proposed as a potential disease management strategy, which among other potential benefits may also improve medication adherence. (19, 150-153)

The utility of noninvasive devices to detect surrogates of lung congestion and cardiac function for telemonitoring purposes, is currently receiving attention. (54, 59, 62) Whether novel sensors for telemonitoring can accurately detect and track subtle haemodynamic changes associated with nonadherence has not yet been investigated. It was thus the aim of this study to quantify the acute deleterious haemodynamic effects and changes in lung congestion, due to nonadherence with heart failure therapy, using novel non-invasive sensor technology.

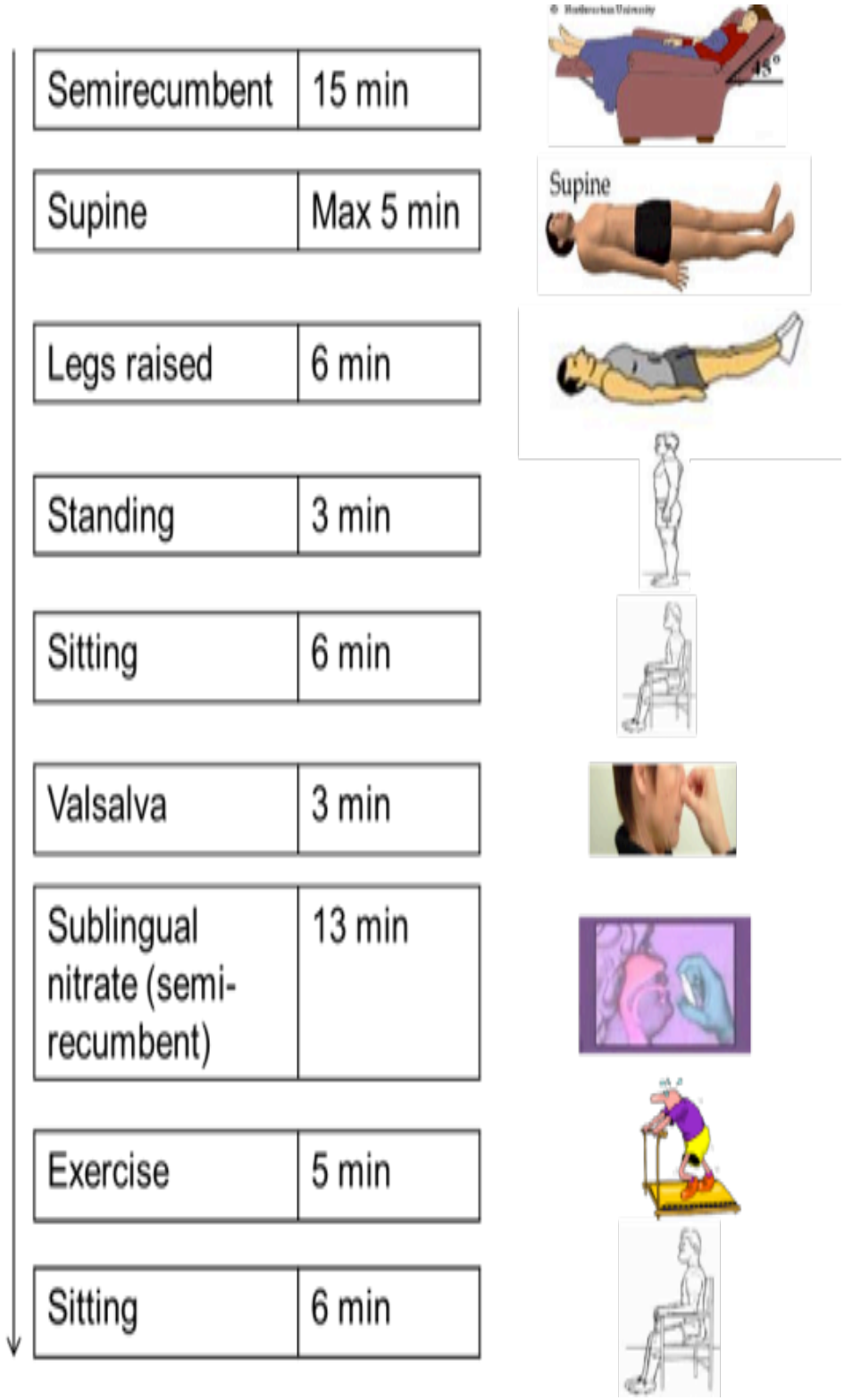
6.3 Methods:

Subjects and study design: The study was a single centre, controlled clinical study. Patients with heart failure were randomly assigned to attend for cardiovascular measurements on three separate days, which were at least 72 hours apart: baseline, day with heart failure medication taken, day with heart failure medication omitted for 48 hours. For patients with hypertension (HTN), measurements were made at baseline and on the days when medication was omitted. Patients were included into the CHF group if: (i) they had a history of CHF > 3months, (ii) they were treated with a loop diuretic, at least 40mg of furosemide or 1mg of bumetanide, (iii) they were treated with beta-blockers and ACE inhibitors (or angiotensin receptor blockers) for at least 6 weeks, (iv) either LVEF <35% or NT-proBNP >400 pg/mL was recorded within the previous year, and (v) they were willing and able to give informed consent. Exclusion Criteria for the CHF group were: (i) patients with breathlessness at rest or on mild exertion, (ii) patients with an admission for worsening heart failure in the previous 6 weeks, and (iii) patients who have required an increase in diuretic therapy in the previous 6 weeks. Patients in the HTN cohort were hypertensive subjects treated with any conventional agent but with no objective evidence of heart failure. Patients were recruited from the heart failure outpatient clinics. All patients gave signed informed consent. The study was performed at the academic cardiology department of the University of Hull, and the study protocol was approved by the local Ethics Committee and conducted according to the Declaration of Helsinki.

6.4 Experimental Protocol

On each study day, patients were asked to take a similar light breakfast with their usual medication but to avoid strong coffee or tea and not take more than 500mls of liquid. At baseline, each patient was asked to empty their bladder. Tanita scales were then used to measure baseline weight, total body water and distribution, bioelectrical impedance, fat and muscle mass distribution. Breathlessness and fatigue during activities of daily living were explored with the aid of the quality of life questionnaire. After a short clinical examination and blood sampling, baseline measurements were performed. Blood pressure and heart rate were recorded with a validated automatic blood pressure (BP) device (GE DINAMAP V100). Cardiovascular function and lung congestion was then measured during a range of physiological manoeuvres (Figure 14) aimed at inducing changes in haemodynamic parameters using: - whole body total electrical bio-impedance (NICas), finger plethysmography (Nexfin, Bmeye, Netherlands) and ankle-brachial sphygmomanometers combined with finger-toe plethysmography (Enverdis), transthoracic spectroscopic bio-impedance using a wearable vest (BIM, Philips) and bio-impedance scales (Tanita).

Figure 14 An overview of the study protocol



6.5 Impedance Cardiography

Global blood flow (Cardiac Index, CI - the global blood flow per minute, and Stroke Index, SI - the global blood flow per beat), respiration and a host of cardiodynamic parameters were assessed noninvasively using the NICaS^{TM} apparatus. This technology uses whole body bio-impedance and the Tsoglin-Frinerman formula for non-invasive determination of CI.(78, 111) Bioimpedance cardiography uses a low-amplitude, high-frequency alternating signal to calculate impedance of the flow of electricity through the chest. The instantaneous changes in electrical impedance and various other parameters are measured, from which stroke volume, cardiac output, cardiac index, and other haemodynamic parameters, including systemic vascular resistance, can be calculated.

6.6 Finger Plethysmography

After calibration, continuous measurements of BP, cardiac index (CI), systemic vascular resistance (SVR) were obtained at baseline in resting semi-recumbent position for 5 minutes using a finger-tip, volume-clamp (Nexfin, Bmeye, Netherlands). Intermittent continuous recordings were made at regular timed intervals during haemodynamic manoeuvres. Finally, continuous measurements were made during exercise, at constant load of 25 watts, on a bicycle ergometer (ERGOLINE GmbH) for 5 minutes. This level of exercise was chosen to simulate a 6-minute walk test commonly used to evaluate patients with heart failure.

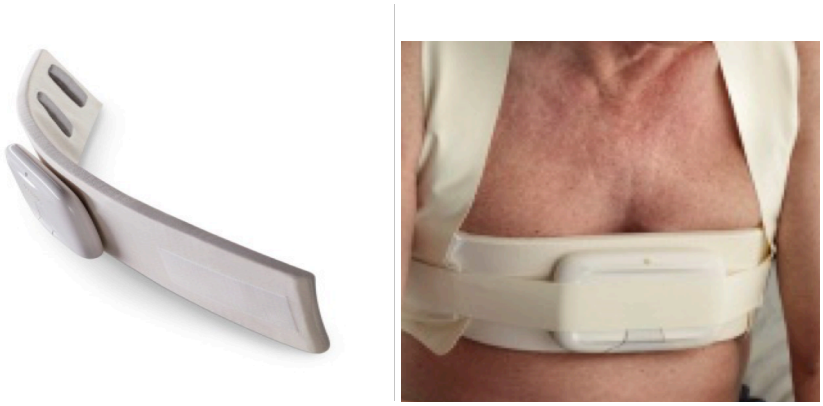
6.7 Pulse wave characteristics

Ankle-brachial sphygmomanometers combined with finger-toe plethysmography (Enverdis) were used to measure pulse-wave characteristics such as aortic pulse wave velocity (PWV) and augmentation index (AIx) in the semi-recumbent position before and after sublingual nitrates.

6.8 Bioimpedance Spectroscopic vest

Figure 15 below shows the transthoracic spectroscopic bio-impedance monitor and an illustration of a subject using a wearable vest (BIM, Philips). The device was worn at pre-specific intervals during postural maneuvers during study days, to detect changes in thoracic congestion during medication taken days vs medication omitted days.

Figure 15 Transthoracic spectroscopic bio-impedance monitor



6.9 Echocardiography

Detailed echocardiographic assessment of ventricular function, valve integrity, and regional wall motion abnormalities was performed by experienced sonographers using a Philips Vivid E9 machine and a 3.5MHz probe. In addition to the qualitative examination of the cardiac chambers and valves, further measurements made via the standard parasternal and apical views included the following: LV end-diastolic and end-systolic volumes (LVEDV and LVESV) using biplane modified Simpson's rule, from which stroke volume (SV) and ejection fraction (EF) were calculated. From the apical four chamber view, peak mitral inflow E and A velocity waves on pulse-wave Doppler, E/A ratio, E-wave deceleration time, isovolumetric relaxation time, and colour M-mode mitral inflow velocity of propagation were measured. The systolic s' and diastolic e' and a' peak velocities were obtained by tissue-Doppler imaging (TDI) at both the septal and lateral mitral origins on four-chamber apical view, and the e'/a' ratio and LV filling index E/e' ratio were calculated as per British Society of Echocardiography guidelines. (112) Peak systolic tricuspid insufficiency gradient was also measured from the apical four-chamber view.

6.10 Statistical analysis

The change in Nexfin^{TM} derived systolic BP was defined as a primary endpoint using the patient as their own control. An average of about 300 individual systolic BP measurements was taken. The power calculation was based upon results of earlier studies in our laboratory. Assuming a standard deviation of 3mmHg then 10 patients were assumed to be needed to have 90% power with $P \leq 0.05$ to show a 5mmHg difference in blood pressure. The data were checked for whether residuals are normally distributed using the one sample Kolmogorov-Smirnov test and most data

were considered normally distributed. Therefore, data were expressed as mean ± standard deviation (SD). Data were analysed by paired Student's t-test. Statistical significance was defined as p value ≤0.05. Statistical analysis has been performed using SPSS 19.0 (SPSS Inc., Chicago, IL, USA)

6.11 Physiological Maneuvers

The impact of physiological maneuvers on haemodynamic parameters in heart failure is a subject of much interest and research. (154) (155) (156) The maneuvers have different effects on the cardiovascular system, such as altering the systemic vascular resistance and inducing changes in the systemic venous return, by changing the speed and volume at which blood returns to the thorax from the peripheral vascular beds. (157) In an ideal state, the venous return is equivalent to the cardiac output because the vascular compartment of the body is a closed loop system. Blood entering the right ventricle equals to the cardiac output. The determinants of venous return are central venous pressure and venous vascular resistance. Dynamic physiological maneuvers affect venous vascular resistance via sympathetic reflex venoconstriction. (158)

Straight leg raising for example, increases venous return and therefore increase the ventricular filling, left ventricular end-diastolic volume and cardiac output. (158) In health, increasing venous return should increase cardiac output without a change in atrial pressure, although thoracic venous capacity may change with posture, or congestion. (155) Intuitively, the thoracic fluid volume (and its compartments – venous capacity, interstitium and lymphatic drainange) increases, leading to a decrease in the bio-electrical impedance. In severe heart failure, where there is

impaired myocardial contractility and vacular tone at rest, increasing venous return will result in an increase in atrial pressure due to volume increase with little or no change in cardiac output. (156) The thoracic fluid volume in this instance remains higher with the increased venous return (due to poor cardiac output) resulting in a markedly decreased bio-electrical impedance.

The healthy heart with intact myocardial contractility efficiently handles intracardiac blood volume changes through dynamic alterations in the myocardial pressure as described by Starling's law of the heart. (159) In contrast, in the diseased state, such as congestive cardiac failure, there is increased vascular tone at rest and impaired myocardial contractility in the presence of intracardiac blood volume changes with dynamic postural changes.

Figure 16 Illustration of the steady state closed loop cardiovascular system

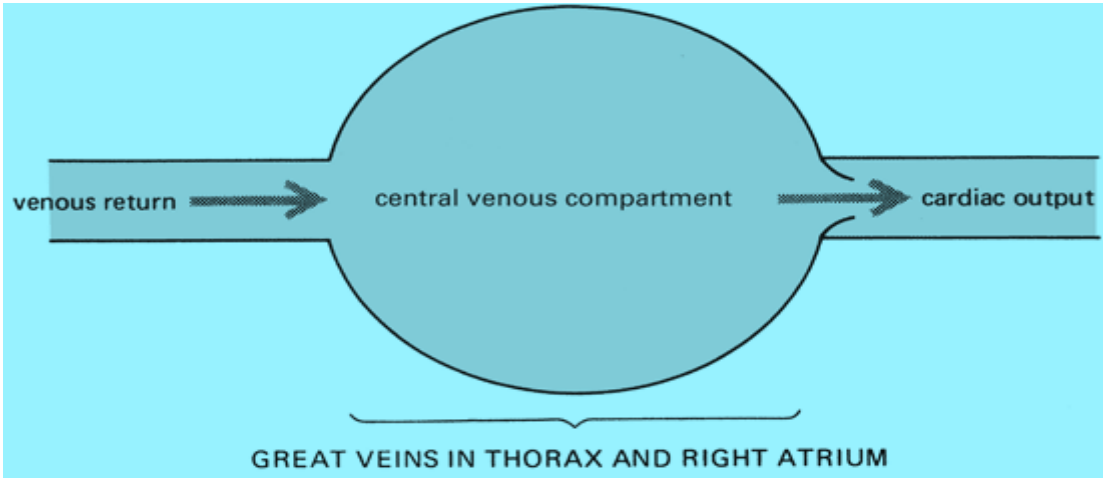


Figure 17 Schematic sequence of the physiological maneuvers used

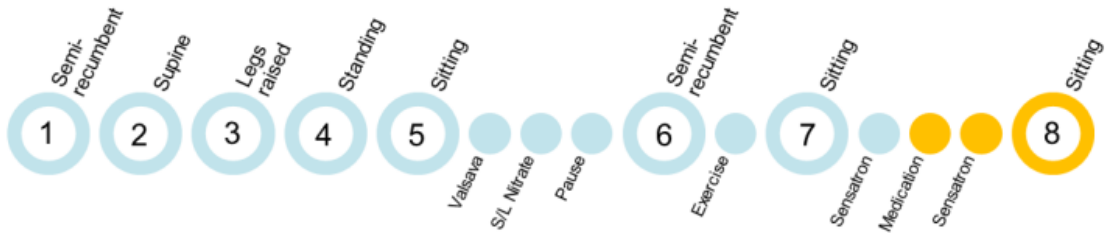
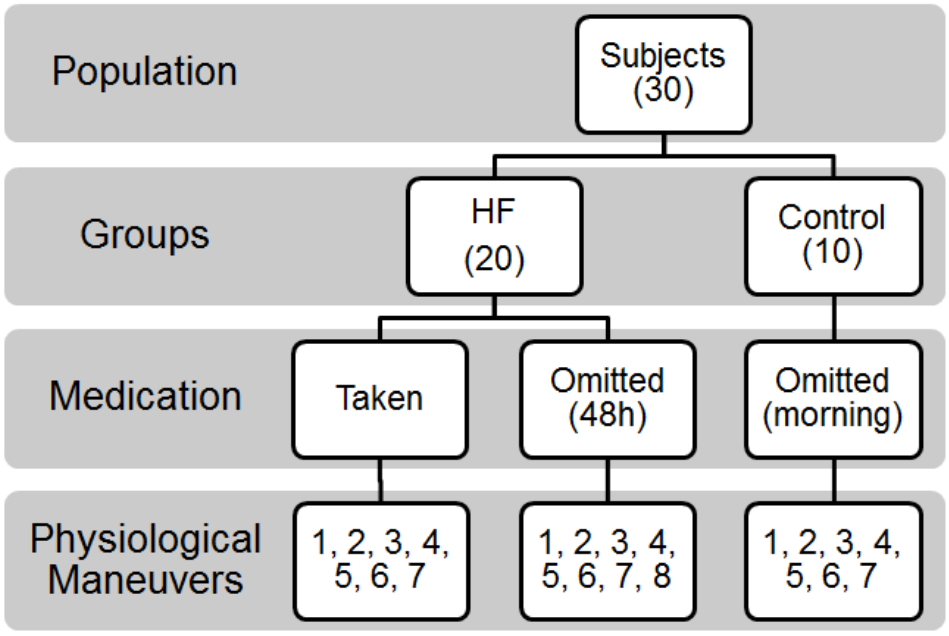


Figure 18 Study population and dynamic postural maneuvers



6.12 Results

Haemodynamic assessments were carried out in a total of 20 patients (16 men) with stable CHF (NYHA ≥ II), aged between 45 and 88 years (mean, 70 ± 11 yrs) and 10 patients (3 women) with hypertension (HTN) aged between 46 and 78 years (mean, 68 ± 8yrs). The mean left ventricular ejection fraction was 33 ± 12% in the CHF cohort and 56 ± 5% in the HTN group. The patients in the hypertension cohort were generally younger and predominantly male. The left ventricular ejection fraction was lower in the heart failure group. There were lower than expected number of patients with congestive heart failure on guideline directed angiotensin receptor inhibiting therapeutic agents.

Table 11 Baseline patient characteristics

	CHF (n = 20)	HTN (n = 10)
Demographics		
Age, years	70 ± 11	68 ± 8
Gender	16 men, 4 female	7 men, 3 female
Systolic BP, mmHg	124 ± 18	134 ± 4
Baseline Heart rate	68 ± 13	63 ± 14
LVEF, %	33 ± 12	56 ± 5
Co-morbidities profile (Combinations)	18 /20 (IHD, HTN, COPD, DM, AF)	8/10 (Hyperlipidaemia or AF)
Medications		
Loop diuretics	20	1
ACEIs / ARBs	14	7
Beta-blockers	20	4
Aldosterone Antagonist	5	2

6.12.1 Changes in Systolic Blood pressure with dynamic maneuvers

Dynamic changes in body posture resulted in significant changes in systolic blood pressure, diastolic blood pressure and heart rate.

Table 12 Changes in blood pressure and heart rate obtained during medication taken vs medication omitted in HF, compared with baseline

Variable	Median [Interquartile range]		p-value
	medtaken	medomit	
SBP Semirecumbent	1.00 [1.00 1.00]	1.12 [1.10 1.18]	0.00009
SBP Supine	0.97 [0.92 1.00]	1.04 [1.02 1.09]	0.00059
SBP LegRaised	0.97 [0.92 1.02]	1.07 [1.01 1.13]	0.00039
SBP Standing	0.98 [0.92 1.03]	1.10 [1.06 1.20]	0.00039
'SBP Sitting'	1.00 [0.98 1.06]	1.13 [1.08 1.19]	0.00025
SBP Semirec nitrate	0.94 [0.89 0.98]	1.03 [0.99 1.09]	0.00014
SBP Sitting6min	1.09 [0.98 1.14]	1.18 [1.15 1.26]	0.01124
DBP Semirecumbent	1.00 [1.00 1.00]	1.12 [1.05 1.19]	0.00102
DBP Supine	0.92 [0.89 0.97]	1.06 [0.96 1.13]	0.00170
DBP LegRaised	0.95 [0.91 0.98]	1.04 [0.99 1.09]	0.00112
DBP Standing	1.02 [0.96 1.08]	1.05 [1.03 1.21]	0.01113
DBP Sitting	1.01 [0.95 1.16]	1.16 [1.08 1.22]	0.01237
DBP Semirec nitrate	0.99 [0.94 1.04]	1.08 [1.01 1.13]	0.00331
DBP Sitting6min	1.00 [0.95 1.09]	1.13 [1.00 1.22]	0.00740
HR Semirecumbent	1.00 [1.00 1.00]	1.07 [1.02 1.14]	0.00285
HR Supine	0.96 [0.95 1.01]	1.03 [0.96 1.17]	0.01762
HR LegRaised	0.97 [0.93 1.01]	1.08 [0.97 1.14]	0.00151
HR Standing	1.08 [1.04 1.14]	1.18 [1.12 1.26]	0.00319

Table 13 shows a change (Δ) of haemodynamic parameters obtained during "medication taken" vs "medication omitted" in subjects with heart failure, in the semirecumbent position, detected using finger-tip, volume-clamp technology (Nexfin Bmeye, Netherlands). Patients had higher heart rate, systolic and diastolic blood pressure in the medication omitted state.

Table 13 Change in haemodynamic parameters during medication taken vs medication omitted in HF patients in the semirecumbent position derived via finger plethysmography technology

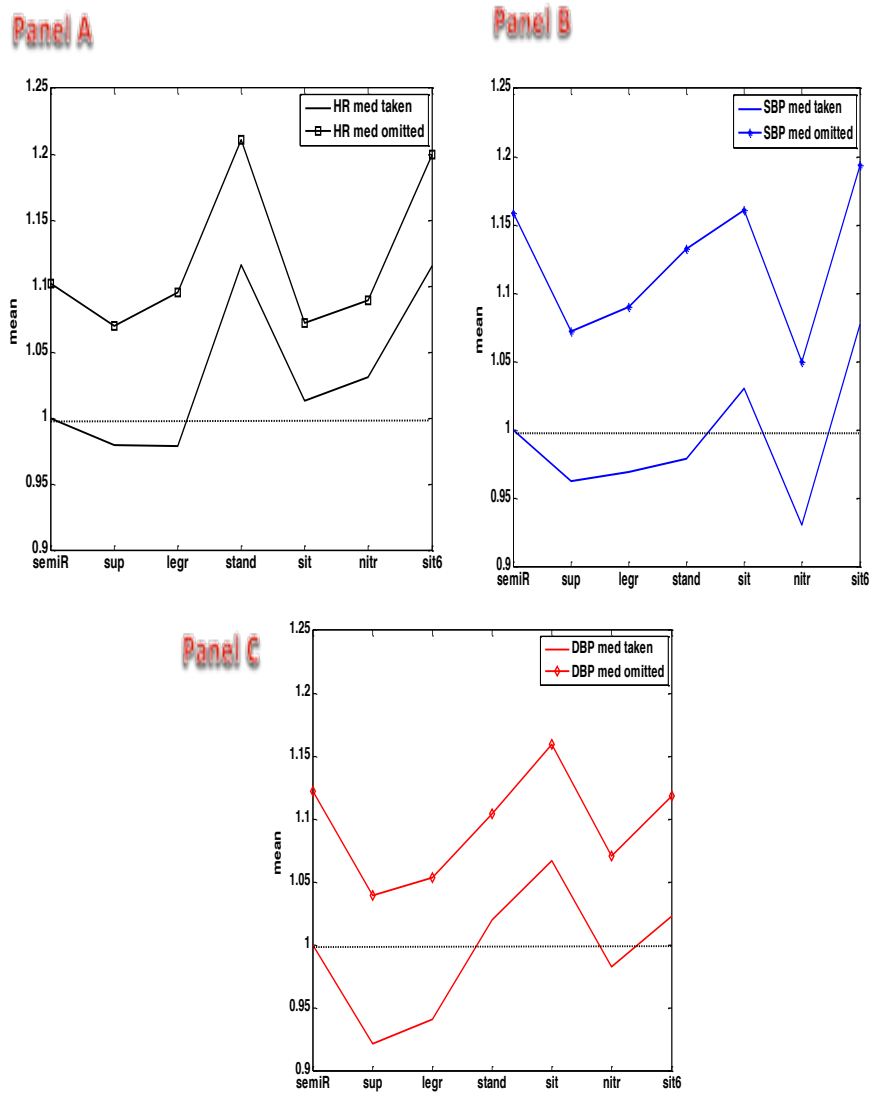
Variable	**Δ** (Medication omitted minus taken)
HR (bpm)	2.3
SBP (mmHg)	2.5
DBP (mmHg)	1.4
CI (L/min/m2)	0.13
SVR (dn*n*cm^{-5})	-218

6.12.2 Detection of systolic blood pressure change during Nitrolingual spray use, using Nexfin device

During the medication omitted study period, a systolic blood pressure change of -9.62 ± 5.8 mmHg was detected, compared to a higher systolic blood pressure change of -23.34 ± 7.9 mmHg during the medication taken study period. p-value 0.12

In Hypertension patients, medication was omitted on the morning of the study day resulting in an observed increase in SBP 4mmHg (interquartile range -7 19).

Figure 19 Schematic representation of the mean change in heart rate (HR), systolic blood pressure (SBP) and diastolic blood pressure (DBP) taken during dynamic maneuvers under medication taken vs medication omitted conditions



The mean change in the blood pressure was very slightly higher when patients had omitted their medication. Similarly, the mean change in heart rate was higher when patients had omitted their medication.

6.12.3 Congestion variables

The average change in the total body water detected using Tanita Bio-electrical scales and Non-Invasive Cardiac System (NiCaS device) was higher during medication omitted study days. Conversely, the basal impedance was significantly lower during the medication omitted days, reflecting the higher congestion status of the patients.

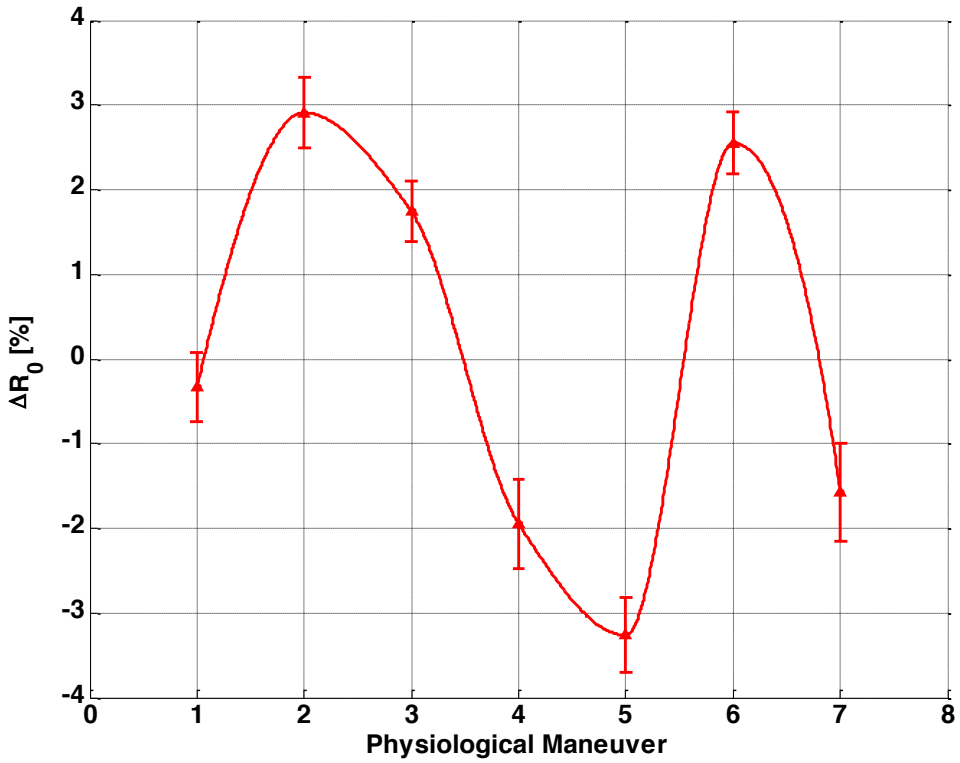
Table 14 Changes in body water and bio-impedance between medication omitted and medication taken state

	Δ (Medication omitted minus taken)
Bio-impedance Scales (Tanita)	
TBW, %	0.57 ±1.0
Basal impedance, R (ohms)	-7.7 ±14.7
NiCas	
TBW, %	0.06 ±1.8
Basal Impedance, R (ohms)	-11.7% ±18

6.12.4 Detection of bio-impedance change using novel Bioimpedance Vest (BIM)

Bio-electrical impedance was observed to vary significantly with physiological maneuvers, during medication omitted study days and medication taken days, as well as higher impedance values in the hypertension group, suggesting less congestion.

Figure 20 Impedance changes across physiological maneuvers



The reference for each value is the mean impedance across maneuvers of the corresponding session. The supine and semi recumbent positions have higher impedance values with a slight reduction in the bio-impedance with passive straight leg raising maneuver. The sitting position and sitting post sublingual nitrate administration study periods were observed to have lower impedance values.

Figure 21 displays Impedance changes across physiological maneuvers for patients with hypertension, heart failure on medication (HFv1) and heart failure after medication omission for 48 hours (HFv2). Patient with heart failure who had omitted their medication had higher baseline impedance but more pronounced response to sublingual nitrates.

Figure 21 Impedance changes across physiological maneuvers for patients with HTN, HF before and after medication omitted

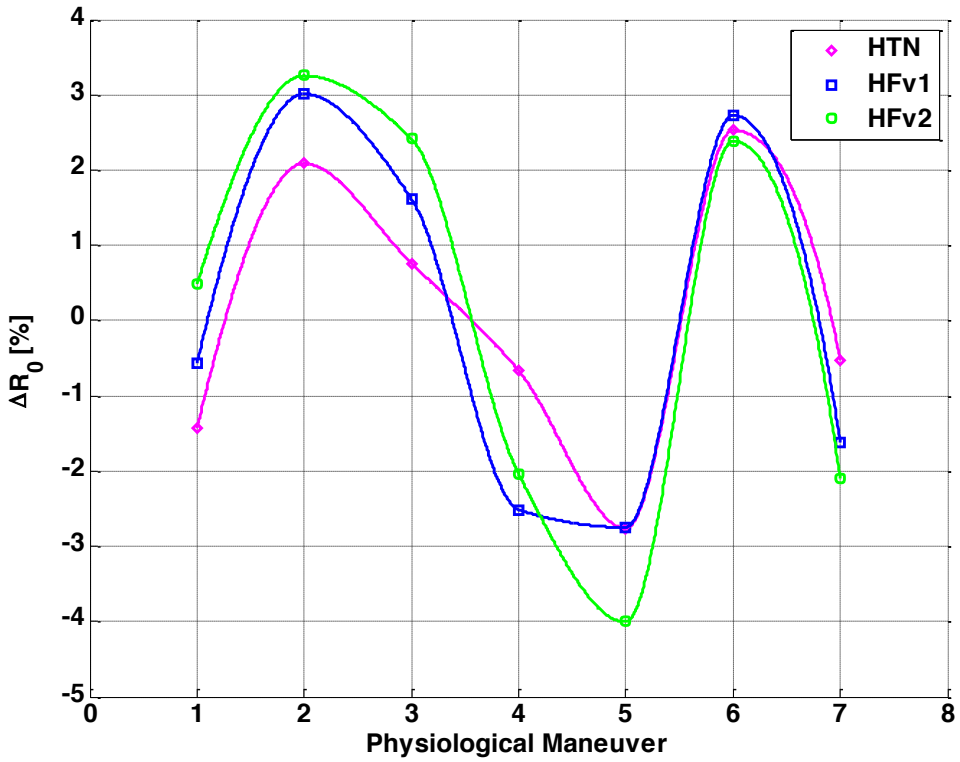
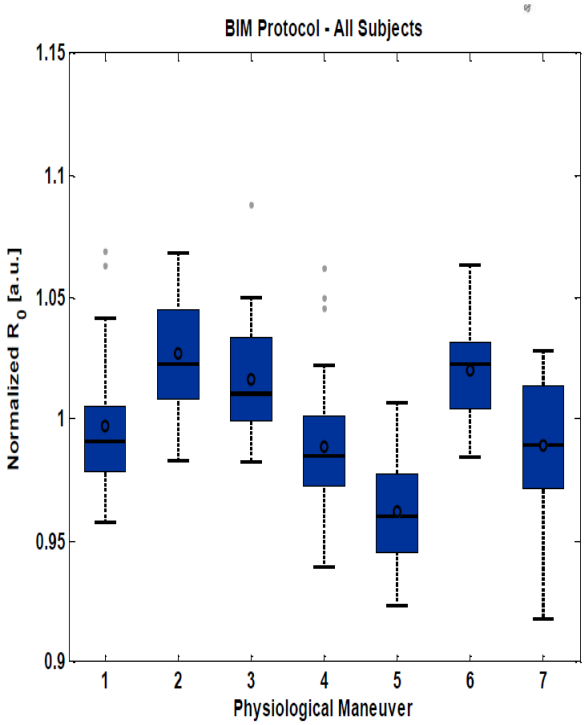


Figure 22 Box and Whisker plots showing comparison of changes in bio-impedance with dynamic maneuvers



Dynamic changes in bioimpedance with changes in body position due to lung congestion. The fluctuations in bioimpedance were highest during the lying position and after application of sublingual nitrates.

Key:

1= Semi recumbent (BIM, Nexfin, NiCas)

2= Supine (BIM, Nexfin, NiCas)

3= Supine with legs raised to 45^0(BIM, Nexfin, NiCas)

4= Sitting (BIM, Nexfin, NiCas)

5= Standing (BIM, Nexfin)

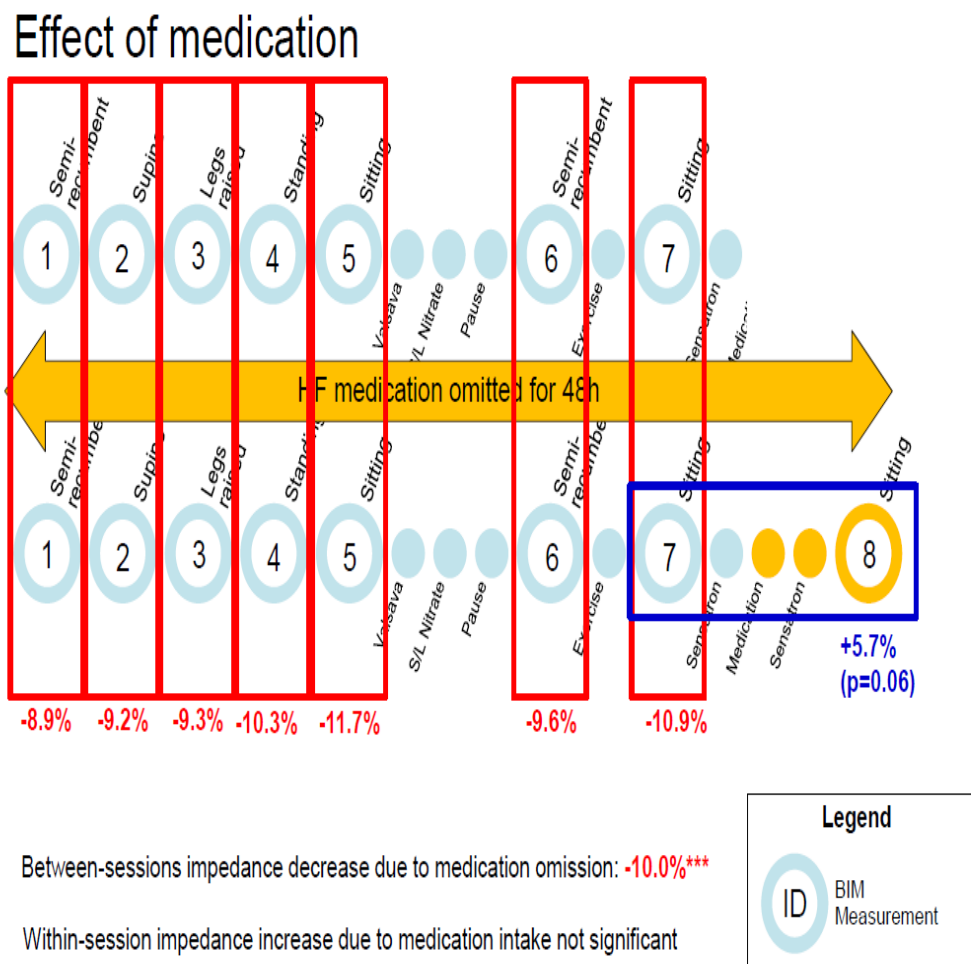
6= Sitting performing valsalva manoeuver (Nexfin)

7= Semirecumbent after sublingual nitrate (Nexfin, BIM, NiCas, Enverdis)

8 = Exercise (Nexfin)

9 = Sitting after exercise (Nexfin, BIM)

Figure 23 Changes in bio-impedance with omission of medications in patients with heart failure



There were low bio-impedance values detected when patients' were studied after omission of medication for 48hours. The response to physiological maneuvers was also more pronounced in this study phase. There were no immediate significant changes in the bio-impedance at the end of the study, 1 hour after medication ingestion, perhaps reflecting the short monitoring period post medication ingestion.

6.13 Discussion

We observed small statistically significant changes in standard heart rate and blood pressure measurement (using a validated automatic blood pressure (BP) device (GE DINAMAP V100) when patients with heart failure omit their medication for 48 hours. Beat-to-beat blood pressure and heart rate measurements using finger-tip, volume clamp technology (Nexfin) appears more substantial changes. The results of multi-modality assessment of congestion status using bio-impedance scales (Tanita), Impedance cardiography (NiCas) and Bio-impedance vests (BIM) appear to be consistent, showing a modest increase in body water, and a decrease in bio-impedance. The magnitude of the changes is surprisingly modest, however if patients omit medication for a longer period of time, one might speculate larger effects. On the other hand, up to10% change in bio-impedance was observed, reflecting significantly increased congestion in patients suffering from heart failure when their medication is omitted for as short a period of time as 2 days.

The results of the study demonstrate that nonadherence to heart failure has potentially deleterious cardiovascular effects, which can be easily detected non-invasively using novel devices that may be deployed for telemonitoring. The value of heart rate control in heart failure is well recognised. Higher resting heart rate is associated with worse clinical outcomes, especially hospitalisation for heart failure and cardiovascular death. (160, 161) Additionally, hypertensive heart failure patients have altered loading conditions of the left ventricle, which precedes lung congestion and subsequent heart failure decompensations.(63, 64) Thus, it was somewhat intriguing that we found hardly any change in heart rate and blood pressure when patients did not take their medication for 2 days. Clearly, this might be due to a variety of reasons such as half-life of medication, renal and liver function etc.

Another important observation of the present study is that there are significant changes in non-invasive haemodynamics and bioimpedance that appear to be more exaggerated in heart failure patients during physiological manoeuvres compared to the control group with hypertension. The observed difference may be related to the poor cardiac output and elevated left ventricular filling pressures, which are hallmarks of systolic heart failure.

6.14 Study limitations

We did not measure the peak concentration of the medication used. Our study measured non-invasive measures of haemodynamics after a patient had ingested oral medication under direct observation. The onset of actions of some medications may be slow and only reaching peak some time after completion of the study. Additionally, we recruited hypertension subjects as controls. It is well known that hypertensive patients may have supra normal left ventricular filling pressures and a degree of diastolic heart failure.

6.15 Clinical implications:

Nonadherence with cardiac failure medication leads to intrathoracic fluid accumulation. In our study, a significantly lower intrathoracic bioimpedance was detected when patients' medications were omitted for 48 hours, due to fluid accumulation. The non-invasive devices used in the study accurately tracked the expected physiological changes in heart rate, blood pressure and bioimpedance, during the study.

6.16 Conclusions

Nonadherence to cardiovascular therapy has an acute deleterious impact on intrathoracic fluid accumulation in patients with heart failure.

6.17 Acknowledgements

The analysis and results presented in this chapter are a joint effort between our research unit at the Department of Academic Cardiology, University of Hull and researchers at Philips, Eindhoven, The Netherlands. The results of Bio-impedance Monitor (BIM) were presented at the Computing in Cardiology conference in 2013 (Conference extract: Sensitivity of a wearable bioimpedance monitor to changes in the thoracic fluid content of heart failure patients, Dovancescu, S. ; Torabi, A. ; Mabote, T. ; Caffarel, J. ; Kelkboom, E. ; Aarts, R. ; Korsten, E. ; Cleland, J.Publication Year: 2013, Page(s):927 – 930). The preliminary results of the Vitals signs was also presented at The International Conference on Health Informatics. Conference extract: (I. G. Chouvarda, T. Mabote, A. Torabi, J. Caffarel, M. van Gils, J. Cleland, N. Maglaveras. Medication Incompliance and Vital Signs in Heart Failure Patients.Proceedings pp 51-54. Volume 42 of the series IFMBE)

Chapter 7

Conclusions and future considerations

7.1 Thesis Hypothesis and rationale

Remote monitoring of heart failure patients is in rapid evolution, as a disease management strategy, with the aim to improve patient involvement in their disease, improve patient education as well as reduce heart failure hospitalizations and mortality. Various modalities such as invasive pulmonary artery and left atrial pressure monitoring are being tested in clinical trials, for future use in telemonitoring. Whether non-invasive sensors can be used to detect subtle changes in haemodynamic deterioration in heart failure patients and guide therapeutic decisions remains unclear. It was thus the aim of my research to establish whether novel non-invasive devices, which are currently not used for telemonitoring could be employed for such use.

7.2 Summary of thesis findings:

A thorough review of relevant literature found that supporting evidence for the role of telemonitoring in clinical practice exists in various forms. Furthermore, extensive literature review was undertaken, to corroborate the evidence for the hypothesis that non-invasive devices can be used to measure non-invasive surrogates of haemodynamics and systemic fluid congestion.

To achieve the goal set out, three clinical studies and a meta-analysis were conducted. These studies were presented in chapters 4, 5 and 6. The first study was a prospective observational study described in chapter 4, investigating the effect of environmental temperature on haemodynamics in patients with heart failure, with particular emphasis on non-invasively detecting changes in haemodynamics and markers of congestion. From this study, it is apparent that environmental temperature has striking influences on haemodynamics.

The second study presented in chapter 5, was a prospective observational study investigating whether there could be subtle changes in haemodynamics induced by modulations in the sympathetic tone in patients with heart failure, which can be altered by music. The use of telemonitoring devices should in principle take into account the role that patients' environment and activities of daily living, which may alter a patient's blood pressure and heart rate. A trend towards a lower heart rate and blood pressure was observed during soothing music. Similarly, changes in haemodynamics were detected non-invasively, with a good degree of consistency.
The third study described in chapter 6, was a prospective controlled clinical study investigating the role of nonadherence to heart failure therapy in patients with heart failure. Substantial differences in bioimpedance, systolic and diastolic blood pressure as well as heart rate were detected non-invasively from subjects under different clinically induced congestion status. It is thought that this study may serve as a benchmark to guide future clinical trials in the field of telemonitoring of heart failure, which focus on noninvasive detection of haemodynamics. The study provides key insights into the deleterious effects that patients who are nonadherent to therapy may be facing. Measurements of bio-electrical impedance obtained via non-invasive devices remain challenging to interpret given the large variability in the values obtained at rest and the lack of reference values.
The research presented in the thesis answers important clinical questions and opens the door for future research. Harnessing smart technologies for remote monitoring in heart failure seems logical for several reasons. The majority of patients with heart failure do not have typical indications for implantation of intra-cardiac devices, which precludes them from having invasive monitoring of intracardiac pressures. Secondly, there is some evidence that intracardiac devices may contribute to adverse events such as device infections and hospitalization due

to false alerts. Non-invasive monitoring aims to fill the gap in remote patient monitoring, where an easy to use device may provide substantial information about a patient's status, which can then be targeted with therapeutic interventions.

7.3 Future research

The clinical findings from the three studies have highlighted several areas where there is need for further research. The clinical studies presented in the thesis were single centre small studies. The work needs to be validated in large multicentre clinical trials for the purpose of scientific validity and robustness. Second, the role of soothing music to favourably modulate the sympathetic tone in heart failure, could improve the quality of life of patients with heart failure. Nonadherence is a particularly significant problem in various fields of clinical medicine. There is scope for developing programs to specifically target reducing nonadherence. To this, there is further research underway in our unit, to specifically assess the haemodynamic changes which result from optimising heart failure therapy with nitrates and hydralazine, with novel non-invasive sensors. Finally, there may be scope for future randomized controlled trials following on from this research, to test the hypothesis that heart failure therapy guided by non-invasive surrogates of haemodynamics is superior to usual care.

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Appendices

GP Letter CHD_Hypertension Document

Dear Dr

I am writing to inform you that your patient – INSERT PATIENT NAME AND ADDRESS – has volunteered to participate in a clinical trial titled

A Study of Non-Invasive Sensors to Detect Changes in Congestion and Haemodynamics in Patients with Coronary Heart Disease/Hypertension.

We have recruited your patient because they have coronary heart disease/hypertension and will act as a comparison group. Your patient will attend the Daisy Building at Castle Hill Hospital for a number of study days. We shall evaluate changes in haemodynamic and cardiac function with a variety of non-invasive monitoring technologies, with long term application to telemonitoring programmes for detecting worsening chronic heart failure.

We do not anticipate that participation in the study will reveal any significant clinical findings that would not have already become apparent in the course of their normal care. Neither do we expect any adverse events in the course of the study. However, if there are any clinically significant findings or developments during the study, then we will inform you immediately.

Should you have any questions or concerns, please contact my colleague, Dr Thato Mabote in the Academic Cardiology department at Castle Hill Hospital; Telephone Number: (01482) 461813, or email: thato.mabote@hey.nhs.uk

Yours sincerely,

Professor John Cleland

GP Letter CHF

Dear Dr

I am writing to inform you that your patient – INSERT PATIENT NAME AND ADDRESS – has volunteered to participate in a clinical trial titled

HEARTCYCLE: *A Study of Non-Invasive Sensors to Detect Changes in Congestion and Haemodynamics in Patients with Chronic Stable Heart Failure*

We have recruited your patient because they have Chronic Stable Heart Failure. Your patient will attend the Daisy Building at Castle Hill Hospital on two study days. Prior to one of the study days, we will ask patients to stop their heart failure medication for 48 hours. We will give them a telephone call on the second day to make sure they are feeling alright. They will be advised to restart medication if there has been any deterioration in their condition. On each study day, we will evaluate changes in haemodynamic and cardiac function with a variety of non-invasive monitoring devices, with long term application to telemonitoring programmes for detecting worsening chronic heart failure.

We do not anticipate that participation in the study will reveal any significant clinical findings that would not have already become apparent in the course of their normal care. Neither do we expect any adverse events in the course of the study. However, if there are any clinically significant findings or developments during the study, then we will inform you immediately.

Should you have any questions or concerns, please contact my colleague, Dr Thato Mabote in the Academic Cardiology department at Castle Hill Hospital; Telephone Number: (01482) 461813, or email: thato.mabote@hey.nhs.uk

Yours sincerely,

Professor John Cleland

Patient Consent form

CONSENT FORM

Title of Project: HEARTCYCLE: **Assessing the Acute Haemodynamic Effects of Hydralazine and Nitrates, singly and in combination, in Patients with Chronic Heart Failure using Novel Non-invasive Sensor Technologies.**

Principal Investigator: Dr John Cleland

		Please initial box
1.	I confirm that I have read and understand the patient information sheet dated 11th November 2013 (version 2.0) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	
2.	I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected.	
3.	I understand that relevant sections of my medical notes and data collected during the study may be looked at by individuals from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.	
4.	I understand that blood samples and information will be stored for up to 10 years after the study has finished, and may be used in future ethically approved studies carried out by other researchers or companies. Data and samples used in future studies will be confidential and personal details will not be made available.	
5.	I agree to my GP being informed of my participation in the study.	
6.	Should I choose to withdraw consent, I agree that information obtained from me in this study up to that point may still be used.	
7.	I agree to take part in the above study	

Name of Patient	Date	Signature
Name of person taking consent	Date	Signature

Patient Information Letter

<<GP headed paper>>

<<insert address of patient>>

<<insert date>>

Dear <<insert name of patient>>

I am writing on the behalf of the Department of Cardiology at the University of Hull to invite you to consider taking part in a clinical study to investigate how health monitoring equipment already in use within hospital clinics can also be used in "long-distance" tele-monitoring. This technology makes it possible for us to discover changes in a patient's symptoms (such blood pressure, heart rate, weight) on a daily basis without the patient having to leave their homes. About 100 patients with heart disease are already being monitored remotely via the internet directly from their homes by a nurse-led team at Hull and East Yorkshire Hospitals NHS Trust.

In order to do this, patients will be invited to visit the Daisy Building at Castle Hill Hospital and undergo some tests using this equipment. The study team will look at how the equipment responds to patients with symptoms of heart disease or hypertension in situations similar to real life – such as sitting, lying, standing or light exercising and withholding medication for a short period, eating spicy or salty food etc.

If you would like to find out more about this study, you can speak to Dr. Thato Mabote at the Department of Cardiology, Castle Hill Hospital (Telephone: 01482 461813).

Yours sincerely
<<insert name of GP>>

Case report form - Heart cycle

Heart Cycle: Novel Non-Invasive Sensors

Patient Initials: ……. **Visit Date**:…/…./2013 **Pt Code:** HC-…….. Cy….

ALL INCLUSION CRITERIA MUST BE ANSWERED "YES" FOR PATIENT TO BE SUITABLE FOR TRIAL ENTRY:

(Tick boxes to confirm)

[Legally able to provide written informed consent] Yes ☐ No ☐

[Clinical diagnosis of Heart Failure] Yes ☐ No ☐

Objective evidence of cardiac dysfunction

- [NT-proBNP >400ng/L and at least one of the following] Yes ☐ No ☐
- Left ventricular ejection fraction (≤45%) Yes ☐ No ☐
- Left atrial dimension >40mm Yes ☐ No ☐

[Treated with at least 40mg/day of furosemide or 1mg/day of bumetanide] Yes ☐ No ☐

[Receiving other guideline-indicated therapy for heart failure] Yes ☐ No ☐

[>75% of patients should be in sinus rhythm] Yes ☐ No ☐

For control Group:

[Legally able to provide written informed consent] Yes ☐ No ☐

[Clinical diagnosis of stable coronary disease or controlled hypertension] Yes ☐ No ☐

ALL EXCLUSION CRITERIA MUST BE ANSWERED "NO" FOR PATIENT TO BE SUITABLE FOR TRIAL ENTRY:

(Tick boxes to confirm NONE apply)

[Patients with implanted pacemakers or defibrillators] Yes ☐ No ☐

[Severe aortic or mitral valve disease] Yes ☐ No ☐

[Breathlessness at rest or on minor exertion] Yes ☐ No ☐

[Chest pain at rest or on mild or moderate exertion] Yes ☐ No ☐

[Patients deemed too unstable to miss 48 hours of heart failure treatment] Yes ☐ No ☐

For control Group:

[Patients with implanted pacemakers or defibrillators] Yes ☐ No ☐

[Severe aortic or mitral valve disease] Yes ☐ No ☐

[Systolic Blood Pressure >160mmHg] Yes ☐ No ☐

Patient Initials: ……. **Visit Date: …/…./2013** **Patient Code:HC…….cy….**

[Receiving either furosemide or bumetanide] Yes ☐ No ☐

[Atrial Fibrillation] Yes ☐ No ☐

[Breathlessness at rest or on minor exertion] Yes ☐ No ☐

[Chest pain at rest or on mild or moderate exertion] Yes ☐ No ☐

[Patients deemed too unstable to miss 48 hours of heart failure treatment] Yes ☐ No ☐

HAVE ALL INCLUSION AND EXCLUSION CRITERIA SATISFIED? Yes ☐ No ☐

HAS THE PATIENT READ AND UNDERSTOOD THE PIS? Yes ☐ No ☐

HAS THE PATIENT SIGNED AND DATED THE CONSENT FORM? Yes ☐ No ☐

Decision: **Inclusion / Exclusion**

If excluded, specify reason **……**

Study doctor:

Name	**Signature**	**Date**

Reminder

Has one copy of the signed informed consent form been filed in the patients casenotes together with a copy of the GP letter? Yes ☐ No ☐

Patient Initials: ……. **Visit Date:…/…./2013** **Patient Code:HC…..…cy...**

VISIT [1]

1. Medical history

Date of diagnosis of … (enter disease under investigation)

Major health problems in the past, current acute and chronic diseases

Known drug insensitivity and allergy

Current medication

Medication	Indication	Dose

Patient Initials: ……. **Visit Date:…/…./2013** **Patient Code:HC…….cy…**

VISIT [1]

2. Clinical Examination

(Section of clinical examination relevant to the protocol)

Cardio-vascular:

Pulmonary:

……

physical examination (JVP, Oedema, creps)→expected to be normal

……

Any changes to medication?

……

Similar diet on the three days prior to each visit/ should follow general dietary recommendations as advised for HF. Yes ☐ No ☐

1st & every alternative pt will be asked: take their medication as usual prior to visit but **Omitt HF Med (diuretic, ACEi, B-B, AldosteroneA) for 48h prior to the second visit**

Pt will be phoned the day before study → omission of therapy is not causing problems. Yes ☐ No ☐

The second & every other pt will have the order to study condition reversed.

If Pt feel any **worsening condition** or gain **weight >2kg** (4.5 pounds)→contact research staff &/or to take their Med as usual.

Studies will be conducted approximately **one week** apart & study should generally be completed within **one month of consent**

Control group (HTN/CAD): omit their Med **only on the morning of study**.

Congestion:	
NYHA	1, 2, 3, 4
Breathlessness walking on flat	no problem, mild, moderate, marked
Angina	Y/N
JVP Raised	none, mild, moderate, marked
peripheral oedema	none, mild, moderate, marked
Fine lung crepitations	none, some, obvious
Low cardiac output:	
Fatigue	none, mild, moderate, marked
Dizzy when standing up quickly	none, mild, moderate, marked
Cool peripheries despite (at room temperature)	none, mild, moderate, marked
Peripheral cyanosis	None, mild. moderate, marked

Patient symptom assessments questionnaire and congestion with low cardiac output will be repeated every visit.

Patient Initials: ……**Date of Visit:** …/…/2013 **Pt Code:** HC…… ..…-Cy1 (B=with med, C=withhold med, P1=pt1)

Patient symptom assessment (1)

Symptoms last 24 hours	
General symptom questionnaire	
Did you experience breathlessness last night?	a) none b) once c) twice or more
Did you feel shortness of breath at rest today?	a) none b) once c) twice or more
How is your energy level today?	1=very bad, 2, 3, 4, 5=very good
Did you tolerate exercise better than yesterday?	Y/N

Patient symptom assessment (2) (Breathlessness):

-If you don't currently do an activity because it makes you too breathless or don't do it for another reason (for instance you have arthritis) but think it would make you breathless if you tried then please score accordingly.

-For instance, if the weather is very bad and you have not gone out of your house you may not have been troubled by breathlessness but you may think that you would get breathlessness walking outside on the flat at a normal pace for someone of your age, in which case you should answer 6 rather than 8.

Over the past 24 hours, I got out of breath:
□ 1 even just sitting or lying down
□ 2 getting dressed or showering
□ 3 walking slowly on the flat
□ 4 doing light housework or shopping
□ 5 walking at a normal pace on the flat
□ **6** climbing a gentle slope or flight of stairs
□ 7 climbing a moderate slope or 2 flights of stairs at a normal pace
□ 8 breathlessness is not a problem

Patient symptom assessment (3) (Oedema

- Over the past 24 hours, did you have swollen ankles or legs (oedema)?	Y/N
If Yes, then: Please rate the swelling over the past 24 hours.	
1 Legs above the knee	Y/N
2 Legs up to the knee before noon	Y/N
3 Legs up to the knee in the evening	Y/N
4 Marked ankle swelling before noon	Y/N
5 Marked ankle swelling in evening	Y/N
6 Some ankle swelling before noon	Y/N
7 Some ankle swelling in the evening	Y/N

Baseline (familiarisation)	Empty bladder , **Ht**……, **chest circumference**…..….. **Wt**……..	
	TANITA	
	Questionnaire (describe symptoms last 24h).	
	ECG	
	Physical examination, explain cycle including Valsalva M	
	Standard-sitting: BP …. **HR**…. **RR**….	
	BIM: Vest size…... Belt size…..	
	BIM (seated): 5min	
	Nexfin: 5min + **SENSATRON** (semi-recumbent): 5min	
lying Down	**BP** …. **HR**….	
standing	**BP** …. **HR**….	

VISIT [2]

HAS THE PATIENT CONFIRMED WILLINGNESS TO CONTINUE IN THE STUDY AND HAS THIS BEEN DOCUMENTED IN THE PATIENTS CASENOTES? Yes ☐ No☐

1. Events since previous visit

Intercurrent disease since previous visit

Additional treatment and changes to medication since previous visit

Adverse events since previous visit (intercurrent diseases are always AEs). AE form has to be completed for each AE. The form is provided by R&D.

Serious adverse events since previous visit – SAEs that are related to the study treatment/procedures and unexpected will require reporting on the NRES SAE report form. The form is available at:
http://www.nres.nhs.uk/applications/after-ethical-review/safetyreports/safety-reports-for-all-other-research

2. Clinical Examination

(Section of clinical examination relevant to the protocol)

Cardio-vascular:

Pulmonary:

……

congestion:	
NYHA	1, 2, 3, 4
Breathlessness walking on flat	no problem, mild, moderate, marked
Angina	Y/N
JVP Raised	none, mild, moderate, marked
peripheral oedema	none, mild, moderate, marked
Fine lung crepitations	none, some, obvious
Low cardiac output:	
Fatigue	none, mild, moderate, marked
Dizzy when standing up quickly	none, mild, moderate, marked
Cool peripheries despite (at room temperature)	none, mild, moderate, marked
Peripheral cyanosis	None, mild. moderate, marked

Patient Initials: ……**Date of Visit:** …/…/2013 **Pt Code:**… HCM- A… P …-Cy1
(A=Baseline, B=with med, C=withhold med, A1=day1, P1=pt1)

Patient symptom assessment (1)

Symptoms last 24 hours	
General symptom questionnaire	
Did you experience breathlessness last night?	a) none b) once c) twice or more
Did you feel shortness of breath at rest today?	a) none b) once c) twice or more
How is your energy level today?	1=very bad, 2, 3, 4, 5=very good
Did you tolerate exercise better than yesterday?	Y/N

Patient symptom assessment (2) (Breathlessness):

-If you don't currently do an activity because it makes you too breathless or don't do it for another reason (for instance you have arthritis) but think it would make you breathless if you tried then please score accordingly.

-For instance, if the weather is very bad and you have not gone out of your house you may not have been troubled by breathlessness but you may think that you would get breathlessness walking outside on the flat at a normal pace for someone of your age, in which case you should answer 6 rather than 8.

Over the past 24 hours, I got out of breath:
□ 1 even just sitting or lying down
□ 2 getting dressed or showering
□ 3 walking slowly on the flat
□ 4 doing light housework or shopping
□ 5 walking at a normal pace on the flat
□ **6** climbing a gentle slope or flight of stairs
□ 7 climbing a moderate slope or 2 flights of stairs at a normal pace
□ 8 breathlessness is not a problem

Patient symptom assessment (3) (Oedema

- Over the past 24 hours, did you have swollen ankles or legs (oedema)?	Y/N
If Yes, then: Please rate the swelling over the past 24 hours.	
1 Legs above the knee	Y/N
2 Legs up to the knee before noon	Y/N
3 Legs up to the knee in the evening	Y/N
4 Marked ankle swelling before noon	Y/N
5 Marked ankle swelling in evening	Y/N
6 Some ankle swelling before noon	Y/N
7 Some ankle swelling in the evening	Y/N

Pt arrives 0 min, cy1 and cy2 will also be repeated on both visit 1 and 2

Pt arrives 0 min	Omitted HF Med 48h prior to visit (diuretic, ACEi, B-B, Aldosterone A) Y/N	
	Empty blader	
	Joan: TANITA, Blood test, Questionnaire (describe symptoms last 24h). **Wt…… Ht…..**	
	Thato: Physical examination, explain cycle including Valsalva M	
	BP-sitting …. **HR**…. **RR**….	

Preparation: wet the west for BIM, AO measurement for ENVERDIS (sternal notch to above symphysis pubis).

Cy1	
Preparation	Nicas, Nexfin, BIM, WATCH BP, ENVERDIS, ……
Semirecumbent (**SR**)15 min	A: Nicas-5min→remove
	J: + start Nexfin(SR)-5min→stop
	J: + BP……. HR……..
	T: BIM-5min: (after removing NICAS)
Supine (**SP**) 5 min, pt tolerated for…….. min	T: BIM-3min
	A + **start Nexfin (SP)** (5min)→continue to next step…
	J: + BP…… HR……
Leg raised (**LR**) 6min	J: **+ Mark Nexfin (LR)**→continue to next step
	T: +BIM-3min
	A: start Nicas-3min→stop
	J: +BP…….…. HR……..
Standing1 (**St**), 3 min ***Arm should be supported at heart height & not hanging down by the side**	A: + **mark Nexfin** (**St**) when stood up & measure for 3min& stop
	T: BIM-3min
	J: +BP…….…. HR……..
Sitting (**Sit1**) 6 min	T: BIM-3min
	A: start Nicas (3min) after BIM and continue to next step…
	J: **+ Start Nexfin (sit 1)**-3min→continue to Val Manoeuvre …..
	J: +BP…….…. HR……..
Valsalva Manoeuvre (**VM**) 3min **Sitting** ***breath holding attempted for 30**	T: Val Manoeuvre
	A: **Mark Nicas (VM)** →continue for next step…
	J: **+ mark Nexfin** (**VM**) measure for 3min→stop
	T: ENVERDIS (both Lt & Rt)
Semirecumbent&Nitrate (**GTN**)13min ***Pt with pronounced headache with Nitrate may have this omitted**	A: + Mark Nicas (**GTN**)-5min & remove before BIM
	A: **+ start Nexfin**(**GTN**) →stop end of GTN.
	T: **Nitrate**
	Leave for 5 min
	T: + BIM-3min (after removing Nicas)
	J: ENVERDIS (Rt side only)
	J: +BP…….…. HR……..
Exercise **3** min (25-50=(try **35**)Watts)	J: **start Nexfin(Sit 2)**
Sitting2 (**Sit2**) 6 min	T: +BIM-3min
	A: Start Nicas after BIM and continue for 3 min

CY2	
Preparation	Echo, Nexfin, SENSATRON, WATCH BP
Semirecumbent (**SR**) 30 min	A:Detailed Echo:20min→leg raise 20-30^{o} LVOT-D&LVOT-VTI)
	T: SENSATRON: tap as **start** & **after 5min**
	J: + **Start Nexfin(SR)** -5min→ continue for next step…
	J: +BP…… HR……..
Supine (**SP**) 5 min A& T:analysing echo & entering data	J: **+ Mark Nexfin (SP)**-5min→stop
	T: **+ SENSATRON**: tap as **start** & **after 5min**
	J: +BP…… HR…….
Leg raised (**LR**) 6 min	J: **+ Start Nexfin** (**LR**) (3min)→continue for next step..…
	T: + SENSATRON: tap as **start** & **after 3min**
	J: +BP…… HR……..
Standing1 (**St**) 3 min **Arm should be supported at heart height & not hanging down by the side**	J: **+ mark Nexfin** (**St**) → continue for next step…
	T: + SENSATRON: tap as **start** & **after 3min**
	J: +BP…… HR……..
Sitting (**sit1**)3 min	J: **+ mark Nexfin** (**Sit 1**) for 3min→stop
	T: + SENSATRON: tap as **start** & **after 3min**
	J: +BP…… HR…….. RR……
Valsalva Manoeuvre (**VM**)3min ***breath holding attempted for 30**○○ ○○○	T: Val Manoeuvre
	mark Nexfin (VM) →continue for next step…
	+ SENSATRON: tap as **start** & **after 3min**
Semirecumbent&Nitrate (**GTN**) 10min ***Pt with pronounced headache with Nitrate may have this omitted**	GTN
	J: **+ mark Nexfin (GTN)**-5min→ stop
	T: + SENSATRON: tap as **start** & **after 3min**
	J: +BP…… HR……..
Exercise **3** min (35Watts)	
Sitting2 (**sit2**) 6 min	A: **Start Nexfin (sit 2)**
	T: + SENSATRON: tap as **start** & **after 3min**
	J: +BP…… HR……..
	Empty Blader, volume:……
Cy2= 75min	**TANITA**

15 min Break

Patient Initials: ……. Date of Visit:…/…/2013 Patient Code:…HC-… …..P …-Cy2-
Patient Initials: ……. **Date of Visit: …/…/2013 Patient Code:….HCM- …..P …-Cy2-**

If withheld Med→ Med	
Semirecumbent 55min All measurement should continue for 55min	Nicas+ SENSATRON: tap as start & continue to 55min, Nexfin
	BIM-5min→remove
End of 55 min-10 min	TANITA, Empty Blader, volume:……
25min	A: Detailed echo+leg raised
5min	Blood test
All Post Med=100min	Echo-JVP

All: ~235min=3h 55min
leg raise Echo=20-30° =4 pillows
A=Azam, J: Joan, T: Thato

Patient Initials: ……. **Visit Date: …/…./2013 Patient Code:…..HC3-A**

VISIT [3] LAST STUDY VISIT PER PROTOCOL

1. Events since previous visit

Intercurrent disease since previous visit

Additional treatment and changes to medication since previous visit

Adverse events since previous visit (intercurrent diseases are always AEs). AE form has to be completed for each AE. The form is provided by R&D

Serious adverse events since previous visit – SAEs that are related to the study treatment/procedures and unexpected will require reporting on the NRES SAE report form. The form is available at:
http://www.nres.nhs.uk/applications/after-ethical-review/safetyreports/safety-reports-for-all-other-research

3. Clinical Examination

(Section of clinical examination relevant to the protocol)
Cardio-vascular:
Pulmonary:
……
Have there been any protocol deviations or violations?
If so, please specify: ……

Patient Initials;……. **Date of Visit:…/…./2013 Patient Code:….. HCM-A…P….**

Chief/Principal investigator/Study doctor

Patient`s status: ☐ **Completed** ☐ **Withdrawn**

If withdrawn, please specify reason: ……

"I confirm that the contents of this CRF are accurate and complete"

Name	**Signature**	**Date**

congestion:	
NYHA	1, 2, 3, 4
Breathlessness walking on flat	no problem, mild, moderate, marked
Angina	Y/N
JVP Raised	none, mild, moderate, marked
peripheral oedema	none, mild, moderate, marked
Fine lung crepitations	none, some, obvious
Low cardiac output:	
Fatigue	none, mild, moderate, marked
Dizzy when standing up quickly	none, mild, moderate, marked
BP-standing	…../…..
BP-lyingDown	…../…..
DiastolicBP-lyingDown	
Cool peripheries despite (at room temperature)	none, mild, moderate, marked
Peripheral cyanosis	None, mild. moderate, marked

Patient symptom assessments questionnaire and congestion with low cardiac output will be repeated every visit.

Patient Initials: ……**Date of Visit:** …/…/2013 **Pt Code:**… HCM- A… P …-Cy1 (A=Baseline, B=with med, C=withhold med, A1=day1, P1=pt1)

Patient symptom assessment (1)

Symptoms last 24 hours	
General symptom questionnaire	
Did you experience breathlessness last night?	a) none b) once c) twice or more
Did you feel shortness of breath at rest today?	a) none b) once c) twice or more
How is your energy level today?	1=very bad, 2, 3, 4, 5=very good
Did you tolerate exercise better than yesterday?	Y/N

Patient symptom assessment (2) (Breathlessness):

-If you don't currently do an activity because it makes you too breathless or don't do it for another reason (for instance you have arthritis) but think it would make you breathless if you tried then please score accordingly.

-For instance, if the weather is very bad and you have not gone out of your house you may not have been troubled by breathlessness but you may think that you would get breathlessness walking outside on the flat at a normal pace for someone of your age, in which case you should answer 6 rather than 8.

Over the past 24 hours, I got out of breath:
□ 1 even just sitting or lying down
□ 2 getting dressed or showering
□ 3 walking slowly on the flat
□ 4 doing light housework or shopping
□ 5 walking at a normal pace on the flat
□ **6** climbing a gentle slope or flight of stairs
□ 7 climbing a moderate slope or 2 flights of stairs at a normal pace
□ 8 breathlessness is not a problem

Patient symptom assessment (3) (Oedema

- Over the past 24 hours, did you have swollen ankles or legs (oedema)?	Y/N
If Yes, then: Please rate the swelling over the past 24 hours.	
1 Legs above the knee	Y/N
2 Legs up to the knee before noon	Y/N
3 Legs up to the knee in the evening	Y/N
4 Marked ankle swelling before noon	Y/N
5 Marked ankle swelling in evening	Y/N
6 Some ankle swelling before noon	Y/N
7 Some ankle swelling in the evening	Y/N

Pt arrives 0 min, cy1 and cy2 will also be repeated on both visit 1 and 2

Pt arrives 0 min	Omitted HF Med 48h prior to visit (diuretic, ACEi, B-B, Aldosterone A) Y/N	
	Empty blader	
	Joan: TANITA, Blood test, Questionnaire (describe symptoms last 24h). **Wt……**	
	Thato: Physical examination, explain cycle including Valsalva M	
	Joan: **WATCH-BP** …. **HR**…. **RR**….	

Preparation: wet the west for BIM, AO measurement for ENVERDIS (sternal notch to above symphysis pubis),

Patient Initials: ……. Date of Visit: …/…/2013 **Pt Code**:….HCM- ……P …-Cy1-

Cy1	
Preparation	Nicas, Nexfin, BIM, WATCH BP, ENVERDIS, ……
Semirecumbent (**SR**)15 min	A: Nicas-5min→remove
	J: + start Nexfin(SR)-5min→stop
	J: + BP……. HR……..
	T: BIM-5min: (after removing NICAS)
Supine (**SP**) 5 min, pt tolerated for…….. min	T: BIM-3min
	A + **start Nexfin (SP)** (5min)→continue to next step…
	J: + BP…… HR……
Leg raised (**LR**) 6min	J: + **Mark Nexfin (LR)**→continue to next step
	T: +BIM-3min
	A: start Nicas-3min→stop
	J: +BP…… HR……..
Standing1 (**St**), 3 min ***Arm should be supported at heart height & not hanging down by the side**	A: + **mark Nexfin** (**St**) when stood up & measure for 3min& stop
	T: BIM-3min
	J: +BP…… HR……..
Sitting (**Sit1**) 6 min	T: BIM-3min
	A: start Nicas (3min) after BIM and continue to next step…
	J: + **Start Nexfin (sit 1)**-3min→continue to Val Manoeuvre ..…
	J: +BP…… HR……..
Valsalva Manoeuvre (**VM**) 3min **Sitting** ***breath holding attempted for 30**	T: Val Manoeuvre
	A: **Mark Nicas (VM)** →continue for next step…
	J: + **mark Nexfin** (**VM**) measure for 3min→stop
	T: ENVERDIS (both Lt & Rt)
Semirecumbent&Nitrate (**GTN**)13min ***Pt with pronounced headache with Nitrate may have this omitted**	A: + Mark Nicas (**GTN**)-5min & remove before BIM
	A: **+ start Nexfin**(**GTN**) →stop end of GTN.
	T: **Nitrate**
	Leave for 5 min
	T: + BIM-3min (after removing Nicas)
	J: ENVERDIS (Rt side only)
	J: +BP…… HR……..
Exercise **3** min (25-50=(try **35**)Watts)	J: **start Nexfin(Sit 2)**
Sitting2 (**Sit2**) 6 min	T: +BIM-3min
	A: Start Nicas after BIM and continue for 3 min
	J: +BP…… HR……..
Cy1=65 Min	Echo-JVP

Patient Initials: ……. Date of Visit:…/…/2013 Patient Code:…HC-… …..P …-Cy2-

CY2	
Preparation	Echo, Nexfin, SENSATRON, WATCH BP
Semirecumbent (**SR**) 30 min	A:Detailed Echo:20min→leg raise 20-30^{o} LVOT-D&LVOT-VTI)
	T: SENSATRON: tap as **start** & **after 5min**
	J: + **Start Nexfin(SR)** -5min→ continue for next step…
	J: +BP…… HR……..
Supine (**SP**) 5 min A& T:analysing echo & entering data	J: **+ Mark Nexfin (SP)**-5min→stop
	T: **+ SENSATRON**: tap as **start** & **after 5min**
	J: +BP…… HR……
Leg raised (**LR**) 6 min	J: **+ Start Nexfin (LR)** (3min)→continue for next step..…
	T: + SENSATRON: tap as **start** & **after 3min**
	J: +BP…… HR……..
Standing1 (**St**) 3 min **Arm should be supported at heart height & not hanging down by the side**	J: **+ mark Nexfin (St)** → continue for next step…
	T: + SENSATRON: tap as **start** & **after 3min**
	J: +BP…… HR……..
Sitting (**sit1**)3 min	J: **+ mark Nexfin (Sit 1)** for 3min→stop
	T: + SENSATRON: tap as **start** & **after 3min**
	J: +BP…… HR…….. RR……
Valsalva Manoeuvre (**VM**)3min ***breath holding attempted for 30**○○ ○○○	T: Val Manoeuvre
	mark Nexfin (VM) →continue for next step…
	+ SENSATRON: tap as **start** & **after 3min**
Semirecumbent&Nitrate (**GTN**) 10min ***Pt with pronounced headache with Nitrate may have this omitted**	GTN
	J: **+ mark Nexfin (GTN)**-5min→ stop
	T: + SENSATRON: tap as **start** & **after 3min**
	J: +BP…… HR……..
Exercise **3** min (35Watts)	
Sitting2 (**sit2**) 6 min	A: **Start Nexfin (sit 2)**
	T: + SENSATRON: tap as **start** & **after 3min**
	J: +BP…… HR……..
	Empty Blader, volume:……
Cy2= 75min	**TANITA**

If withheld Med→ Med	
Semirecumbent 55min All measurement should continue for 55min	Nicas+ SENSATRON: tap as start & continue to 55min, Nexfin
	BIM-5min→remove
End of 55 min-10 min	TANITA, Empty Blader, volume:……
25min	A: Detailed echo+leg raised
5min	Blood test
All Post Med=100min	Echo-JVP

Favourable Ethical Approval – Future Research

NRES Committee Yorkshire & The Humber - Leeds West

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12 March 2013

Professor John Cleland
Professor of Cardiology
University of Hull
Department of Academic Cardiology
Castle Road
Castle Hill Hospital
HU165JQ

Dear Professor Cleland

Study title:	**Assessing the Acute Haemodynamic Effects of Hydralazine and Nitrates, singly and in combination, in Patients with Chronic Heart Failure using Novel Non-invasive Sensor Technologies.**
REC reference:	**13/YH/0059**
IRAS project ID:	**123158**

The Research Ethics Committee reviewed the above application at the meeting held on 08 March 2013. The Committee would like to thank Dr Mabote for attending.

Ethical opinion

Clarification was sought on the device; Dr Mabote explained that at present several devices are used to assess patients, this new device is to be tested against 2 of these, and against standard assessment tools.

The recruitment procedure was raised; Dr Mabote explained the department has a database of patients who have expressed an interest in taking part in research; they would be contacted by telephone if they are eligible. Potential participants will also be approached who are attending for follow up appointments. Dr Mabote

confirmed that it would be made clear to all participants they can withdraw from the study if they wish to.
The members of the Committee present gave a favourable ethical opinion of the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below

Ethical review of research sites
NHS Sites
The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).
Non NHS sites
The Committee has not yet been notified of the outcome of any site-specific assessment (SSA) for the non-NHS research site(s) taking part in this study. The favourable opinion does not therefore apply to any non-NHS site at present. I will write to you again as soon as one Research Ethics Committee has notified the outcome of a SSA. In the meantime no study procedures should be initiated at non-NHS sites.
Conditions of the favourable opinion
The favourable opinion is subject to the following conditions being met prior to the start of the study.
Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.
Management permission ("R&D approval") should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.
Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.
Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.
For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.
Sponsors are not required to notify the Committee of approvals from host organisations
1 The GP letter should include the explanation 'the study is for testing a non invasive device'.
It is responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).
You should notify the REC in writing once all conditions have been met (except for site approvals from host organisations) and provide copies of any revised documentation with updated version numbers. The REC will acknowledge receipt and provide a final list of the approved documentation for the study, which can be made available to host organisations to facilitate their permission for the study. Failure to provide the finalversions to the REC may cause delay in obtaining permissions.

Approved documents

The documents reviewed and approved at the meeting were: *Document*	*Version*	*Date*
GP/Consultant Information Sheets	1.0	18 January 2013
Investigator CV		07 June 2011
Letter of invitation to participant	1.0	02 December 2012
Other: GP letter-control group	1.0	18 January 2013
Participant Consent Form	1.0	18 January 2013
Participant Consent Form: Control	1.0	18 February 2013
Participant Information Sheet	1.0	07 January 2013
Participant Information Sheet: Control	1.0	07 January 2013
Protocol	1.0	07 January 2013
REC application		18 February 2013

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website. Further information is available at
National Research Ethics Service website >

After Review **13/YH/0059** **Please quote this number on all correspondence**

We are pleased to welcome researchers and R & D staff at our NRES committee members' training days – see details at http://www.hra.nhs.uk/hra-training/
With the Committee's best wishes for the success of this project.

Yours sincerely
pp
Dr Rhona Bratt

Chair
Email: nrescommittee.yorkandhumber-leedswest@nhs.uk

Abbreviations

ACEI – Angiotensin converting enzyme inhibitors

ARB – Angiotensin Receptor Blockers

CHF / HF – Congestive heart Failure / Heart failure

CHD – Coronary heart disease

CI – Cardiac Index

DBP – Diastolic blood pressure

GP – General Practitioner

HTN – Hypertension

NT – proBNP – N Amino Terminal pro Brain Natriuretic peptide

LVEDP – Left Ventricular end diastolic pressure

LVESV – Left ventricular end systolic pressure

SBP – Systolic blood pressure

SVR – Systemic vascular resistance