The Philips wearable biosensor in transcatheter aortic valve implantation treatment workflow

Usability and feasibility of the wearable biosensor

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Usability and feasibility of the wearable biosensor

For the title of Master of Science in Technical Medicine

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"Not everything that counts can be counted,
and not everything that can be counted counts."

- Albert Einstein

Preface

Before you lies '*The Philips wearable biosensor in transcatheter aortic valve implantation treatment workflow. – Usability and feasibility of the wearable biosensor*', describing the rationale and first results of the TELE-TAVI study. This study examines a patch sensor and additional phone receiver for tele-monitoring in-TAVI patients. The thesis has been written to obtain the master's degree in Technical Medicine at the University of Twente. It is the result of my graduation internship at the Amsterdam UMC, location AMC, from February 2018 to March 2019.

The TELE-TAVI study concept was designed by Martijn van Mourik and Marije Vis, who started the collaboration with Philips and medical ethical approval, which took over a year. My activities within this study was the realization, execution and (first) analysis of the TELE-TAVI. It was a long, bumpy road, but the study is almost at its end.

I would like to thank all my supervisors who helped me accomplish this thesis. My supervisors at the Amsterdam UMC, Martijn van Mourik and Marije Vis, your advice and supervision helped me to complete this thesis. Hermie Hermens and Ainara Garde-Martinez from the University of Twente, you assisted me in the technical difficulties of the project and widen my scope. Paul van Katwijk, thank you for the guidance in this process. Erik ten Berge, I am delighted that you are part of my gradation committee. I also wish to thank all of the participants, without whom I would not have been able to conduct this study.

To my other colleagues at the Amsterdam UMC, I would like thank you for your insights into research. I want to thank the members of my group intervision for the helpful meetings and advices.

Finally I would like to thank my family, friends, and especially my love, for being helpful and supportive during my internship and time studying Technical Medicine at the University of Twente.

Carlijn Braem

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Abstract

Transcatheter aortic valve implantation (TAVI) is currently standard care for intermediate to high risk patients in patients with aortic valve stenosis, which is associated with aging and has a high burden on health care. Current screening tools however are insufficient as frailty is not included. A wearable sensor could allow for an in-depth analysis for screening TAVI patients. Besides, post-procedure monitoring and TAVI follow-up could benefit from extended monitoring. This thesis reviews the usability and feasibility of the Philips wearable biosensor for TAVI workflow.

The TELE-TAVI study is an observational, prospective, investigator initiated pilot, started in June 2018 in the Amsterdam UMC, location AMC (Amsterdam, the Netherlands). The wearable biosensor (Philips Medical Systems, Andover, Massachusetts, USA) is a lightweight, wireless, wearable medical-grade biosensor, that can measure vital signs and detects posture for up to 4 days. Healthy volunteers and patients in work-up for TAVI were included. Healthy volunteers were enrolled and received one biosensor to test the system technically. TAVI patients received the wearable biosensor thrice; before the TAVI procedure (T0), directly post TAVI procedure on the cardiac care unit (CCU) (T1) and 6-weeks after the TAVI procedure (T2). The reliability of the biosensors vital signs was compared to a standard care monitor (Philips MP70 monitor, Philips Healthcare, Eindhoven, the Netherlands). Posture detection reliability was tested with walking exercises and compared to diaries and data collection reliability was assessed. TAVI patient experience with the system was reviewed with the post study system usability questionnaire (PSSUQ) and a custom made questionnaire. Activity was estimated with the integral of the modulus of the accelerometer output (IMA), and with thresholds activity classification and daily activity levels were computed.

At February 22nd of 2019, a total of 6 healthy and 24 TAVI patients were enrolled in the TELE-TAVI study. Eighteen and eight TAVI patients completed measurements at T1 and T2, respectively and ten patients dropped out. The TAVI population is 76.6 (± 4.8) years old, 75% male. Vital signs limit of agreement was between -3.9 -7.0 and -8.1 and 7.8 for heart and respiratory rate respectively. Walking was detected by the biosensor if the gait speed was higher than 0.7 m/s. After one day, posture detection diverged substantially. Of the 96 recording hours, 56.2% is recorded with no gaps in the data. 45 wearability questionnaires were received and the PSSUQ showed an overall system satisfaction of 63.2% (± 30.7%). Sensor wear was comfortable, but the sensor fell off in 31% of the patients IMA correlates with gait speed ($r2 = 0.8$ and $p<0.01$). No, low, medium and high activity levels are 63.3%, 25.2%, 10.9% and 0.6%, respectively and daily activity levels are 40.8%, 28.7%, 12.2% and 0.6%.

Patients tolerated wearing the biosensor well and activity classification can give insight in patient activity patterns. The feasibility of the wearable biosensors is as of yet insufficient, as the reliability of the biosensor is deficient compared to the predefined criteria. Data collection reliability is low and posture detection is unusable, as detection deteriorates within a day. . The usability of the wearable biosensor shows great promise to improve TAVI work flow and encourages research in sensor technology in elderly.

Contents

Chapter A: Appendix

Abbreviations

Abbreviation	
6MWT	Six minute walk test
AF	Atrial fibrillation
AoS	Aortic valve stenosis
BLE	Bluetooth Low-Engery
BMI	Body mass index
Bpm	Beats per minute
Brpm	Breaths per minute
CCS	Canadian Cardiovascular Society grading of angina pectoris
COPD	Chronic obstructive pulmonary disease
ECG	Electrocardiogram
EuroSCORE	European system for cardiac operative risk evaluation
G	Gravitional force (9.81 m/s^2)
HR	Heart rate
IMA	Integral of the modulus of acceleration
IQR	Interquartal range
METS	Metabolic equivalent score;
mG	Micro Gravition force (9.81 *10^-3 m/s^2)
mV	Micro Voltage
NYHA	New York Heart Association functional classification.
PSSUQ	Post-study system usability questionnaire
RespR	Respiratory rate
RPC	Reproducibility coefficient
R-R interval	R peak to R-Peak interval in the ECG
SAVR	Surgical aortic valve replacement
SD	Standard deviation
SF36	Short From (36) Health Servey
SPPB	Short physical performance battery
STS	Society of Thoracic Surgery predicted risk of mortality
T0-T2	Measurement times:; T0: pre-operative, T1: direct post-TAVI, T2: follow-up
TAVI	Transcatheter aortic valve implantation
TELE-TAVI	Observational pilot study to assess usability of a wearable patch sensor in monitoring vital signs and activity in TAVI patients.

Chapter 1: Introduction

1.1. Aortic valve stenosis

The Western world is aging, as the life expectancy increases and baby boomers are becoming of age. With this, the number of people with cardiovascular diseases rises, including heart valve disorders.

The heart consist of two smaller and two larger chambers, which are separated with four valves. In aortic valve stenosis (AoS) the valve separating the left ventricle from the aorta, is affected (Figure 1.1) [1]. The leaflets of the aortic valve deteriorate and develop calcifications, which leads to obstruction of left ventricular blood outflow. This results in inadequate cardiac output, decreased exercise capacity, heart failure, and when left untreated death from these cardiovascular causes. The prevalence of AoS increases with age, in which 3.4% of the elderly (>75 years) has severe AoS [2]. It is associated with high burden on health care and patients quality of life [2], [3].

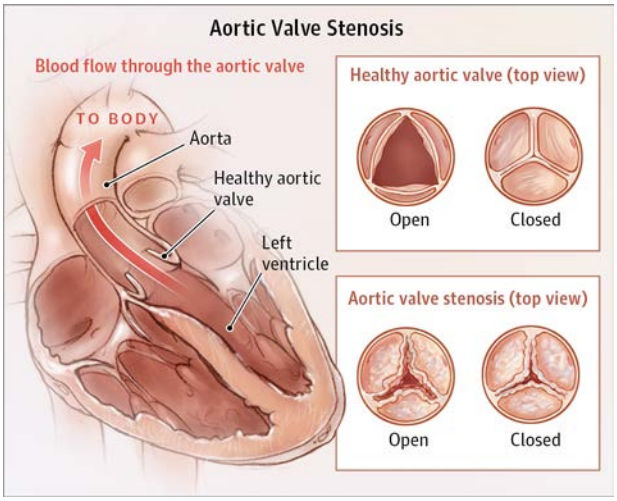


Figure 1.1 *Anatomy of the heart and valves. The left shows a cross-section of the heart, showing the left ventricle and aorta, separated by the aortic valve. In the left upper panel, a healthy aortic valve is shown. The leaflets can open and close fully. In the lower right panel, stenotic aortic valves are shown. Due to the deterioration and calcifications the valves cannot open and close properly [1].*

1.2. Transcatheter aortic valve implantation

Nowadays, an aortic valve replacement is indicated when AoS is severe and the patient experiences symptoms. The aortic valve can be replaced during cardiac surgery; surgical aortic valve replacement (SAVR). An alternative for SAVR is transcatheter aortic valve implantation (TAVI), in which a bio-prosthetic aortic valve is implanted with a catheter inserted in the femoral artery, subclavian artery, ascending aorta, or via the cardiac apex. Of these, the femoral approach is preferred as it is the least invasive and associated with the lowest risk (Figure 1.2) and can be performed without general anesthesia [4].

In the decision making between SAVR or TAVI patients are screened for surgical risk. The European System for Cardiac Operative Risk Evaluation (EuroSCORE) or Society of Thoracic Surgeons (STS) score are used for screening [6], [7]. Both are risk stratification models for mortality after 30 days after cardiac surgery. If patients score high to moderate on these scales (STS or EUROscore II ≥ 4%), they are considered

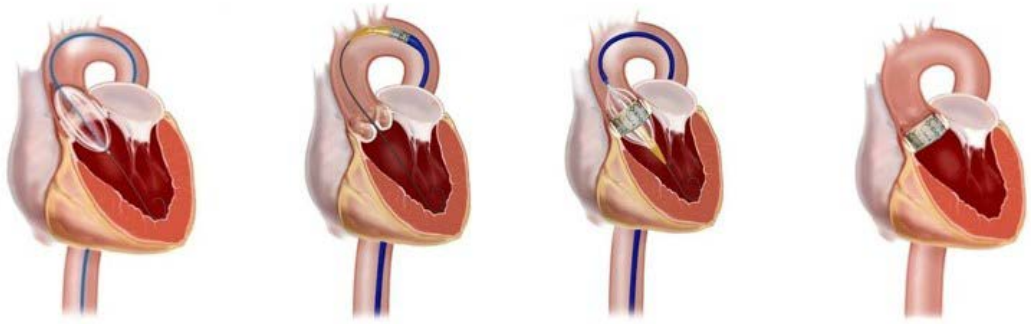


Figure 1.2 *Transcatheter aortic valve implantation. A) Under radiological guidance, a catheter is placed into the left ventricle via the femoral artery and aorta. A balloon is threaded through the diseased aortic valve, after which balloon valvuloplasty is performed to dilate the diseased aortic valve. B) A balloon device with the new valve attached is thread through the diseased aortic valve. C) During pacing of the right ventricle by an external pacemaker wire, the new valve is unfolded using inflation of the balloon. D) The balloon is deflated, after which the new aortic valve will directly function. Modified from the ISAR Heart Centre Munich [5].*

eligible for TAVI [8]. However, both scores are not ideally suited for TAVI procedures and TAVI risk algorithm is needed [4], [9], [10].

Next to the 30-day mortality risk, other clinical patient characters are evaluated for the decision between SAVR and TAVI, such as age and frailty. The TAVI procedure is preferred in patients above 75 years of age. Even so, calendar age is an insensitive and non-specific measure for preoperative risk assessment [11].

1.3. Frailty

Frailty on the other hand is closely related to adverse surgical outcomes, such as mortality, morbidity, and functional decline [11]–[14]. However, it remains difficult to define, due to its multi-factorial and multi-expressional nature. Frailty involves a decline of feedback complexity in physiologic systems, followed by a loss of homeostatic reserves resulting in vulnerability to external stressors. It can be observed as weight loss, muscle weakness, poor endurance and energy, slowness and low physical activity levels [15]. The prevalence of frailty is high among elderly (22.7%) and increases even further with age [12], [13].

There is a vast amount of frailty assessment tools, as a result of the complex and debated definition of frailty. Generally, there are two types of tests, qualitative questionnaires involving frailty phenotype related questions and physical performance tests [16], [17]. Despite the enormous collection of diagnostic tools for frailty, there is no international standard and it is generally acknowledged that there is a need for a standard validated objective frailty assessment tool [14], [16], [18].

Multiple studies attempt to provide a generalized frailty assessment with technology. For example, the use of inertial sensors or accelerometers in a phone or wearable sensors. Hereby several outcomes are analyzed, such as gait, balance, physical performance or activity. These are used individually or in combination with conventional measures [19]. Wearable sensors can also be used to assess the impairment of cardiac autonomic nervous control by analyzing heart rate (HR) and heart rate variability (HRV) characteristics [20]. HRV changes as a consequence of loss in physiologic complexity in frail patietns.

In summary, severe AoS results in inadequate cardiac output and loss of exercise capacity. TAVI has become standard intervention for moderate to high risk patients. Frequently used risk scores are limited in predicting 30-day mortality after TAVI. Frailty, however is closely related to surgical outcome, but a standardized frailty tool is lacking. Frailty and AoS are both associated with declined physical activity and impaired (cardiac) functioning. To date, no research is known attempting to combine physical activity and cardiac physiological parameters as a screenings measure for patients with AoS.

1.4. Wearable biosensor

In 2016, Philips launched the wearable biosensor (Philips Medical Systems, Andover, Massachusetts, USA) a lightweight, wireless, wearable medical-grade biosensor. The sensor records mono-lead ECG, respiratory rate (RespR), skin temperature and tri-axial acceleration for step count and postural positions with a battery life of four days. Next to these computed parameters, the raw data of the sensor can be extracted, such as tri-axial accelerometer, mono-lead ECG and thermometer. The combination of physiological outcome parameters, HR and RespR, and posture detection could allow for an integrated analysis, which can be used for screening TAVI patients.

However, no study is published on the wearable biosensor and only few on its predecessor, the HealthPatch MD (VitalConnect, San Jose, California, USA), who has the same firm- and hardware [21]–[23]. Therefore, reliability of the biosensor is as of yet, largely debated. Also little data is available on the patient perception of the wearable biosensor [24].

1.5. TELE-TAVI study

In the Amsterdam UMC (location AMC, Amsterdam, The Netherlands), a pilot study was set-up to investigate usability and feasibility of the wearable biosensor to monitor cardiac condition and assess frailty and treatment effects in TAVI-patients (TELE-TAVI). In this study two groups of participants were included; healthy subjects and TAVI-patients.

Data collected from the healthy volunteers will be used for algorithm development, reliability assessment and provides the researchers with experience of the biosensor system. In TAVI-patients, the biosensor is attached before, directly after and six weeks after the TAVI procedure, so data on the screening, monitoring and follow-up is collected. Frailty and functional status was assessed pre-procedural and at six weeks follow-up.

The realization of TELE-TAVI entitles a great part of this master graduation. Data from the TELE-TAVI study is used for this master thesis, to assess the usability of the wearable biosensor in the TAVI workflow.

Figure 1.3 *Philips wearable biosensor, on a patient [64].].*

Chapter 2: Research Questions

In Chapter 1 we showed that mortality risk assessments for transcatheter aortic valve implantation is limited. The wearable biosensor could be usable in transcatheter aortic valve implantation workflow, using physiological parameters and activity. However, the reliability and end-user perception is largely unknown. Also, an algorithm for assessment and quantification of physical activity is not yet available for the wearable biosensor.

2.1. Research question

This leads to the following research question:

> *What is the usability and feasibility of the Philips wearable biosensor for transcatheter aortic valve implantation workflow?*

The following sub questions will be addressed in this thesis:

1. How reliable are the Philips wearable biosensors vital signs, posture detection and data collection?
2. How do TAVI-patients experience the use of the Philips wearable biosensor and additional systems?
3. How can we objectively measure physical activity with the Philips wearable biosensor?

2.2. Outline thesis

These research questions are part of the aforementioned TELE-TAVI study. This study is a prospective, investigator initiated study.

The general outline of the master thesis is given in Figure 2.1. The rationale and design of the TELE-TAVI study will be given in Chapter 3. Preliminary results of the TELE-TAVI study are presented in Chapter 4. Data from the TELE-TAVI study is used to assess the reliability of the wearable biosensor, given in Chapter 5. Next, the biosensor user experience during the TELE-TAVI study is presented in Chapter 6. Hereafter, activity classification with the wearable biosensor are given in Chapter 7. Overall implications, conclusions and future perspectives are given in Chapter 8.

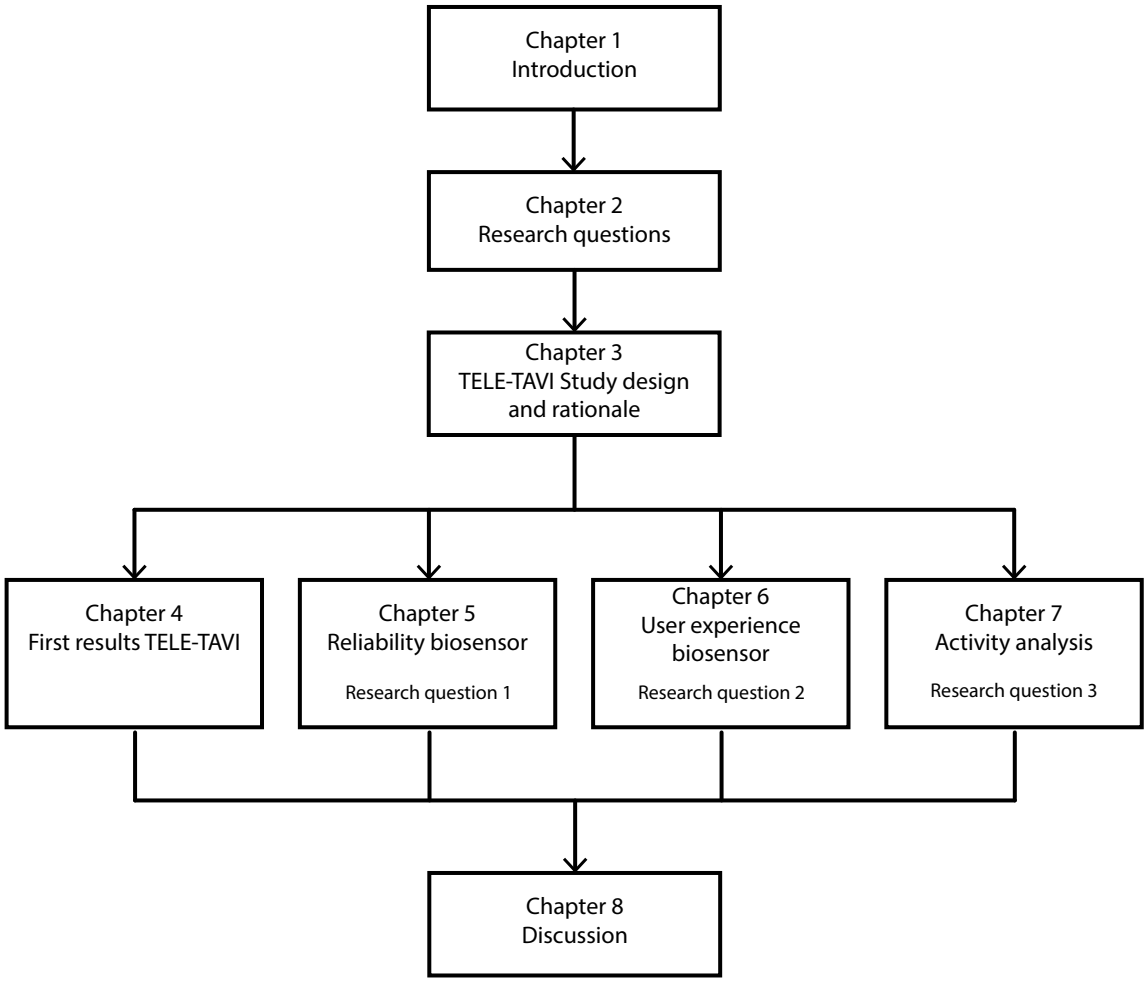


Figure 2.1 *Overview of the chapters in this master thesis*

Chapter 3: Feasibility and usability of a wearable patch sensor in monitoring vital signs and activity in transcatheter aortic valve implantation patients: design and rationale of the TELE-TAVI study.

3.1. Introduction

Severe aortic valve stenosis (AoS) occurs in 3.4% of the elderly (>75 years) in which heart valve replacement is standard treatment [2]. For patients with high or moderate surgical risk, a minimally invasive transcatheter aortic valve replacement (TAVI) is currently standard care [25].Frequently used risk scores are limited in predicting 30-day mortality after TAVI, as major risk factors, such as frailty, are not included [25]. Therefore there is a need for a new pre-surgical assessment [9], [10]. Remote monitoring in a home situation has the potential to objectively assess frailty, as well as to give a better understanding of the patients (cardiac) condition. Compared to a single evaluation in the clinical setting, home monitoring can provide an unbiased evaluation over multiple days. Obtained information could aid the decision making of AoS treatment; surgical, TAVI or conservative treatment.

Monitoring after TAVI is critical, as one major complication is the onset of new conduction disturbances. Therefore telemetry monitoring is now mandatory, which confides patients to the hospital. Home monitoring could extend the monitoring period, without lengthening the patients hospital stay. It could also help in the challenging first part of the rehabilitation, as well as providing objective and reliable information of the post procedural effect of the treatment and status of rehabilitation.

Currently there are wearable devices available on the market that aid monitoring and diagnosing of patients inside and outside the hospital [19], [26]–[28]. These devices measure different vital signs like heart- and respiration rate and more, for example, activity level. The potential of such devices are tremendous, but in daily practice it remains minimal, as more experience with these systems is needed.

The aim of this study is to investigate usability and feasibility of the wearable biosensor to monitor cardiac condition and assess frailty and treatment effects in TAVI-patients. Three potential cases were selected, to show were a wearable sensor could improve TAVI workflow:

T0: Pre-operative screening: a home measurement of vital signs and physical activity. Acquired data will be used to calculate and objectify frailty, clinical symptoms of AoS and give a presurgical evaluation of the patient condition.

T0: Direct post-procedural monitoring: by means of a wearable patch, a patient can be ambulatory monitored to detect early deterioration after the TAVI procedure. Especially cardiac conduction disorders can be monitored.

T0: Follow-up measurement: for analysis of objective clinical results of TAVI patients, extended home measurement can be performed and compared to the obtained pre-operative baseline.

Table 3.1 *Criteria of the Philips wearable biosensors fall detection, as reported by Chan et al. [22]*

Criteria fall detection	
1.	Detection of impact and free-fall
2.	Large differences in acceleration in a small time window
3.	Change from vertical to horizontal posture
4.	Low activity for a specified duration after posture change

bpm indicates beats per minute; brpm, breaths per minute; ECG, electrocardiogram; mV, micro Voltage

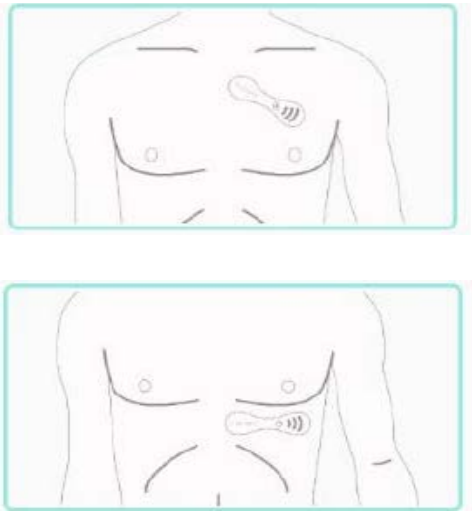


Figure 3.1 *Two allocated sites for wearable biosensor placement, upper left chest and rib cage below chest. [26]*

3.2. Method

3.2.1. General design

To examine the usability and wearability of a patch sensor and additional phone receiver in TAVI patients the tele-monitoring in-TAVI patients (TELE-TAVI) study was conducted. TELE-TAVI is an observational, prospective, investigator initiated pilot. The study started in June 2018 and is still including eligible patients in the Amsterdam UMC, location AMC (Amsterdam, the Netherlands). The trial was in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

3.2.2. Devices

In the TELE-TAVI study, the Philips wearable biosensor and matching Research Kit (Philips Medical System, Andover, Massachusetts, USA) was used. A standard care monitor of Philips (Philips MP70 monitor, Philips Healthcare, Eindhoven, the Netherlands) was utilized as reference. All devices were provided by Philips.

Biosensor

The Philips wearable biosensor is a wireless, lightweight, medical-grade sensor designed for long-term monitoring of vital signs. The single-use patch contains two ECG-electrodes, a tri-axial accelerometer, a thermistor, a zinc-air battery and a Bluetooth Low-Energy (BLE) transceiver. The biosensor is placed on one of two allocated places on the chest (Figure 3.1) and can measure vital signs for up to four days. Specifications of the measured vital signs can be found in Table 3.1.

ECG

Two ECG-electrodes compute a continuous single-lead ECG at a sample rate of 125 Hz, of which heart rate and R-R peak interval is derived. QRS complexes are automatically detected from the single-lead ECG, with a validated algorithm using wavelet transforms [29], [30]. The R-R interval is computed as the time duration between two detected consecutive QRS complexes. The heart rate (HR) is instantaneously computed as the reciprocal of the R-R interval. To smooth the obtained heart rate signal, a 10-beat low-pass filter is applied. [22]

Figure 3.2 *- Next page - Biosensor placement and accelerometer directions: A: Showing biosensor place on a patient with the normal force (Fnormal). The window shows the biosensor and the raw, not calibrated axes (x, y, z). The raw x-axis is pointing downward, perpendicular to the length of the biosensor. The y-axis pointed parallel to the length of the biosensor. The z-axis points from the biosensor up or 'through' the paper. Under the patient, the calibrated axes (posterior to inferior, lateral to medial and inferior to posterior (vertical)) are shown in dark blue. B: Raw accelerometer data in three axes of the transition from sitting to walking (100 steps/min) of Pin 101. First few seconds, the subject is sitting, where after a swing from sitting to standing is seen. The end shows the subject walking (at 15:51:05). C: Shows the modulus of the accelerometer, the magnitude of the forces detected by the accelerometer. Visible in sitting time is a magnitude of 1G, which is the normal force (Fnormal). D: Gives the step count as biosensor output. After 5 seconds walking, the step count increases; first fast, where after, the increase slows down. The first big increase compensates for the 5 seconds lost for determination of the posture change, visible as the (estimated) dashed line.*

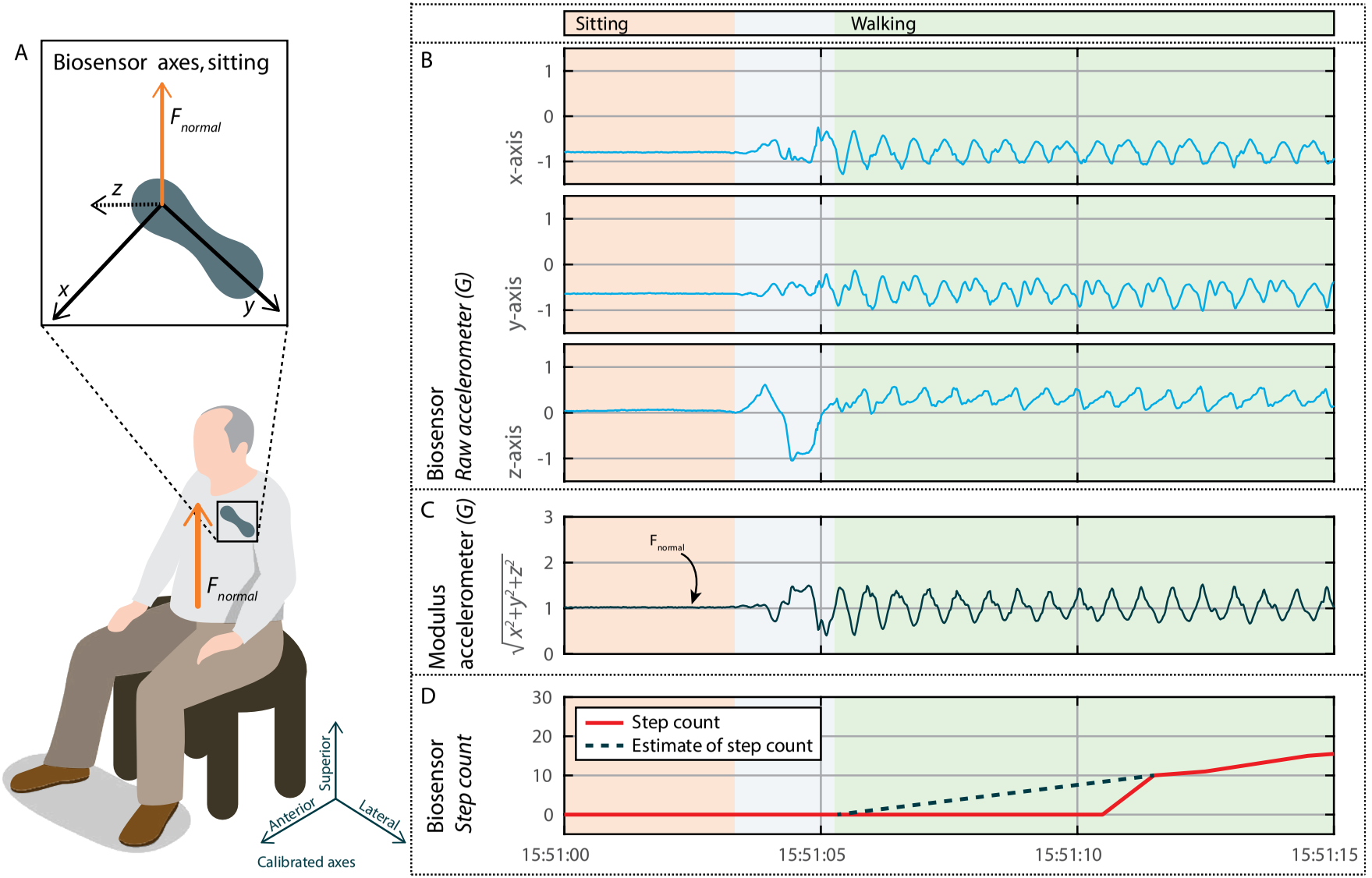

A
Biosensor axes, sitting
F normal
z
x
y
F normal
Superior
Anterior
Lateral
Calibrated axes
Sitting
Walking
B
Biosensor
Raw accelerometer (G)
x-axis
y-axis
z-axis
1
0
-1
C
Modulus
accelerometer (G)
√x²+y²+z²
F normal
3
2
1
0
D
Biosensor
Step count
Step count
Estimate of step count
30
20
10
0
15:51:00
15:51:05
15:51:10
15:51:15

Table 3.2 *Overview of the Philips wearable biosensor output characteristics.*

Data name	Method	Unit	Fs (Hz)	Range		Ref
Single-lead ECG		micro Voltage	125	[-10 10]	mV	
Heart Rate	ECG derived	Beats/minute	0.25*	[30 200]	bpm	[24]
Raw accelerometer (x,y,z)		mG	50	[-4 4]	G	
Position (Posture)	Accelerometer derived	-	1	[0 11]		
Step Count	Accelerometer derived	Steps	1*	[0 65535]	steps	
Fall detection	Accelerometer derived	-	-	-		[22]
Respiratory rate	ECG and accelerometer derived	Breaths/minute	0.25	+	brpm	[23]

bpm indicates beats per minute; brpm, breaths per minute; ECG, electrocardiogram; G, gravitation; mV, micro Voltage

Table 3.3 *Overview of patient monitor output characteristics.*

Data name	Unit	Fs (Hz)	Range		Accuracy	Ref
5-lead ECG	micro Voltage	125				[34]
Heart Rate	Beats/minute	0.98	[15 300]	bmp	± 1% of range	
Impedance pneumography	mG	62.5				[34]
Respiratory rate	Breaths/minute	0.98	[0 120]	brpm	at 0 to 120 brpm: ±1 brpm	

bpm indicates beats per minute; brpm, breaths per minute; ECG, electrocardiogram; mV, micro Voltage

Tri-axial accelerometer

The wearable biosensor contains a tri-axial accelerometer. An accelerometer measures a change of speed compared to the free fall state. When an object is in free fall, the gravitational force only influences the object. This means, that an accelerometer cannot detect gravitational acceleration itself. When the accelerometer is placed on a surface, it will measure the ground reaction force or normal force. Therefore, when an accelerometer is placed on a surface, it measures a force of one gravity unit ($g_0 = 9.81\ m/s^2$) upwards. A tri-axial accelerometer has three perpendicular placed accelerometers, measuring acceleration in three orthogonal directions. As none of the axes is aligned with the normal vector, all accelerometers show some of the normal force when placed on a horizontal surface. This can be seen in Figure 3.2, where a person is sitting up and all the axes a part of the normal vector induces a displacement. Therefore, the wearable biosensor automatically calibrated to obtain a vertical, anterior-posterior and left-right lateral axis. With the calibrated accelerometer falls and posture is detected. Posture is classified as upright, leaning, lying, walking or unknown within five seconds of postural change. Static postures (upright, leaning, lying) are detected based on the angle of the thorax of the individual. Walking is detected based on a threshold in vertical acceleration and the ability to count steps. By peak picking regular peaks in the vertical axis, steps are counted. Falls are detected when several criteria are met, see Table 3.1. The calibrated accelerometer signal is not recorded or available for further analysis.

Respiration

Respiration is not directly measured by the wearable biosensor, but estimated using ECG characteristics and the calibrated accelerometer signal. The R-R interval computed from the ECG modulates due to respiration, which is known as the respiratory sinus arrhythmia. The autonomic nervous system induces a HR increase during inspiration and decrease in expiration, respectively. Next to that, chest movement of the respiration causes movements of the heart and its axis. This is visible as a modulation of the voltage or height of the QRS complex. Chest movements, although small, induce a change in thoracic angle, which can be detected by the accelerometer. Obtaining the respiratory rate (RespR) from ECG or acceleration extensive smoothing and filtering is needed. Hereafter the RespR is estimated from the picked peaks over a

window of 45 seconds, shifting every 4 seconds. [23]

For each individual method, a separate RespR is computed, where after these are combined dependent on the quality of the underlying signals. The algorithm favors the computed breathing rate to be regular, because than it is more likely to reflect the true breathing rate. A quality metric is calculated from the regularity features of the three computed breathing rates. This quality metric is used to make a weighted average of the final estimated breathing rate. [23]

ECG derived respiration has a major limitation, as it can only can detect breathing rates up to half the heart rate, due to aliasing. Therefore, RespR is solely computed with the accelerometer data when the breathing rate is higher than half the heart rate and the accelerometer signal quality is sufficient. [23]

Research Kit

The Research Kits intended use is for clinical researchers to gather, analyze and review patient data retrospectively and conduct offline analysis with the Philips wearable biosensor. The Research Kit contains a smart phone (Kyocera BRIGADIER) preinstalled with the Research Kit mobile application as well as an offline desktop application. The mobile phone with app captures data acquired by wearable biosensor via Bluetooth and saves the data encrypted on the SD-card. The app also provides guidance for the set-up of the biosensor; connecting biosensor to mobile phone, skin adherence of the biosensor, set-up Bluetooth connection sensor and phone, accelerometer calibration, alerts the user of error conditions and gives suggestion to resolve these problems.

Philips MP50 Monitor

As reference, the Philips MP70 monitor (Philips Healthcare, Eindhoven, the Netherlands) was used. Data were retrieved from the monitor with the ixTrend software (ixellence, Wildau, Germany). Signals measured are six ECG derivations (I, II, III, aVR, aVF and a thoracic electrode), impedance pneumography, HR and RespR. Specifications of the monitor can be found in Table 3.3. Descriptions of the heart and respiratory rate derivation from the ECG and impedance signal, respectively, are not disclosed by Philips.

3.2.3. Study population

Healthy subjects

Healthy volunteers were enrolled in the study to test the system technically, address data quality verification and for algorithm development. Subjects older than 18 years and able to follow instruction of the smartphone were asked to voluntarily cooperate in the study. Exclusion criteria were subjects with heart disease, or other severe chronic illnesses, implanted cardiac devices, an allergy to silicone of hydrocolloid adhesives or damaged or very vulnerable skin at the patch location.

After written informed consent was obtained, the biosensor was applied to the chest of the subject. Hereafter the reference monitor was applied to the subject, followed by a series of exercises, including breathing exercises and posture changes. The breathing exercises involved spontaneous and metronome breathing at 10, 15, 20 and 25 breaths per minute in random order, as well as one long and two short breath stops of 15 and 8 seconds, respectively. Next, the subject performed position tasks, involving 2 minute blocks of sitting in bed, sitting, and standing, all separated by 2 minutes of lying down. Hereafter the reference was detached and walking exercises were performed containing blocks of two-minute walking at 50, 75 and 100 steps per minute. Walking pace was set by audible ques from a metronome. Blocks of walking were separated by one-minute blocks of sitting. Furthermore, physical functioning and frailty was examined with grip strength, distance travelled in 6 minutes (6MWT) and the short physical performance battery (SPPB). The SPPB is a simple test examining, balance, walking speed and repeated chair-stands and is a measure of self-resilience. Additionally, 12 leads ECG was recorded and Edmonton frail scale and Short Form (36) Healthy Survey (SF36) were filled in. An overview of the protocol used for healthy subjects can be found in Figure 3.3.

After these measurements, subjects resumed daily activities, while the wearable biosensor was still attached for the remaining battery life. Subjects were asked to keep a diary of their activities, and specifically note sleeping, sitting, walking, stair climbing, sports, transport and when they would feel palpitations, become unwell or fell. When the measurement was finished, subjects filled in the post-study system usability questionnaire (PSSUQ)[31] and a custom-made questionnaire to assess the wearability of the wearable biosensor and its system (Appendix A.3.1).

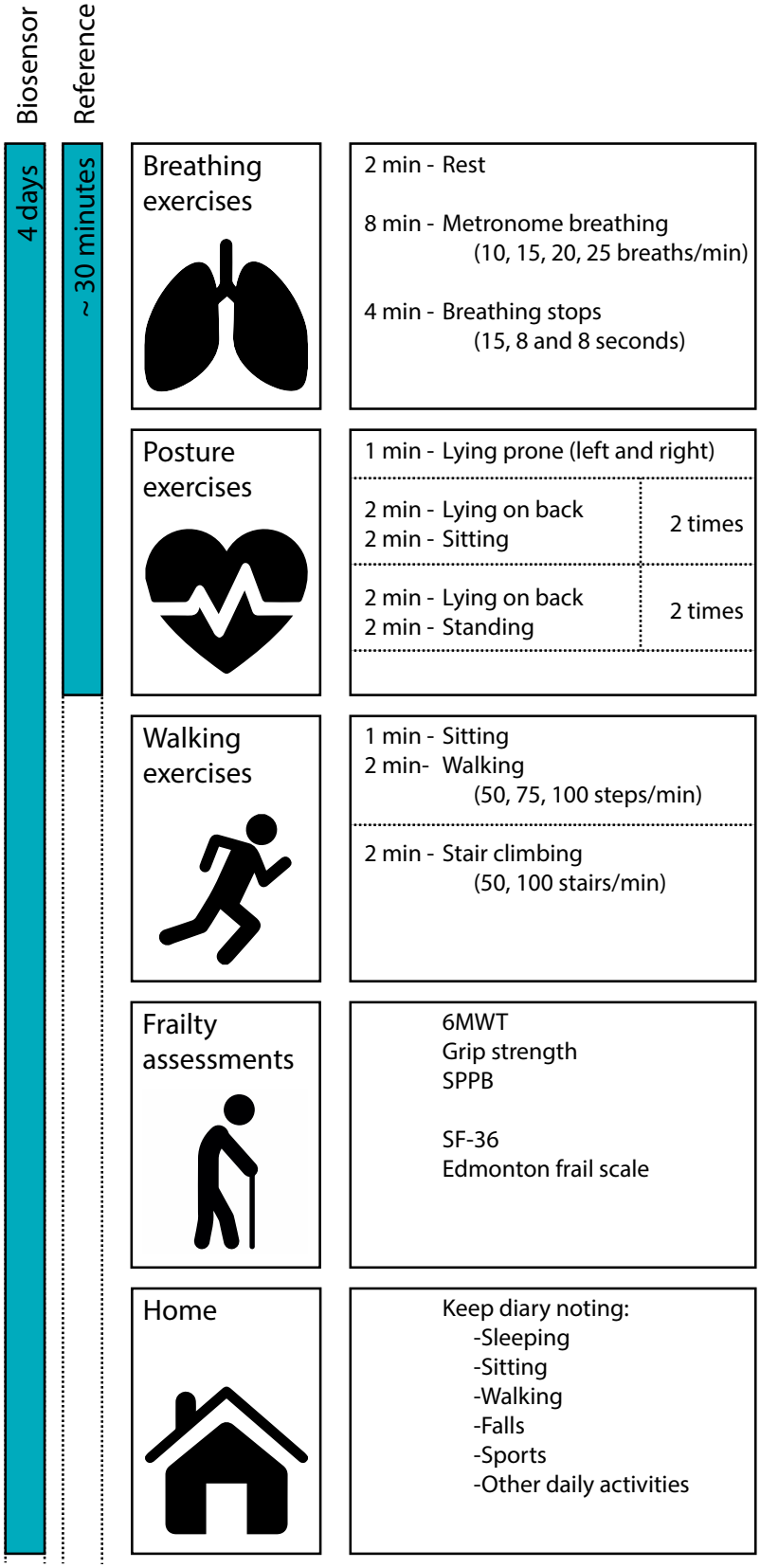


Figure 3.3 *Protocol overview of healthy subjects, including breathing exercises, posture test, exercises, frailty assessment.*
6MWT: six-minute walk test; SF36: Short Form (36) Health Survey; SPPB: short physical performance battery

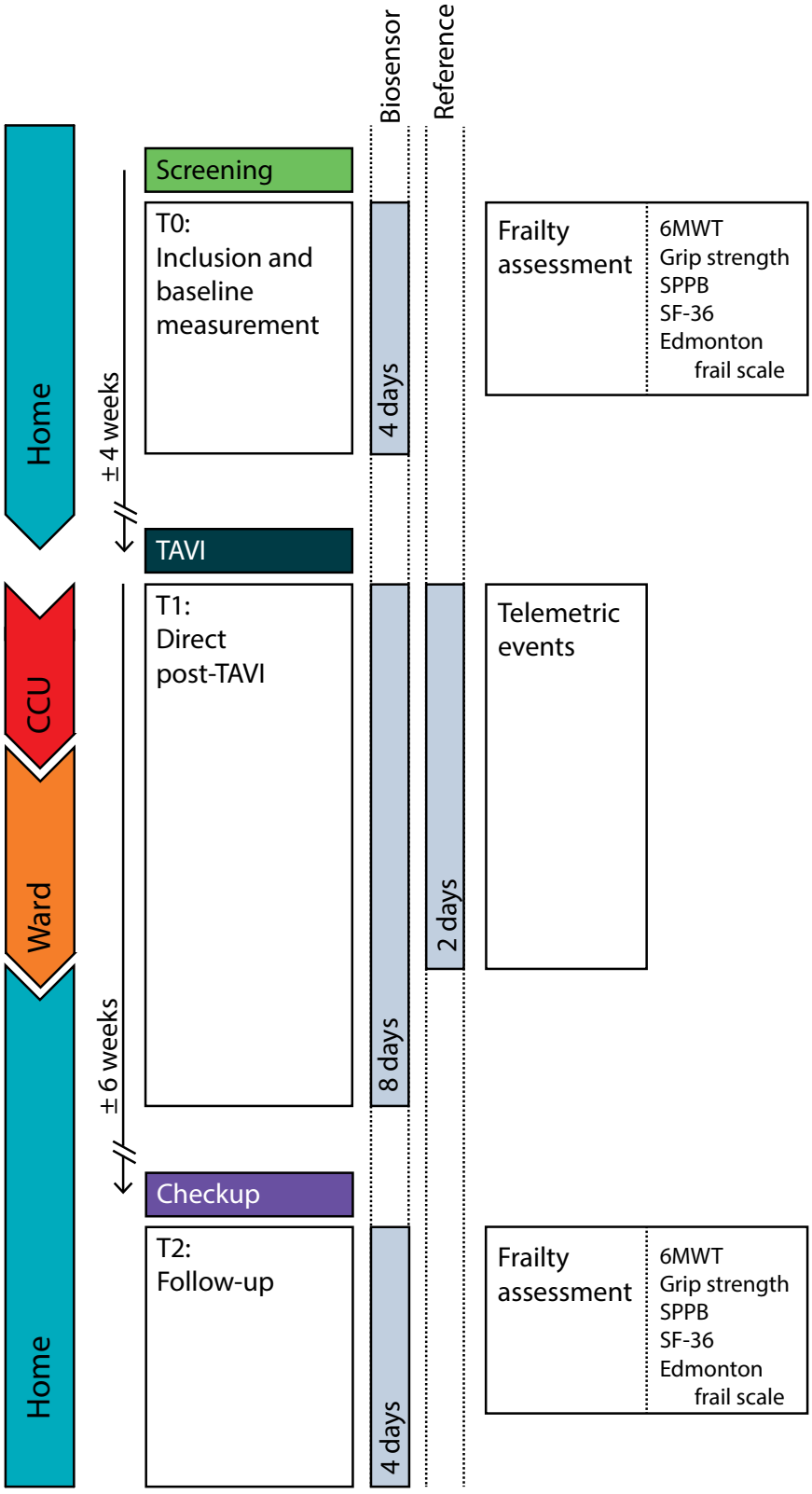


Figure 3.4 *Overview of TAVI patients' protocol. T0: Inclusion and baseline measurement; T1: Direct post-TAVI; T2: Follow-up. At the end of all measurements the PSSUQ and custom-made wearability questionnaire was filled in*

6MWT: six minute walk test; SF36: Short Form (36) Health Survey; SPPB: short physical performance battery; TAVI: transcatheer aortic valve implantation

Table 3.4 *Inclusion and exclusion criteria for the TELE-TAVI study for healthy subjects and TAVI patients.*

Inclusion criteria		
All subjects	**Healthy subjects**	**TAVI patients**
Older than 18 years old		
Able to follow instructions of smartphone and measurement set-up		
Able to provide written consent		
		In work-up for TAVI procedure
		Independent at home or helped by an informal care giver
Exclusion criteria		
All subjects	**Healthy subjects**	**TAVI patients**
Subjects with implanted devices, such as a pacemaker or implantable cardioverter-defibrillator		
Subjects with a damaged or very vulnerable skin around the patch location		
Subjects known with allergy to silicone or hydrocolloid adhesives		
Subjects with a cognitive impairment or inability to understand and follow-up instructions from the researcher and smartphone		
	Subjects with known heart disease	
	Subjects with severe chronic illnesses	Unlikely to get transfemoral TAVI, due to anatomical variations

Table 3.5 *Overview TELE-TAVI study parameters*

	T0	**T1**	**T2**
	Pre-TAVI	**Direct post-TAVI**	**6 weeks after TAVI**
Informed consent	x		
Demographics	x		
Medical history	x		
Risk scores	x		
Biosensor monitoring	4 days	8 days	4 days
High-end monitoring		x	
Frailty	x		x
- *Grip strength*	x		x
- *SPPB*	x		x
- *6MWT*	x		x
- *Edmonton frailty scale*	x		x
SF-36	x		x
Wearability questionnaire	x	x	x
- *PSSUQ*	x	x	x
- *Custom made*	x	x	x

TAVI patients

Eligible patients registered for TAVI workup were asked by phone if they would participate in the study. Patients who were considered for the study were independent at home or helped by an informal caregiver and able to follow instructions of the smartphone. Exclusion criteria were patients with implanted devices, such as pacemakers and implantable cardioverter, damaged or vulnerable skin around the patch location, allergy to silicone or hydrocolloid adhesive materials were excluded from the study. All in- and exclusion criteria are summarized in Table 3.4. Patients' enrolment was on the day of the TAVI workup diagnostic computed tomography, after written informed consent was obtained.

The biosensor patch was applied at three different time-points; pre-operative (T0), direct post-TAVI after the procedure (T1) and at follow-up (T2) (Figure 3.4):

T0: The pre-operative measurement started the day the informed consent of the patient was obtained. After application of the biosensor, physical functioning and frailty was examined with grip strength, 6MWT and the SPPB. Hereafter, patients resumed their daily activities and wore the biosensor until the battery ran out or biosensor fell off with a maximum of four days.

T0: Direct post-procedural measurements started when patients were admitted to the cardiac care unit after the TAVI-procedure. First, the Philips biosensor was attached to the patient and the reference monitor was connected for about two hours by the researchers. Patients received an additional biosensor and were asked to replace the biosensor themselves or with help from an informal caregiver.

T0: Four to twelve weeks after TAVI a biosensor was applied by one of the researchers. Physical functioning and frailty was again examined with the grip strength, 6MWT and the SPPB.

At every measurement time-point, patients received a small kit containing supplies for the study; a phone charger, an instruction booklet, a return envelope, and post-measurement wearability questionnaires (PSSUQ and custom made). At T1, the kit contained an additional replacement biosensor and an alcohol wipe. After each measurement the phone, charger, (un)used biosensor(s) and questionnaires were mailed back to the researchers. An overview of all the TAVI patients study parameters can be found in Table 3.5.

3.3. Discussion

The TELE-TAVI study is designed to assess the feasibility and usability of the Philips biosensor in TAVI patients. TAVI workflow could be improved by remote patient monitoring with a patch, by enhancing screening, post-TAVI monitoring and TAVI follow-up. Analysis should provide whether the wearable biosensor can be used for objective frailty outcomes, clinical symptoms of AoS, activity and cardiac monitoring.

To this day, no clinical study reviewed the usability of sensor technology in TAVI patients. However, the added value of a wearable system for post-TAVI monitoring is described by, Hermans et al.[32]. Recently a study was started to implement remote patient monitoring post-TAVI, as addition to standard care[33]. Still, the TELE-TAVI study is the first study in TAVI patients to address screening and follow-up improvements with sensor technology. Next to that, the TELE-TAVI study likely provide useful feedback for further development of the Philips wearable biosensor.

The TELE-TAVI study is a pilot to address the feasibility of using the wearable biosensor in a larger study population. Statistical power of this study will consequently be small and most of the results will be used to form hypotheses. After careful evaluation of the TELE-TAVI studies results, an additiaonal study will be needed to prove the clinical value of remote patient monitoring.

Chapter 4: Patient characteristics before and after transcatheter aortic valve implantation: First results of the TELE-TAVI study.

4.1. Introduction

Transcatheter aortic valve implantation (TAVI) is an established intervention for intermediate to high mortality risk patients with severe aortic valve stenosis [25]. Currently, routinely used screening scores are not sufficient for screening TAVI patients, as frailty is not included [35], [36]. Next to that, nowadays, telemetry after TAVI confides the patient to the hospital. Furthermore only limited support is available after discharge from the hospital. Sensor technology could improve TAVI workflow in screening, monitoring and follow-up of TAVI patients.

The TELE-TAVI study is started to evaluate the usability and feasibility of a wearable sensor for TAVI workflow: screening, monitoring and follow-up of TAVI patients (Chapter 3). This chapter will present the first results of the TELE-TAVI study.

4.2. Method

The TELE-TAVI study is prospective investigator initiated study, in the Amsterdam UMC (location AMC, Amsterdam, The Netherlands). The study, included healthy volunteers and patients in work-up for TAVI. The local ethics committee evaluated and approved the study design to national and international standards. The design and rationale of the TELE-TAVI is elaborately described in Chapter 3. Here a brief summary of the study will be given.

4.2.1. Devices

The Philips wearable biosensor (Philips Medical System, Andover, Massachusetts, USA) with the Research Kit (Philips Medical System, Andover, Massachusetts, USA) was used for remote patient monitoring. The biosensor is a lightweight, medical degree, patch that can measure vital signs and posture for up to four days. The Research Kit, consist of a mobile phone (Kyocera BRIGADIER), pre-installed with a dedicated application. Reliability of the biosensors vital signs was compared to a standard care monitor of Philips (Philips MP70 monitor, Philips Healthcare, Eindhoven, the Netherlands.

4.2.2. Study population

Healthy subjects

Healthy volunteers were enrolled in the study to test the system technically and to gain experience with the system. Subjects older than 18 years and able to follow instruction of the smartphone were asked to voluntarily cooperate in the study. Exclusion criteria were subjects with heart disease, or other severe chronic illnesses, implanted cardiac devices, an allergy to silicone of hydrocolloid adhesives or damaged or very vulnerable skin at the patch location.

After written consent was obtained, a wearable biosensor was adhered to the chest. Hereafter, breathing, posture and walking exercises were performed. Also physical functioning was tested with the 6 minute walk test (6MWT), short physical performance battery (SPPB) and grip strength. Additionally, 12 leads ECG was recorded and Edmonton frail scale and Short Form (36) Healthy Survey (SF36) were conducted.

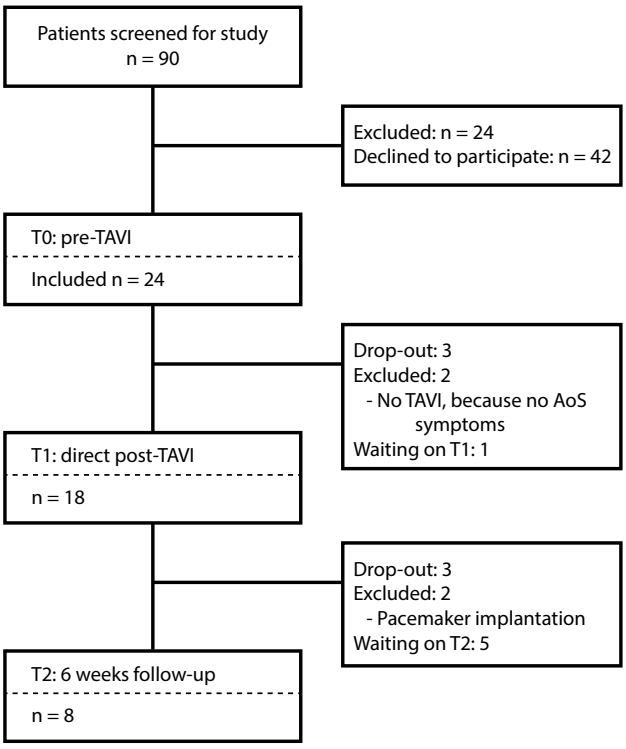


Figure 4.1 *. Study flow diagram of the patients screened for the study. One patient is waiting for a TAVI procedure and five patients are waiting for a follow-up appointment*

Table 4.1 *Drop-out reasons for ten TAVI-patients*

Subject number	Reason	Timing drop out
206	Difficulties with measurements (sensor detachment and problems charging phone), resulting that participation was too much effort	After T1
208	Excluded by researchers as patient detached sensor prematurely after TAVI	During T1
210	Experienced to many, disturbing audible warnings by the phone	After T0
211	Not willing to participate after deterioration post-TAVI	After T1
212	Burden of study too high in combination with transaortic TAVI	After T0
214	Impact of wearing phone too high	During T0
219	Pacemaker implantation	During T1
221	Pacemaker implantation	During T1
223	No symptoms AoS and therefore no TAVI	After T0
224	No symptoms AoS and therefore no TAVI	After T0

TAVI indicates transcatheter aortic valve implantation

TAVI patients

Eligible patients registered for TAVI workup were asked by phone if they would participate in the study. Patients who were considered for the study were independent at home or helped by an informal caregiver and able to follow instructions of the smartphone. Exclusion criteria were implanted devices, such as pacemakers and implantable cardioverter-defibrillator, damaged or vulnerable skin around the patch location, allergy to silicone or hydrocolloid adhesive. Patients' enrolment was on the day of the TAVI workup diagnostic computed tomography, after written informed consent was obtained.

The biosensor patch was applied at three different moments; pre-operative (T0), direct post-TAVI after the procedure (T1) and at follow-up (T2), as shown in Figure 3.4. Physical functioning was assessed at T0 and T2 with the 6MWT, SPPB, grip strength, SF36 and Edmonton frail scale. At every measurement moment, patients received a small kit containing supplies for the study, as well as user-experience questionnaires (PSSUQ and custom made). After each measurement the phone, charger, used biosensor(s) and filled in questionnaires were mailed back.

4.2.3. Statistical analysis

Baseline characteristics of the included TAVI-patients is compared with all screened patients during the inclusion period (June 2018 and February 2019). Grip strength is separated into three groups, stronger, average and weaker, correcting for age and gender following Dodds et al. [37]. Difference in the mean between the groups are tested with a student t-test for continuous variables. To compare the difference in the mean in the proportions of medical history a z-test is used. Characteristics of TAVI-patients who completed measurement T0 and T2 are compared for significant differences and continuous variables are analyzed with the paired t-test. Categorical variables (CCS, NYHA) are tested with Chi-squared test. For the TELE-TAVI study a significance level of 0.05 is chosen.

Table 4.2 *Averaged result of the biosensors precision and bias for HR and RespR, compared to unfiltered and filtered reference monitor, in the healthy subjects and TAVI population with and without atrial fibrillation.*

Characteristics	**TELE-TAVI**		**All TAVI-patients**		
	n = 24		n = 176		p-value
Age	76.6	(± 4.8)	78.8	(± 7.5)	0.15
Male	18	(75 %)	87	(50 %)	**0.02***
BMI	28.0	(± 5.6)	27.4	(± 5.0)	0.57
Medical history					
- Hypertension	16	(67 %)	99	(56 %)	0.33
- Atrial fibrillation	6	(25 %)	51	(29 %)	0.98
- COPD	1	(4 %)	13	(7 %)	**<0.001***
- Diabetes	6	(25 %)	50	(28 %)	0.73
NYHA:					**<0.001***
- I	2	(10 %)	18	(10 %)	
- II	12	(60 %)	42	(24 %)	
- III	6	(30 %)	106	(60 %)	
- IV	0	(0 %)	10	(6 %)	
CCS:					**<0.001***
- No angina	17	(77 %)	2	(1 %)	
- Grade I-II	4	(18 %)	119	(68 %)	
- Grade III	0	(0 %)	21	(12 %)	
- Grade IV	1	(5 %)	24	(14 %)	
METS	6.3	(± 1.4)	5.6	(± 1.5)	**0.03***
Logistic EuroSCORE I	8.8	(± 7.2)	13.7	(± 9.3)	**0.01***
EuroSCORE II	1.8	(± 1.7)	4.2	(± 3.3)	**0.001***
STS (mortality score)	2.0	(± 1.2)	4.2	(± 2.6)	**<0.001***

BMI indicated body mass index; NYHA, New York Heart Association; CCS, Canadian Cardiovascular Society grading of angina pectoris; COPD, chronic obsturctive pulmonary disease; EuroSCORE European System for Cardiac Operative Risk Evaluation;METS, Metabolic equivalent score; STS, Society of Thoracic Surgery predicted risk of mortality;
** significant difference*

4.3. Results

4.3.1. Healthy subjects

During the period of June to September 2018, six healthy subjects volunteered to participate in the study and all completed the study protocol. The subjects are averaged 41 (29-35) years old, have a BMI of 26 (22-30) and 50% is male. In one subject (103), an error of the Research Kits mobile app occurred; the mobile phone was unable to reconnect to the biosensor. As solution, a new phone was given. In three subjects (102, 103 and 106), the patch detached within three days, in which two subjects (103 and 106) attached a new sensor.

4.3.2. TAVI patients

At February 22nd, 2019, 90 patients in work-up for TAVI were screened of which 24 were included (Figure 4.1). Ten subjects dropped out of the study, for varying reasons, which can be found in Table 4.1. In total, 50 measurements are made, of which two data set are lost (206-T0 and T1), due to accidental deletion of the files and loss of biosensors ECG. In 18 patients, a measurement with the reference is available, in which for one patient (208) data were not recorded for two leads and excluded from further analysis. In 2 other patient (213 and 217), lead aVL was recorded instead of aVF. An overview of the retrieved data can be found in Appendix A.1.

Table 4.2 summarizes the patient characteristics at baseline (T0), compared to the all patients screened for TAVI during the inclusion period. The study population is 76.6 (± 4.8) years old, the screened TAVI-population 78.8 (± 7.5). Patients included are predominantly male (77%), which differs significantly from the general TAVI-population in which half is male. Included TAVI patients significantly have lower mortality risk scores, compared to the general population. Patients have higher METS scores, compared to overall TAVI-screening group. Other baseline characteristics are summarized in Table 4.3 The SPPB score show that 46% of the population is not frail and 50% is pre-fail and 4% is frail. The average distance walked in 6 minutes is 409 (± 89) meter. The grip strength is reduced in 8% of the TAVI patients and overall SF36 result is 62%.

Table 4.3 *Baseline characteristics, SF36 and frailty measures, for included TELE-TAVI patients.*

Characteristics	**TELE-TAVI** n = 24	
Quality of life (SF36)		
- Overall	62%	(± 14%)
- Physical functioning	61%	(± 24%)
- Social functioning	78%	(± 23%)
- Limitation of function	56%	(± 43%)
- Limitation of emotions	65%	(± 44%)
- Vitality	73%	(± 19%)
- Mental health	57%	(± 18%)
- Pain	80%	(± 19%)
- General health	54%	(± 18%)
- Health change	33%	(± 20%)
6MWT (distance, m)	409	(± 89 m)
Grip strength	34.0	(± 89.1)
- Male average (kg)	37.7	(± 7.6)
- Female average (kg)	22.7	(± 3.8)
- Stronger[+]	5	(21 %)
- Average[+]	17	(71 %)
- Weaker[+]	2	(8 %)
Edmonton frail scale	3.1	(± 2.4)
- Not frail (0 - 5)	15	(79 %)
- Vulnerable (6 - 7)	4	(21 %)
- Mild frail (8 - 9)	0	(0 %)
- Moderate frail (6 - 7)	0	(0 %)
- Severe frail (12 - 17)	0	(0 %)
SPPB	9	(± 2.7)
- Not frail (> 9)	11	(46 %)
- Pre-frail (4 - 9)	12	(50 %)
- Frail (< 4)	1	(4 %)

6MWT indicates six minute walk test; kg, kilogram; SF36, Short Form (36) Health survey; SPPB, Short Physical Performance Battery.
[+] Classified by Dodds et al. [37]

Table 4.4 shows the study parameters for patients who completed both the screening (T0) and follow-up (T2) measurement. The grip strength is significantly reduced after the TAVI, from 38 (± 9) to 34 (± 11) kg. Significant increase is found in the SF36 health change domain, which compares the current perceived health with a year before.

Table 4.4 *Pre- and post-study variations in patients included in TELE-TAVI that completed follow-up (T2).*

Characteristics	**T0**		**T2**		
	n = 8		n = 8		p-value
NYHA:					[a]
- I	2	(10 %)	2	(33 %)	
- II	12	(60 %)	3	(15 %)	
- III	6	(30 %)	1	(17 %)	
- IV	0	(0 %)	0	(0 %)	
CCS:					[a]
- No angina	17	(77 %)	7	(100 %)	
- Grade I-II	4	(18 %)	0	(0 %)	
- Grade III	0	(0 %)	0	(0 %)	
- Grade IV	1	(5 %)	0	(0 %)	
Quality of life (SF36)					
- Overall	62 %	(± 14 %)	61 %	(± 12 %)	0.56
- Physical functioning	70 %	(± 20 %)	63 %	(± 33 %)	0.77
- Social functioning	70 %	(± 22 %)	67 %	(± 30 %)	0.68
- Limitation of function	50 %	(± 50 %)	38 %	(± 46 %)	0.70
- Limitation of emotions	52 %	(± 50 %)	79 %	(± 40 %)	0.33
- Vitality	53 %	(± 14 %)	57 %	(± 26 %)	0.39
- Mental health	66 %	(± 21 %)	73 %	(± 26 %)	0.57
- Pain	76 %	(± 14 %)	67 %	(± 30 %)	0.50
- General health	48 %	(± 16 %)	53 %	(± 23 %)	0.34
- Health change	28 %	(± 16 %)	56 %	(± 32 %)	**0.04***
6MWT (distance, m)	391	(± 108)	445	84	0.13
Grip strength	38	(± 9)	34	(± 11)	**0.02***
- Male average (kg)	41	(± 6)	38	(± 10)	0.09
- Female average (kg)	27	(± 1)	22	(± 3)	0.32
- Stronger	3	(37 %)	3	(37 %)	
- Average	5	(63 %)	3	(37 %)	
- Weaker	0	(0 %)	2	(26 %)	
Edmonton frail scale	2.5	(± 2)	3.5	(± 2.7)	0.39
- Not frail (0 - 5)	5	(83 %)	5	(83 %)	
- Vulnerable (6 - 7)	1	(17 %)	0	(0 %)	
- Mild frail (8 - 9)	0	(0 %)	1	(17 %)	
- Moderate frail (6 - 7)	0	(0 %)	0	(0 %)	
- Severe frail (12 - 17)	0	(0 %)	0	(0 %)	
SPPB	10	(± 2)	10	(± 1)	0.70
- Not frail (> 9)	4	(57 %)	5	(71 %)	
- Pre-frail (4 - 9)	3	(43 %)	2	(29 %)	
- Frail (< 4)	0	(0 %)	0	(0 %)	

6MWT indicates six minute walk test; CCS, Canadian Cardiovascular Society grading of angina pectoris; NYHA indicates New York Heart Association; SF36, Short Form (36) Health survey; SPPB, Short Physical Performance Battery.

[+] *Classified by Dodds et al. [37]*

*** Siginificant change*

[a] *No p-value unavailable as one category has zero patients in both T0 and T2 (NYHA IV, CCS Grade III)*

4.4. Discussion

The TELE-TAVI study is designed to evaluate the Philips wearable biosensors usability and feasibility in TAVI patients, pre- and post-TAVI as well as at follow-up. It is the first non-commercial study of the Philips wearable biosensor. This chapter presents the first results of the TELE-TAVI study.

The TELE-TAVI is a small pilot study, but less patients agreed to participate than expected. The study was designed to minimize the participation burden, as additional hospital visits are not needed. Next to that, the wearable biosensor is considered non-invasive. However, low inclusion rates are likely caused as patients were not experienced with mobile phone use and and find handling a phone a daunting taks.

Overall, the population in this study is younger, includes more men, which have less comorbidities, a better functional status and lower risk scores, compared to other reports (81-83 years old; 32.5-46.6% men; 67.6-81.6% hypertension, 34.6-41.2% atrial fibrillation, 24.6% COPD; STS-score of 4.0-6.1 and EUROSCORE II of 3.7-5.1) [38], [39]. When compared to all patients that are screened for TAVI, included patients have lower mortality risk and better functional capacity, but age is not significantly different. The reported lower age is likely caused by a shift to younger TAVI patients, as reported by Kesteren et al. [38].

Less data is available to compare the health surveys (SF36 and Edmonton frail scale), functional status (SPPB) and physical function (6MWT and grip strength), to other studies with aortic valve stenosis patients. However, patients in this report performed much better on all domains (SF36 score of 26.1-43.3% [40], 24% frail TAVI patients by the Edmonton frail scale [41]; SPPB score of 8.2 +- 3.2 [42] and 6MWT distance of 72-240 meter [40]). Notable is that the patient population in all reports are older, which could account for some of the differences. However, it seems that only patients with a better health status were willing to participate in the study. This is cause for careful interpretation of the study results, as the study population is not representative for the general TAVI population.

Surprising result was the significant decrease of grip strength post-TAVI. Grip strength is indicator for muscle mass in elderly. The decrease in grip strength, could be attributed that patients were not yet fully recovered from the procedure. Next to that, a siginifant improvement was found in the health change domain of the SF36, indicating that patients are feeling better than compared to a year ago. However, there was no significant change found in the general health domain and therefor this should be carefully interpreted.

Although, the population does not represent a real-world TAVI population, much can be learned from the TELE-TAVI study. Biosensors parameters are collected at screening, monitoring and at follow-up of TAVI patients and will show potential possibilities, improvements and limitations of the Philips wearable biosensor in TAVI workflow

Chapter 5: Reliability of the Philips wearable biosensor in monitoring vital signs and activity

5.1. Introduction

Wearable wireless sensing is an upcoming technology for measuring vital signs continuously and unobtrusively. They can change the field of patient monitoring, screening and follow-up, at home and in-hospital. It possibly allows for sooner hospital discharge, earlier deterioration detection and can play a role in personalized health. However, implementing this technology in every day healthcare remains a challenge as knowledge of the reliability, involving the accuracy of measured data and consistency of continuous data collection, of these systems is limited [43].

Only few studies review the reliability of wearable sensors [43]. Not a single study is published on the reliability of the biosensor (Philips Medical System, Andover, Massachusetts, USA) and only few on its predecessor, the HealthPatch MD (VitalConnect, San Jose, California, USA), which has the same firm- and hardware [21]–[23].

Only one independent in-hospital study is published, reviewing the HealthPatch reliability of the measured heart and respiratory rate (HR, RespR, respectively), in 25 patient on a surgical step down unit [21]. They showed the HealthPatch can accurately measure HR (within 10% error), but the RespR was not reliable compared to bedside impedance pneumography. With a 15 minute median filter, the accuracy of the RepsR improved. Similar results were found by an in-house research [44]. Data were available in 94% of the time and in halve of the patients there was no data interruption.

Validation research of HR, RespR and activity measured by the HealthPatch was done by VitalConnect in 25 healthy people [22]. Accurate HR was measured in rest and during activities of daily living. Also RespR was accurate during metronome breathing, compared to a capnograph. Yet it must be noted only a third of the RespR data was compared and only at the places the breathing rate was most constant. The error in RespR increased in spontaneous breathing and during activities of daily living. Nonetheless, it showed that the combined respiratory rate estimation with ECG and acceleration (as described in Chapter 3) was far superior than one modality estimation [23].

On the accuracy of the posture and activity of HealthPatch only little data is published. Research from VitalConnect showed that posture detection was 80.1% accurate in an test environment [22], but details on the study protocol are missing. Additionally, step count analysis of the Health Patch was similar to manually counted steps, but appeared sensitive to ‘step-like’ moves, for example cycling. Falls were detected in 92.5% in simulated falls and no false positive falls were detected during other simulated daily activities.

In short, research on the reliability of the wearable biosensor is limited and focuses more on vital signs, such as HR and RespR. It appears that HR is measured accurately by the HealthPatch, but RespR validation showed varying results. Very limited research is reported on the validity of the activity or posture detection and needs more attention. This chapter validates the accuracy of the HR and RespR, the reliability of posture detection and continuous data collection of the wearable biosensor.

5.2. Method

Reliability assessment of the Philips wearable biosensor is part of the TELE-TAVI study, which reviews telemedicine in transcatheter aortic valve implantation intervention workflow. In the TELE-TAVI study 6 healthy volunteers and 24 TAVI-patients participate. All patients provided written informed consent. The protocol is extensively described in Chapter 3 and a relevant summary will be given here.

TAVI patients received the wearable biosensor thrice; before the TAVI procedure (T0), directly after the TAVI procedure on the cardiac care unit (CCU) (T1) and 6-weeks after the TAVI procedure (T2). At T0 and T2 patients performed the functional test (six minute walk test (6MWT), short physical performance battery and grip strength), while they were wearing the sensor. After the procedure (T1), patients were connected to a standard care monitor (Philips MP70 monitor, Philips Healthcare, Eindhoven, the Netherlands) as reference for the biosensor.

After signed written informed consent, the Philips wearable biosensor was attached to the healthy subjects. Hereafter, patients completed a protocol including breathing, posture and walking exercises. During the breathing and posture exercises, the reference monitor was connected. Next to that, functional test (6MWT, SPPB and grip strength) were performed. Hereafter, healthy subject resumed daily activities and kept a diary on their activities.

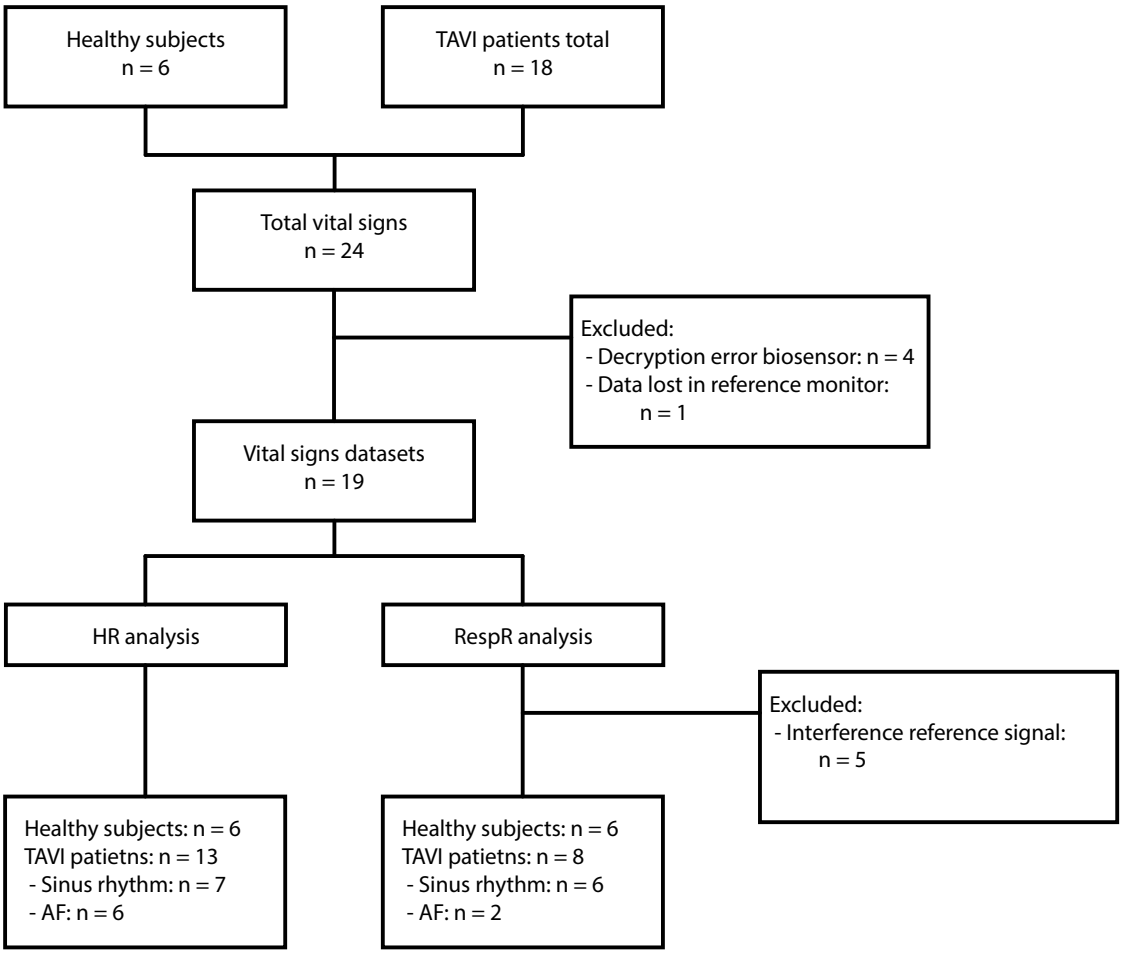
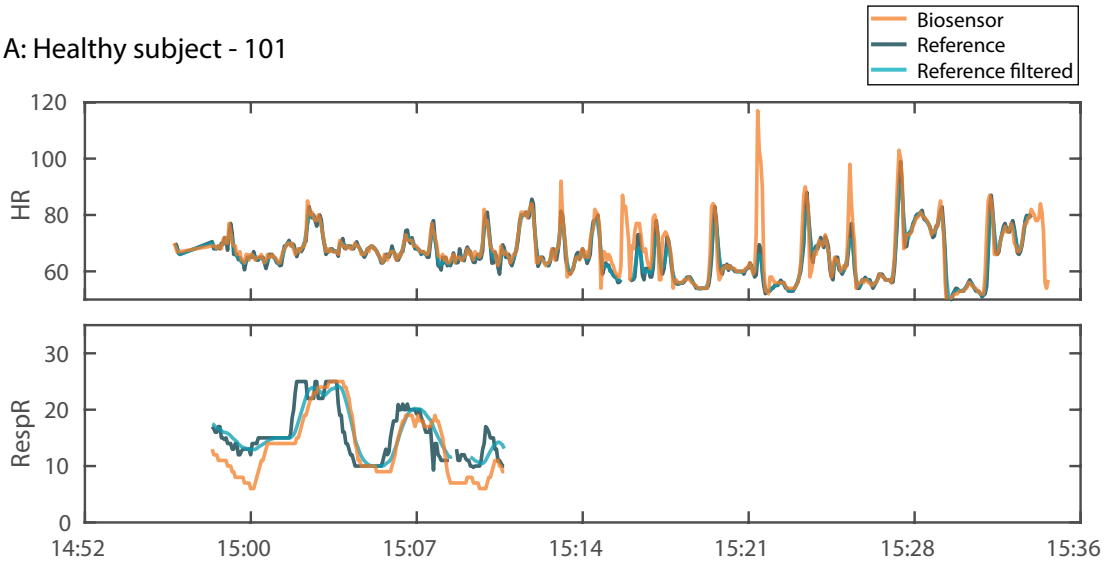


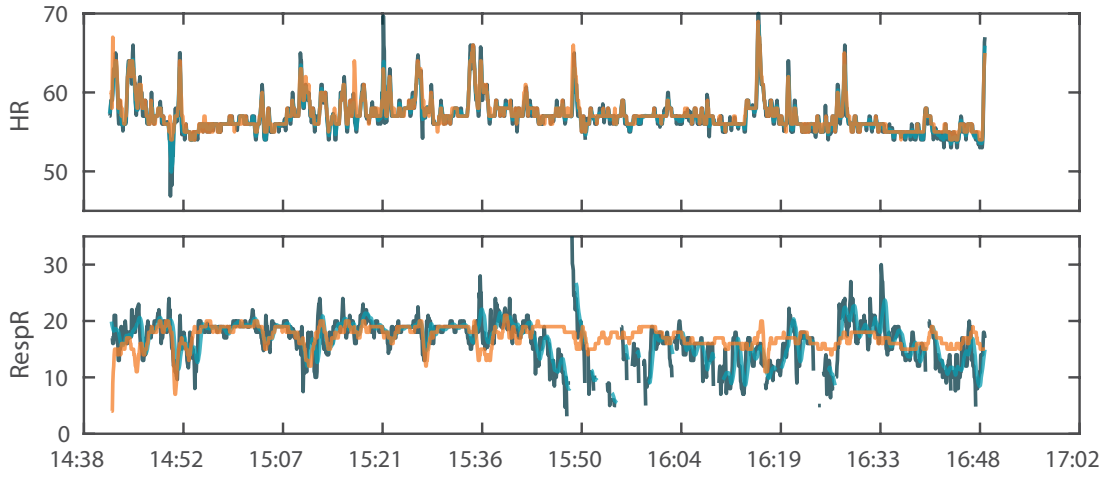
Figure 5.1 *Flowchart of vital signs datasets used for analysis of biosensors HR and RespR precision.*

Figure 5.2 *-Next page- Three examples, showing the HR and RespR of the biosensor and reference, not filtered and filtered. A: shows data of a healthy subject during the breathing exercises and posture changes, RespR is only shown during breathing exercises. B; gives the HR and RespR of TAVI patient directly post-TAVI (T1). Hereafter the RespR has a larger variance for reasons unknown. C: Shows HR and RespR data of TAVI-patient known with AF.*

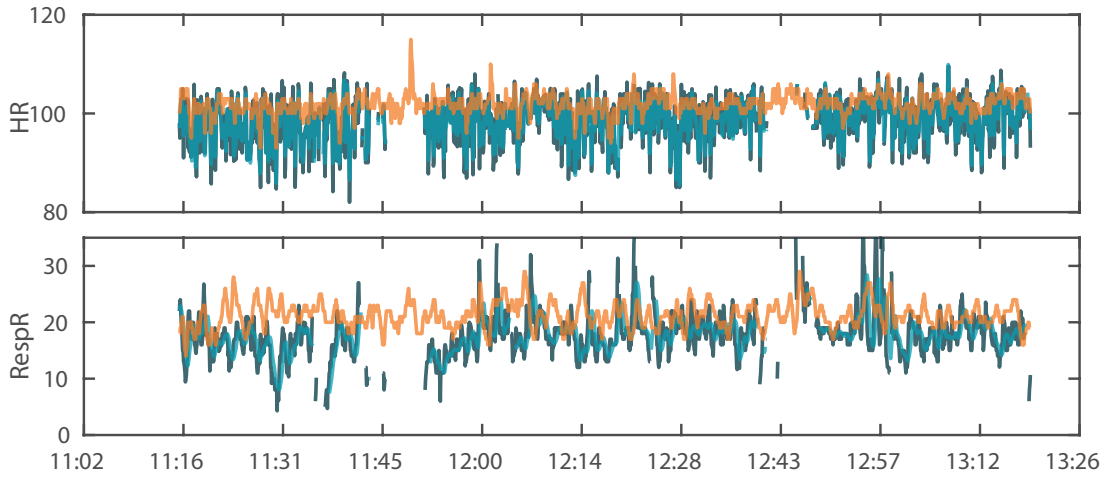
A: Healthy subject - 101



B: TAVI patient with sinus rhythm - 213



C: TAVI patient with AF - 219



5.2.1. Vital signs

To assess the reliability of the biosensors vital signs, HR and RespR from the biosensor was compared to the reference monitor. In healthy subjects the data from breathing exercises and posture test was used. Breathing exercises contains breathing normal , breathing at the rate of metronome and breathing stops, whilst sitting. During posture exercises, healthy volunteers were lying, sitting or standing for 2 minutes, which induced orthostatic heart rate changes. For the analysis of the RespR, only the breathing exercises were applied, as the reference experienced too much perturbations from the posture changes. From TAVI-patients, data of the direct post-TAVI measurement (T1) is used, during the time they were connected with the reference monitor. TAVI patients were subdivided into two groups, sinus rhythm or atrial fibrillation (AF), by reviewing telemetry results at the time the reference monitor was connected.

Table 5.1 *Skewness and kurtosis (± SD) of difference of the biosensors and reference filtered and unfiltered data.*

	Skewness		Kurtosis	
HR	1.4	(± 4.6)	10.9	(± 80.1)
HR filtered	1.9	(± 5.3)	48.9	(± 101.0)
RespR	-0.5	(± 3.3)	5.1	(± 3.3)
RespR filtered	-0.1	(± 2.0)	4.0	(± 2.0)

HR indicates heart rate; RespR, respiratory rate

Signal analysis

Data from the biosensor was decrypted using the Research Kit (Philips Medical System, Andover, Massachusetts, USA) and were retrieved in CSV format. From the reference monitor, data were saved in CSV format with ixTrend (ixellence GmbH, Wildau, Germany). All data were stored and processed using Matlab (The MathWorks, Natick, Massachusetts, USA). Missing data were interpolated with empty values (not-a-number).

Data of the two modalities were synchronized with a perturbation in the data induced by the researcher. Hereafter outliers bigger than 100 times the average were removed from the biosensors data. For the reference data outliers bigger than 10 or 5 times were removed in the HR and RespR, respectively.

The biosensor and reference monitor have different filter settings (Chapter 3), which will induce an error in the reliability analysis. As the biosensor has more extensive filtering, the data from the reference monitor was filtered more to mimic the biosensors filter settings. The biosensor HR has a 10-beat low-pass filter [22], which cannot be reproduced in the obtained data, since the reference HR is sampled at a regular frequency. To mimic this filter, first the HR of the reference monitor was averaged over the full recording. With this averaged HR, a window length was calculated that on average should contain 10 heart beats. The calculated averaging window was used in a moving average filter over the reference data. If more than 60% of the data were available, the HR was averaged over the filtered window, otherwise the sample was replaced by an empty value. Hereafter, the data of the reference was interpolated to the biosensors timestamp and empty values were discarded.

The biosensors RespR is averaged over a 45 second window [23]. This was imitated by computing the RespR for every biosensors sample with the previous 45 seconds. When 20% of the data were missing, the RespR was not computed but replaced with an empty value and discarded hereafter. The unfiltered reference RespR was interpolated to the biosensors timestamp.

The primary outcome was bias and precision of HR and RespR of the biosensor compared to the high-end monitor. Precision is computed as the reproducibility coefficient (RPC; 1.96*SD or 1.45*IQR) and limit of agreement (LOA), in which LOA is the bias ± RPC. This reference standard reports an accuracy for HR of ±1% beats/min and ±1% breaths/min for RespR [34]. HR and RespR were considered to be acceptable for clinical purposes if within ±10% or ±3 breaths/min of the reference monitor, respectively.

Distribution of the difference data (biosensor – reference) was checked with skewness and kurtosis, to determine whether parametric statistical analysis could be used. Skewness is a measure of the asymmetry of the data around the sample mean. If skewness is negative, the data are spread out more to the left of the mean. The skewness of the normal distribution (or any perfectly symmetric distribution) is zero. Kurtosis is a measure of how outlier-prone a distribution is and for a normal distribution equals 3. Distributions that are more outlier-prone than the normal distribution have kurtosis greater than 3; distributions that are less outlier-prone have kurtosis less than 3.

Table 5.2 *Averaged result of the biosensors precision and bias for HR and RespR, compared to unfiltered and filtered reference monitor, in the healthy subjects and TAVI population with and without atrial fibrillation.*

		n	Bias	RPC		Lower LOA	Upper LOA
			Beats/min	(%)	Beats/min	Beats/min	Beats/min
HR	Healthy	6	0.5 ± 1.0	3.1 ± 2.9	4.4 ± 4.5	-2.6 ± 1.6	3.5 ± 2.5
	TAVI	13	0.0 ± 3.2	2.9 ± 10.7	3.7 ± 9.3	-2.9 ± 7.2	2.9 ± 12.8
	- Sinus	7	0.0 ± 0.0	1.5 ± 1.2	2.6 ± 1.9	-1.5 ± 1.2	1.5 ± 1.2
	- AF	6	3.3 ± 3.0	12.2 ± 6.7	12.6 ± 6.1	-8.8 ±7.5	15.5 ± 9.2
	All	19	1.5 ± 3.3	5.4 ± 5.4	6.5 ± 5.9	-3.9 ± 4.5	7.0 ± 7.7
HR filtered	Healthy	6	0.5 ± 0.5	2.4 ± 2.4	3.5 ± 3.8	-1.9 1.3	2.9 ± 3.6
	TAVI	13	0.2 ± 3.1	1.8 ± 8.9	2.4 ± 7.9	-1.6 ± 5.8	2.0 ± 12.1
	- Sinus	7	0.0 ± 0.1	1.0 ± 0.4	1.7 ± 0.7	-0.9 ± 0.5	1.0 ± 0.4
	- AF	6	3.2 ± 3.5	10.4 ± 6.0	10.7 ± 5.1	-7.2 ± 7.5	13.6 ± 8.2
	All	19	1.5 ± 3.2	4.7 ± 4.5	5.7 ± 5.0	-3.1 ± 4.0	6.2 ± 6.8
			Breaths/min	(%)	Breaths/min	Breaths/min	Breaths/min
RespR	Healthy	6	-1.5 ± 0.9	8.1 ± 1.5	50.6 ± 10.6	-9.6 ± 2.1	6.6 ± 1.4
	TAVI	8	0.8 ± 1.6	7.9 ± 1.5	57.3 19.2	-7.0 ± 1.4	8.7 ± 2.8
	- Sinus	6	0.0 ± 0.8	7.4 ± 1.5	54.5 ± 21.0	-7.4 ± 1.4	7.4 ± 2.0
	- AF	2	3.2 ± 0.5	9.1 ± 0.2	65.6 ± 14.1	-5.9 ± 0.6	12.3 ± 0.3
	All	14	-0.2 ± 1.8	7.9 ± 1.5	54.4 ± 15.9	-8.1 ± 2.1	7.8 ± 2.5
RespR filtered	Healthy	6	-1.5 ± 0.9	6.2 ± 2.4	40.1 ± 14.3	-7.7 ± 2.8	4.6 ± 2.2
	TAVI	8	0.8 ± 1.6	6.4 ± 1.3	43.9 ± 12.5	-5.7 ± 1.2	7.2 ± 2.6
	- Sinus	6	0.0 ± 0.7	6.0 ± 1.2	41.7 ±13.7	-6.0 ± 1.1	6.0 ± 1.7
	- AF	2	3.1 ± 0.4	7.6 ± 0.4	50.7 ± 5.2	-4.5 ± 0.8	10.7 ± 0.0
	All	14	-0.2 ± 1.7	6.3 ± 1.7	42.3 ± 12.9	-6.5 ± 2.2	6.1 ± 2.7

RespR indicates respiratory rate; HR, heart rate, SD=Standard deviation; AF,Atrial fibrillation; TAVI,transcatheter aortic valve stenosis patients

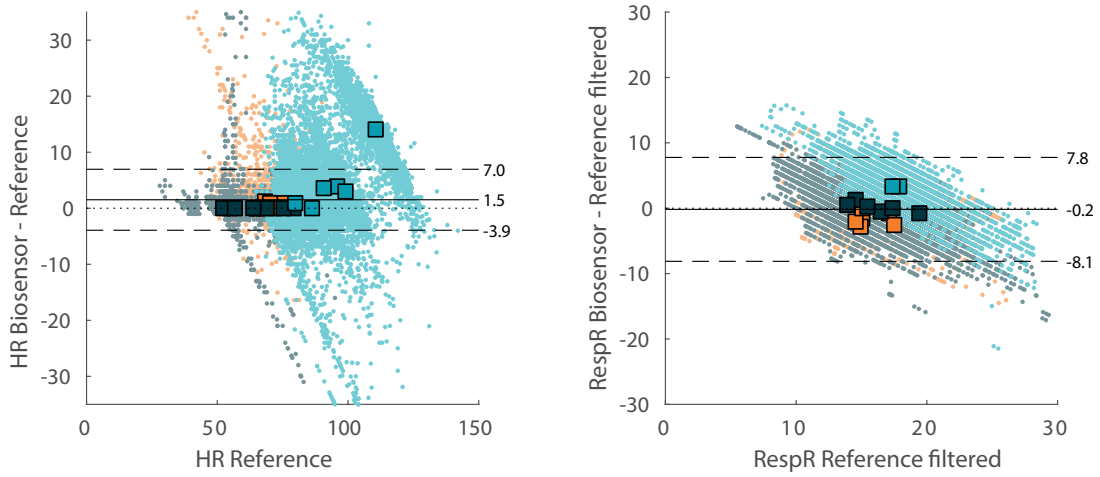


Figure 5.3 *Shows the averaged Bland-Altman figures comparing the biosensor with the reference, for all the subjects. Left HR is compared with the unfiltered reference HR and right RespR is compared with the filtered reference. The squares represent the averaged bias per patient, in which orange are healthy subjects and dark and light blue are TAVI patients with sinus rhythm and AF, respectively. The small faint dots are individual data points. In the left panel, the HR of the TAVI patients with AF is given.*

For all data, HR and RespR, filtered and unfiltered, the lag between the biosensor and reference data was estimated using cross-correlation.

5.2.2. Posture detection

Determining the reliability of the posture detection is more difficult as no gold standard is available. Therefore, posture detection is validated with observation. There are only a few postures detected by the biosensor, as shown in Figure 5.6. Of these postures, only walking was easily reviewed. Percentage of walking detected during the 6MWT was analyzed of healthy subjects and TAVI patients. Also the walking exercises of the healthy subjects were used. Walking should be detected more than 80% of the time. Other detection of posture was compared to the diaries of the healthy subjects. Hereof, multiple examples are selected to show the reliability of the biosensors posture detection.

5.2.3. Data collection

To examine the data collection reliability, biosensors data of the healthy subjects and the pre-TAVI (T0) and follow-up (T2) measurement was used. With this, the measurement reliability of one biosensor can be assessed. Measures for data collection reliability are, first point of data loss, total measured time and percentage of data loss. First point of data loss is defined as the first time point of a gap longer than 2 minutes, 15 minutes, 1 hour or 4 hours occurs. For this analysis the electrocardiogram (ECG) was used, as this has the highest sample frequency of the biosensors output, giving it the most accurate representation of the data loss due to connection failure. Total measurement time is the length of the biosensor measurement, which is expected to be 96 hours. Of the measurement time, at least 80% should be usable data, so recorded without any data loss.

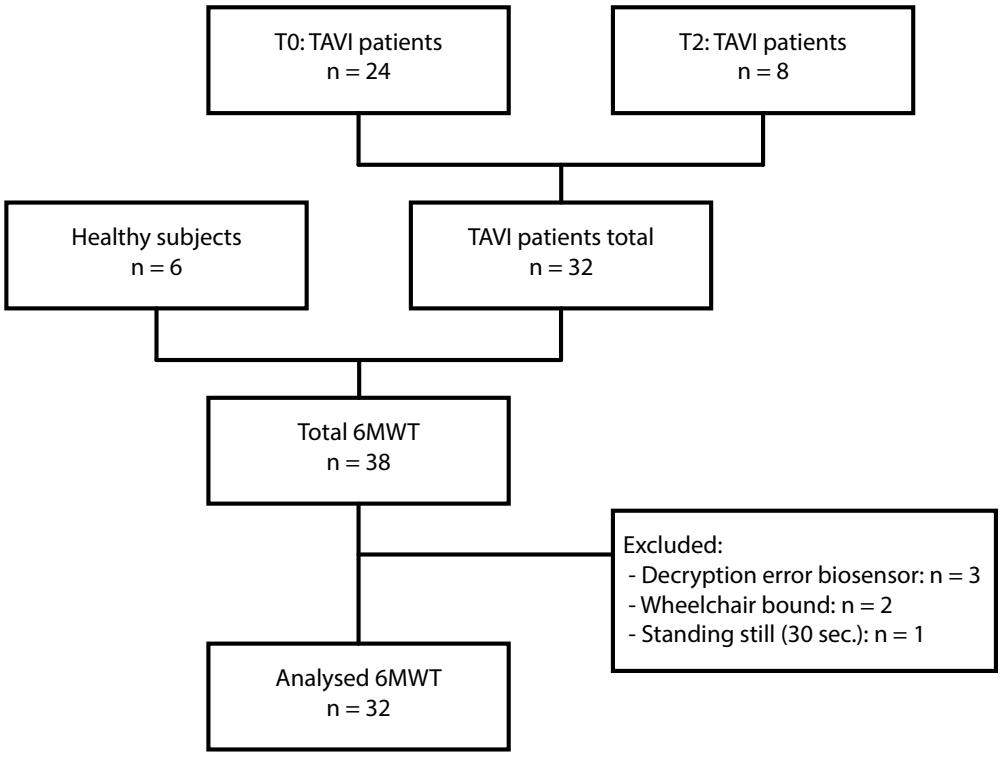
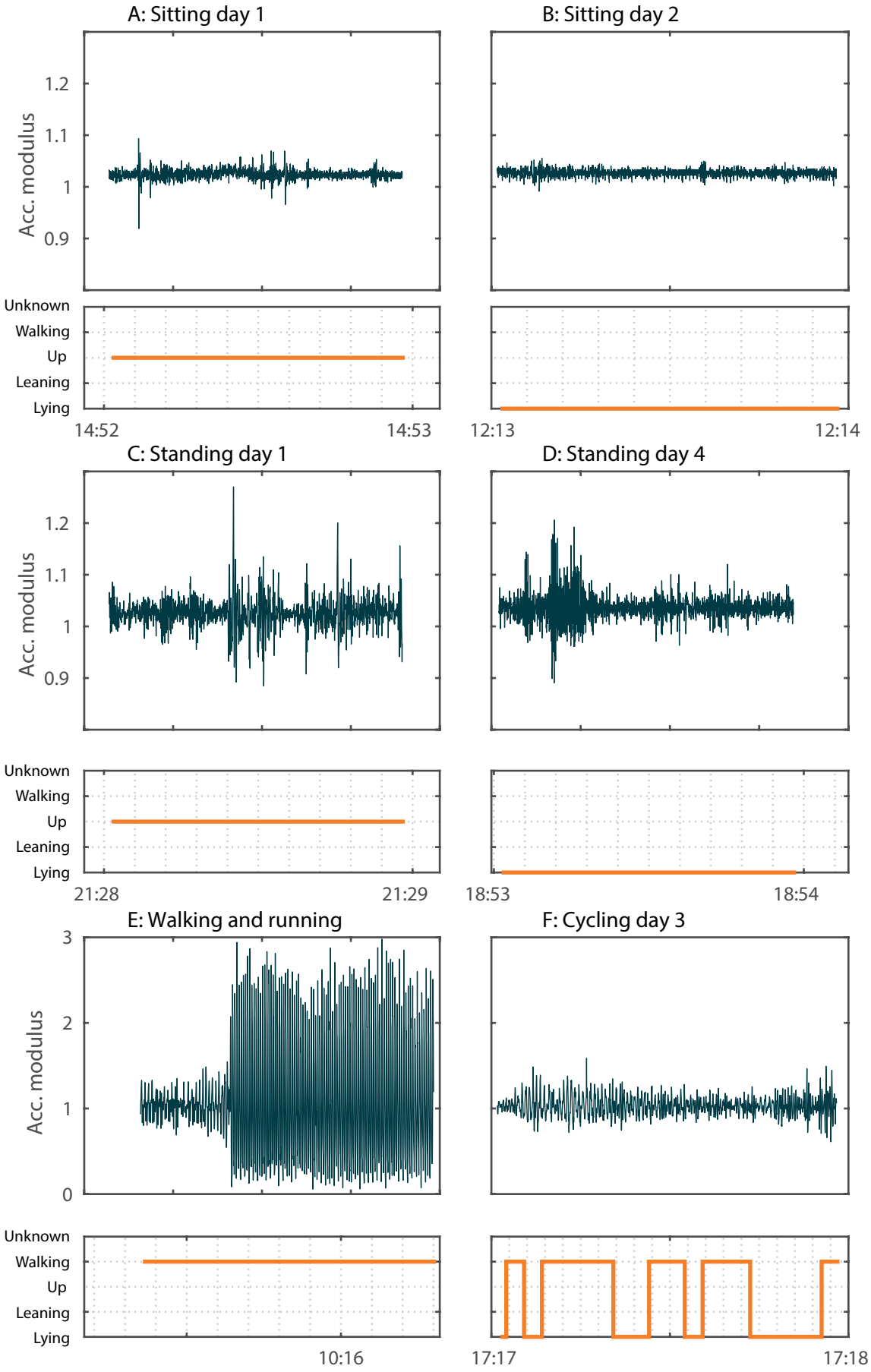


Figure 5.4 *Flowchart of 6MWT for walking detection analysis*

Figure 5.5 *-Next page- Shows acceleration modulus and activity classification for several activities as noted in the diary, during multiple days of subject 101. Panel A and B displays sitting, at day 1 and 2. Panel C and D, show standing at day 1 and 4. Panel E shows the data of walking and running. Panel F, illustrates that activity detection of cycling alternates between walking and lying*


A: Sitting day 1
B: Sitting day 2
C: Standing day 1
D: Standing day 4
E: Walking and running
F: Cycling day 3
Acc. modulus
Unknown
Walking
Up
Leaning
Lying
14:52
14:53
12:13
12:14
21:28
21:29
18:53
18:54
10:16
17:17
17:18

5.3. Results

5.3.1. Vital signs

In total, 24 datasets were available for the vital signs reliability analysis, of which 6 and 18 were datasets from the healthy subjects and TAVI patients, respectively. From the 18 TAVI patient datasets, 5 were not analyzed, as the biosensor data were not available due to decryption problems (4) or due to data loss in the reference (1). In the remaining TAVI-patients, 6 showed atrial fibrillation or flutter (AF) on the telemetry during hospital stay. Of all the TAVI-patients, 5 datasets were excluded in the analysis of the RespR, due to electrical interference of the respiratory impedance signal. Overall, there are 19 datasets for analysis, of which 6 from healthy subjects and 7 with AF. For RespR analysis, 14 datasets were used, containing 6 from healthy subjects and 2 AF TAVI-patient. An overview of the used data can be found in Figure 5.1

Figure 5.2 shows an example of the data used for analysis of the biosensors reliability for a healthy subject and two TAVI patients. In the healthy subject (Figure 5.2 A), shows large fluctuations in the second halve, caused by the orthostatic changes in HR. A large peak is visible in the biosensors HR at 15:21. The biosensors RespR shows lag, compared to the unfiltered reference (dark blue). There is no lag visible between the filtered reference and biosensors RespR. Lag was detected in the RespR of 4 TAVI-patients, which in 3 cases disappeared after filtering. Figure 5.2 B shows HR and RespR data of a TAVI patient with sinus rhythm. HR has a small range, but the biosensor HR are visually very similar to the reference HR. Around 15:50, the reference monitor RespR data is lost and unexpected peak is visible. This is probably caused by a movement artefact. The HR of the TAVI patient with AF (Figure 5.2 C) the HR is higher and variance is The HR variance in the reference is larger than of the biosensor.

Skewness and kurtosis was computed for the difference data (biosensor-reference), shown in Table 5.1. The kurtosis for HR is on average 10.9 (± 80.1) and 48.9 (± 101.0) difference data, for the unfiltered and filtered reference HR. Appendix A.2.1 had more detailed information on the distribution of the difference data.

Table 5.2 shows bias and precision, comparing the biosensor with the reference monitor. The bias in the unfiltered HR was 1.5 and LOA ranged between -3.9 (± 4.5) and 7.0 (± 7.7). The agreement between the biosensor and reference monitor is broader for TAVI patients with AF ([-8.8 ± 7.5 to 15.5 ± 9.2]). Filtering the reference HR did not change the outcome of agreement. The unfiltered RespR resulted in bias -0.2 and the LOA ranged from 8.1 (± 2.1) to 7.8 (± 2.5). Filtering the RespR narrowed the LOA to the range of -6.5 (± 2.2) and 6.1 (± 2.7). Figure 5.3 shows the averaged Bland-Altman figures for the unfiltered HR and filtered RespR. The bias and dispersion of individual data points is larger in AF subjects, than healthy subjects. The difference in biosensor and reference RespR disperses for all groups similarly. Appendix A.1.2 gives more detailed data on the precision and bias of the wearable biosensor.

Table 5.3 *Averaged results of the walking detection*

		n	Walking	
			Detected (%)	Speed (m/s)
Healthy	100 steps/min	6	99.4 ± 1.5	1.19 ± 0.08
	75 steps/min	6	74.8 ± 34.3	0.77 ± 0.09
	50 steps/min	6	0.8 ± 1.2	0.43 ± 0.12
	6MWT	6	99.8 ± 0.4	1.57 ± 0.13
TAVI	6MWT	25	96.5 ± 6.1	1.15 ± 0.26

6MWT indicates six minute walk tes; SD,standard deviation; km/h,kilometer per hour; TAVI, transcatheter aortic valve stenosis patients; n, number of subject

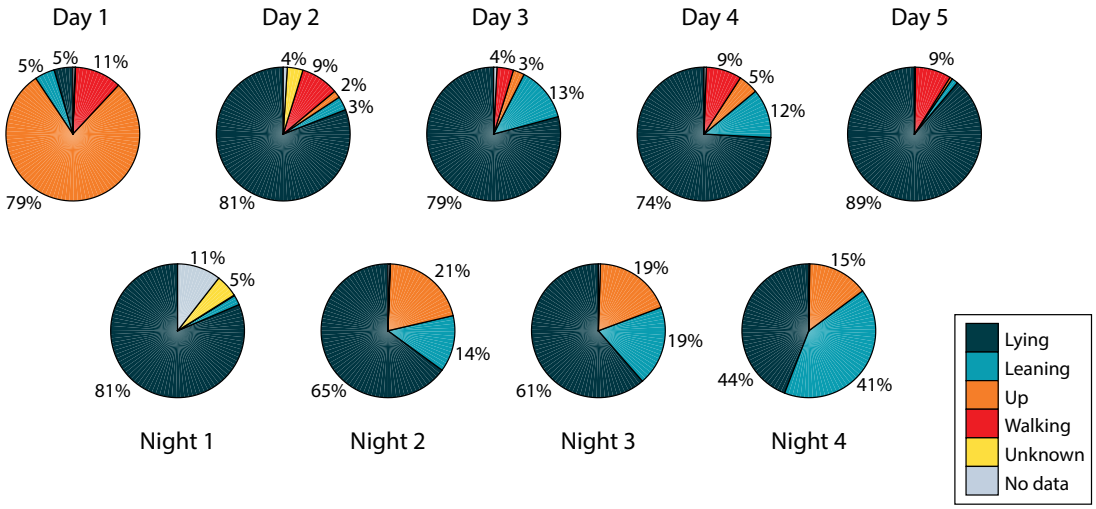


Figure 5.6 *Illustrates the activity classification of the biosensor during days and nights of subject 101. The days and nights were separated on basis of the dairy notes*

5.3.2. Posture detection

In total, all 6 healthy subjects completed the walking protocol and 6MWT. Of the 24 TAVI patients, 8 were seen for a T2 measurement. One TAVI patient was not able to perform the 6MWT at T0 and T2, as she was wheelchair bounded. Of the 36 6MWT, 3 were not analyzed as biosensor data were lost. The reliability analysis assumes participants walk constantly during the 6MWT. One patient stood still for about half a minute during the 6MWT and was therefore excluded for this analysis. In total 32 6MWT were used to analyze the walking detection of the wearable biosensor. An overview of the included 6MWT is visible in Figure 5.4

Walking was detected 99.8% and 96.5% of the time during the 6MWT in healthy subjects and TAVI patients, respectively. Walking detection declined for slower paces in the walking exercises, at a pace of 0.43 m/s, 0.8% (± 1.2%) was detected as walking. Appendix A.1.3, shows all results of the 6MWT and walking exercises.

Figure 5.5 shows multiple examples from the biosensor posture classification from a healthy subject, compared to the diary. Panel A-B and C-D show sitting and standing, respectively. The first day, both are sitting and standing is correctly classified as ‘upright’ (Figure 5.5 A and C), the acceleration looks visually similar. However, a day or few days later both are detected as laying down. Walking and running are both classified as walking (Figure 5.5 E), but walking has a much smaller acceleration variance than running. Cycling is detected as ‘lying down’ or ‘walking’ (Figure 5.5 F).

The biosensors activity classification for every day and night was made (Figure 5.6). The days and nights were separated on basis of the dairy notes. The first day and night show an appropriate portion of ‘upright’ and ‘lying down’, respectively. In the following days however, the biosensor detected mostly ‘lying down’ during the day, which does not coincide with the subjects diary. As well as during the night, more ‘upright’ and ‘leaning back’ is detected, which was not confirmed by the diary.

5.3.3. Data collection

In total 35 datasets were analyzed to determine the reliability of the data collection (Table 5.4), 12 (34%) measurements had data available for more than 80%. On average, 56.2% of the 96 hours of data is usable and the measurement length was 60:51:58 (± 32:10:07). A total of 13 (37%) had uninterrupted data, but in 22 (63%) data sets, data loss was apparent, ranging from a few minutes to 59 hours. Figure 5.7 shows the survival analysis for ‘time to first data failure’. It shows that 29% had usable data at when eliminating 2 minute gaps. Appendix A.1.4 gives the tables and survival graphs for data collection and first point of data loss.

5.4. Discussion

This chapter investigated the reliability of the Philips wearable biosensor, as part of the TELE-TAVI study. In this research the reliability of the biosensor vital signs, posture detection and data collection are investigated. In all three domains, there is room for improvement.

Vital signs

Assessment of the vital signs accuracy, HR and RespR of the biosensor was compared to the reference monitor. Preliminary results show that the biosensor can likely accurately measure HR within 10% deviation in people with sinus rhythm. However, in patients with AF this accuracy is not met and filtering HR did not change this. The difference is probably present due to the different filter settings of the biosensor and reference. Additional filtering was not able to adjust for this error. RespR, on the other hand, seems inaccurate in both research groups. Although, filtering the RespR improves the results, as the LOA decreases and lag disappears.

These results are comparable to earlier work with the similar VitalConnect HealthPatch [21]. They hypothesized that poor agreement in the RespR was due to frequent outliers and implausible variability in the RespR values as a result of movement artifacts. This could also be the case in this TAVI-population of this study. However in the healthy subjects, the respiratory signal was mostly undisturbed (see Figure 5.2 A), as patients were sitting during the breathing exercises. However, the biosensors RespR did not coincide well with the reference. As noted by Breteler et al., RespR might still be usable for slow trend monitoring [21].

A limit of this study is that the range of the HR is narrow (40-120 beats/min), and the accuracy of the HR is only assessed in this limited range. Of this limited range, the higher HR frequencies is from the TAVI population with AF, in which the accuracy was not met. Therefor the accuracy of the biosensor within 40-90 beats/min can only be called accurate.

Another limitation of this study is the use of the impedance pneumography as reference for the RespR. It is widely considered that capnography is the gold standard for RespR. Impedance pneumography was used in this study as it was easier to implement the standard care routine. Unfortunately, also a lot of datasets were lost due to technical problems, which made the sample size for the RespR considerably smaller.

The kurtosis in the difference data (biosensor – reference) was very high for HR, which implies the difference data is outlier prone. This is likely caused by the sudden spikes in HR of the biosensor, as can be seen in Figure 5.2. On closer inspection of the data, these spikes in HR are likely caused by disturbances in the ECG, which are not sufficiently filtered out. This unbalanced distribution will influence the parametric results greatly and therefor the HR bias and precision is estimated non-parametrically.

Inaccuracy of the HR in AF patients is likely caused by different settings of the wearable biosensor and reference monitor. The reference HR was filtered to mimic the HR from the biosensor. However, it did not alter the outcome. The filters from the biosensor could not be replicated and the reference monitor

Table 5.4 *Average length of the measurements, data loss and usable data of the wearable biosensor, in the groups' healthy subjects and TAVI patients.*

	n	Length measurement (hh:mm:ss)	Data loss (hh:mm:ss)	Data not lost	Usable data (hh:mm:ss)	Usable data
Healthy	6	62:39:50	06:45:01	92.5%	55:54:48	58.2%
(± SD)		(± 37:29:21)	(± 16:14:56)	(± 17.5)	(± 34:37:36)	(± 36.1)
TAVI	29	60:29:39	06:55:36	90.4%	53:34:03	55.8%
(± SD)		(± 31:41:52)	(± 16:24:38)	(± 21.4)	(± 32:22:33)	(± 33.7)
All	35	60:51:58	06:53:47	90.8%	53:58:11	56.2%
(± SD)		(± 32:10:07)	(± 16:07:08)	(± 20.6)	(± 32:15:16)	(± 33.6)

n indicates number of subjects; SD, standard deviation; hh:mm:ss, hours:minutes:seconds.

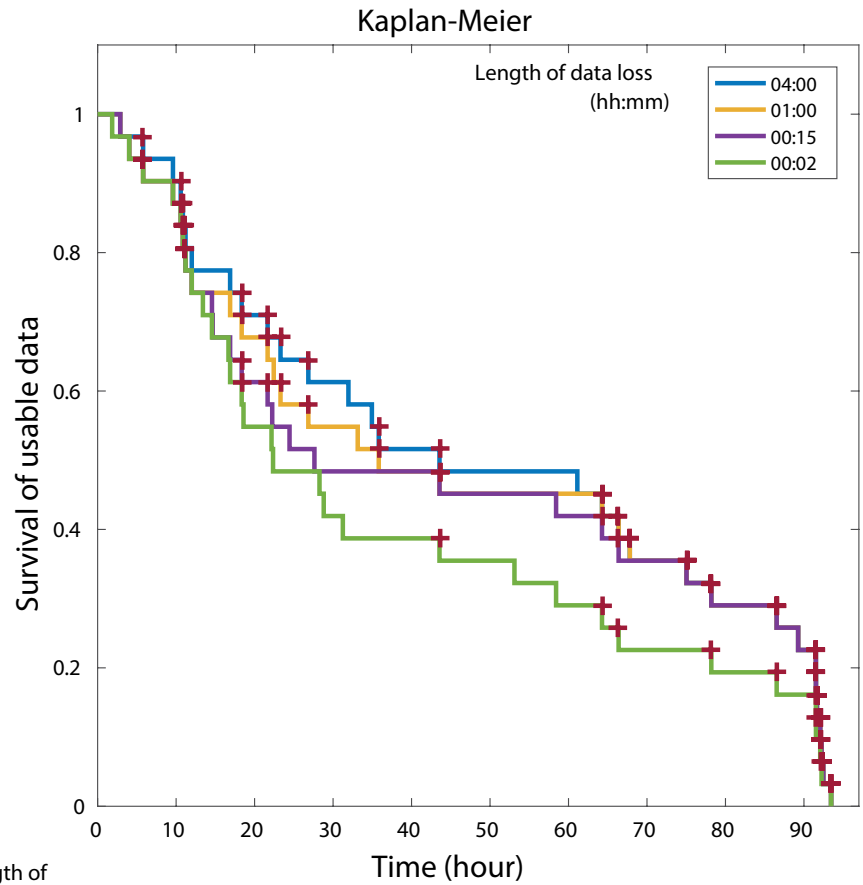
has own filters, which most likely causes these differences. There is still a need for reliability analysis in AF patients, as about 40% of the patients getting TAVI have AF [38], [39].

Surprisingly, the biosensors HR agreed better in TAVI-patients with a sinus rhythm, than in the healthy subjects. Appendix A.1.2 shows that in healthy subject, the LOA is very large. Upon closer inspection of the data, this is likely caused by an inaccuracy of the reference monitor. During the breathing exercise, the reference HR dipped from 60 beats/min to 30 beats/min. During this dip also some data was missing. This indicates the reference monitor was probably inaccurate at this moment.

In conclusion, preliminary results show that the biosensors HR seems accurate for sinus rhythm and can be used for further data analysis. The RespR is likely to be inaccurate compared to impedance pneumography. However, further research should determine the cause of this inaccuracy.

5.4.1. Posture detection

This is the first independent research into the activity classification of the wearable biosensor. For this purpose, walking detection was analyzed for different walking speeds and posture was compared to the activity diaries. Result shows that the walking detection is accurate above 0.7 m/s, but



Length of data loss (hh:mm)	Number recordings:									
04:00	31	28	22	19	16	15	15	11	9	7
01:00	31	27	21	17	15	14	14	11	9	7
00:15	31	27	19	15	15	14	13	11	9	7
00:02	31	27	17	13	12	11	9	7	6	5

Figure 5.7 *Gives the Kaplan-Meier figure for the survival of usable data, due to measurement length or data loss, with gaps of 2 minutes, 15 minutes, 1 hour and 4 hours. Every plus sign represents the end of a measurement. Under the figure, the number at risk are shown, every 10 hours.*

degrades fast when walking slower. Posture detection is limited, as only a few outcomes are possible and posture classification deteriorates within a day.

This report has limitations, as no validated analysis are used for the posture detection, because there were none available. Therefore, quality assessment were made by comparing it to exercises and diaries. The precision of the diary, differed greatly between subjects, which made it hard to make a generalized analysis. In further research, diaries could be made more homogenous by giving stricter instruction how and what to note. Determining the walking detection accuracy was better controlled as it was overseen by a researcher.

Despite this limitations, it is clear that walking is detected well above 0.7 m/s. Implications of this threshold seem to be of minor influence in TAVI patients, as only one TAVI patient (209) walked slower. This indicates that in most TAVI patients the biosensor is able to detect walking accurately. However, one has to consider that the cohort in this study has a better functional status than compared to other studies reporting over a general TAVI population (Chapter 4).

More surprising is the result that the posture classification of the biosensor deteriorates much after one day, which makes it unusable in practice. It is hypothesized, that the signal analysis is somehow affected during the night. However, it is not known how posture is exactly detected (Chapter 3), therefore the real error cannot be pinpointed.

The biosensors algorithm for posture detection, unfortunately does not include a detection for running. In Figure 5.5 shows that the difference between walking and running is clearly visible in the acceleration data. The ability to classify running, would especially be valuable when the biosensor is used in sports and sport revalidation. Detection of running is not essential for TAVI patients, as it unlikely these patient will run frequently.

In conclusion, data from the posture classification is not reliable and unusable for further analysis. Walking and step count could be used in activity analysis, but is limited as a standalone parameter.

5.4.2. Data collection

Data collection reliability is an essential part for the usability of the wearable biosensor. To our knowledge, this is the first study reporting data collection reliability in an at home setting with the current set-up. The found reliability is low due to a combination of short recording times and large gaps in the data.

The data collection reliability found in this study is worse, than in other work in a hospital step-down unit [21]. The divergence in results is likely caused by the different study environments. In this study, biosensors were attached in hospital, where after study participants resumed their daily lives. As a result, there was less support for the patients in this study compared to an in-hospital research. Also, when the sensor or receiver malfunctioned, we could not replace it quickly.

The suboptimal data collection reliability ensues further analysis greatly, as only a few datasets have enough data eligible for in depth analysis. Therefore, measurement length should be improved and data gaps should be diminished. Reasons for short measurement lengths and data gaps will be reviewed by means of wearability questionnaires in Chapter 6.

5.5. Conclusion

This chapter investigated the reliability of the Philips wearable biosensor for vital signs, posture detection and data collection in the TELE-TAVI study. Preliminary outcomes suggests that HR is the most reliable vital sign, but needs to be further analyzed in patients with AF. The RespR seems to be unreliable compared to the reference monitor, but could maybe be used for slow trend monitoring. Posture detection was limited and deteriorates fast over time. Data collection was below the predetermined limit and complicates further in-depth analysis of the biosensor data.

Chapter 6: End-user experience of the Philips wearable biosensor and Research Kit in the TELE-TAVI study

6.1. Introduction

The population is aging and mobile health applications are becoming more common in the health care of the elderly. Acceptance of technology by elder patients relays heavily on the ease of use [45]. Elderly encounter different usability problems, as a result of physical decline, aging characteristics and disease complexities [46].

To assess the usability of a mobile system, the TELE-TAVI study is conducted. It is hypothesized that a wearable sensor can aid the transcatheter aortic valve implantation (TAVI) workflow. The system can only provide benefits, when its use is accepted by the intended population; elderly TAVI patients. Therefore, the user experience of the biosensors system is investigated as part of the TELE-TAVI study.

6.2. Method

To test the usability of the Philips wearable biosensor and additional systems, data from the TELE-TAVI study is used (Amsterdam UMC, location AMC, Amsterdam, The Netherlands). Patients with severe aortic valve stenosis, received the system at three moments: two weeks pre-TAVI (T0), post-TAVI (T1) and at 6 weeks follow-up (T2). After every measurement a questionnaire was filled in by the study participant about the used devices. This questionnaire contained the post study system usability questionnaire (PSSUQ) and a custom made questionnaire, targeting specific questions on the use of the wearable biosensor and the mobile phone.

6.2.1. Devices

The system used in the TELE-TAVI study is a wearable patch sensor (Biosensor, Philips Medical System, Andover, Massachusetts, USA) and Research Kit (Philips Medical System, Andover, Massachusetts, USA), which contained a mobile phone (Kyocera Brigadier, Android version 5.1.1) with smart phone application. The mobile phone with application captured data acquired by the biosensor and provided guidance in English for the set-up of the biosensor and gave feedback during the measurement. Set-up guidance involved giving instruction for preparing the skin, activating the biosensor, connecting the biosensor with the mobile phone, and accelerometer calibration. After the initial set-up, the application gave information on the battery life of the biosensor and connection of the signal. The screen also suggested to stay within 10 meter distance of the phone. Visible and audible warnings were given, in case the biosensors signal is not detected or the sensors adherence failed.

In the TELE-TAVI study, the researcher set-up and adhered the biosensors first, in all time points (T0-2). During this process, patients were engaged in participating and working with the phone and app. Patients received information booklets about the biosensor and its use, which were approved by the local ethics committee. Directly post-TAVI (T1), an extra sensor was supplied and patients had to change the sensor at home by themselves, or with the help of an informal caretaker. When patients were still admitted to the academic hospital, a researcher helped with changing the biosensor.

Table 6.1 *Questions of the custom made questionnaire, with answers for Likert scales 1 and 7.*

	Questions	1	7
1	How was wearing the biosensor?	Comfortable	Uncomfortable
2	Did you experience itchiness caused by the biosensor?	No itch	Much itch
3	Did you experience skin irritation?	No irritation	Much irritation
4	Did the biosensor remained adhered to the skin?	Stayed adhered	Came off
5	Was the biosensor easily removable from the skin?	Easy	Much difficulty
6	Was removing the biosensor painful?	Not painful	Very painful
7	Were you activities limited because of the measurement?	No limitation	Much limitation
8	Did have to phone with you?	Always	Never
9	Changing the biosensor was easy.	Strongly agree	Strongly disagree

6.2.2. PSSUQ

One of the questionnaires used to assess the user experience of system was the post study system usability questionnaire (PSSUQ) [31]. This 19-item questionnaire evaluates the perceived satisfaction after system use. The questionnaire is divided in four categories; overall system use (SysUse), information quality (InfoQual) and interface quality (IntQuality). Answers were based on a 7-point Likert scale, from strongly agree (1) to strongly disagree (7) and a “not applicable” option. Missing data or not applicable data were interpolated. Hereafter, scores were calculated for every category as an average percentage of agreement (100% strongly agree, 0% strongly disagree), as suggested by the questionnaire developers.

6.2.3. Custom made questionnaire

A custom made questionnaire, similar to the PSSUQ, was added to evaluate specific biosensor system related questions (Table 6.1). It had 9 questions, with a Likert scale between 1 and 7 and a “not applicable” option. Questions involved the wearability, burden of the biosensor, as well as a specific question about the difficulty of changing sensors. All questions with accompanying Likert scale answers can be found in Table 6 1. Missing values were not used in the analysis. The custom made questionnaire was followed by an empty page, were further feedback, supplementary notes and practical restrictions could be entered. The used custom made questionnaire is included in Appendix A.3.1.

6.2.4. Statistical analysis

Primary outcomes are PSSUQ percentages and custom made questionnaire answers. Furthermore, a paired t-test was used to evaluate if there is significant difference in the PSSUQ over the three measurements for all four categories. Next to that, we examined whether the PSSUQ results were related to the length of usable data (Pearson correlation). Usable data were defined as the data measurement length without gaps, due to data loss.

6.3. Results

In total 45 (90%) questionnaires were received, after measurement with the wearable biosensor. Of these, 21, 16 and 8 were received from the pre-TAVI, post-TAVI and follow-up measurement, respectively. Of the received questionnaires, 3 PSSUQ were not filled in and 2 custom made questionnaires were missing. In 28 times feedback was given in the open comment section.

The PSSUQ results (in Table 6.2), show that system usability satisfaction is 63.2% (± 30.7). Appendix A2.1, gives the PSSUQ results per patient. Here, it is visible that the in-patient variation between the four domains is low, but the interpatient variation is large. There was no significant difference found between the answers of T0, T1 and T2, on all PSSUQ domains. Also no correlation was found between the length of usable data and PSSUQ outcomes. No significant difference was found between the answers at T0, T1 or T2.

The overall results of the custom made questionnaire are shown inFigure 6.1. Most patients experienced no discomfort (74%), itch (91%), and skin irritation (95%) and were not limited in daily activities by the measurement (79%). Removing the sensor from the skin was easy (83%) and not painful (86%). Patients

said that they always carried there phone around (93%). In 31% of the TAVI patients, the biosensor fell off. Changing the sensor at T1 was easy for 56%, but 19% did not attempt to change the sensor.

In the open feedback page, the same 14 (31%) patients wrote that the sensor fell off. Another frequent note was that the audible warning signaling that the sensor signal was out of range, was often heard, even when the phone was nearby. As patient 204 commented after T0 (translated from Dutch):

"Very many (too many) warnings of connection failure, while he was in the pocket of my shirt or trousers. And that day and night!"

Also several commented that the changing the biosensor was rather challenging. For example, Pin 209 wrote:

"New adherence of the biosensor causes some problems. Needed to sort out the workings of a couple of things. I can imagine that not everybody can do this alone".

Only one patient (Pin 211) described having difficulty with the foreign language.

6.4. Discussion

This chapter explored the end-user experience of the wearable biosensor and additional phone and application, in elderly TAVI patients in context of the TELE-TAVI study. Results demonstrate that patients experienced the wearable biosensor as comfortable and easy to use. However, the phone and applications experience varied much, but overall was lower than expected.

Limitation of this part of the TELE-TAVI study is that only a part of the screened TAVI patients (35%, see Chapter 3) participated. The participants in the study were probably patients open to and experienced with mobile phones and technology. Therefore, this study will probably overestimate the positive results of the overall TAVI population. The results of the PSSUQ are limited as patients experienced difficulty with the complicated sentence structure. The custom made questionnaire on the other hand was easier, but is not validated. Missing in both the questionnaires is comfortability with own phone use of participants. It seems that this played a major role in the satisfaction and ease of system use. Although the research methods are limited, the results provide a great and quantified insight in the use of the wearable biosensor and the additional systems.

The varying experience with the phone and mobile application has probably multiple reasons. One is of course, the skill of the patient with a smartphone. Also the applications language was English, while patients first language was Dutch. Surprisingly, only one patient complained about language difficulty. More patients explained that they could not understand English during the inclusions. But most patients seemed to have enough understanding of the language to handle the phone. Also there were a great number of steps and procedures for setting up the biosensor and phone, which made the system complicated. Therefore, the author suggest it is better to simplify the system, preferably without using a phone.

Wearing the biosensor was experienced as overall comfortable, but in almost a third of the patients the sensor fell off. Early detachment of the sensor has had major impacts on the clinical usability of the data obtained with the biosensor. Therefore, one could argue the adherence layer of the biosensor should be improved. Only, this could influence the wearability negatively. This makes for a difficult balance; patient would probably be more reluctant to wear the sensor for long periods of time.

Table 6.2 *Overview of answers PSSUQ*

		Mean	(± SD)
1	Overall	63.2 %	(±30.7)
2	SysUse	65.0 %	(±31.9)
3	InfoQual	61.7 %	(±34.7)
4	IntQual	61.7 %	(±31.5)
	Mean (2-4)	62.8 %	(±32.7)

PSSUQ indicates post-study system usability questionnaire, SD, standard deviation

There was no significant relation found between the PSSUQ outcomes at T0, T1 and T2. A positive relation could have indicated that there is a learning curve for patients in using the system. Also, no relation was found between the PSSUQ outcomes and the amount of usable data. If the PSSUQ results also correlated with the patients ability to handle the system, it could have suggested that the data loss is not caused by the user, but rather a system error.

An unexpected finding was the feedback on the phones

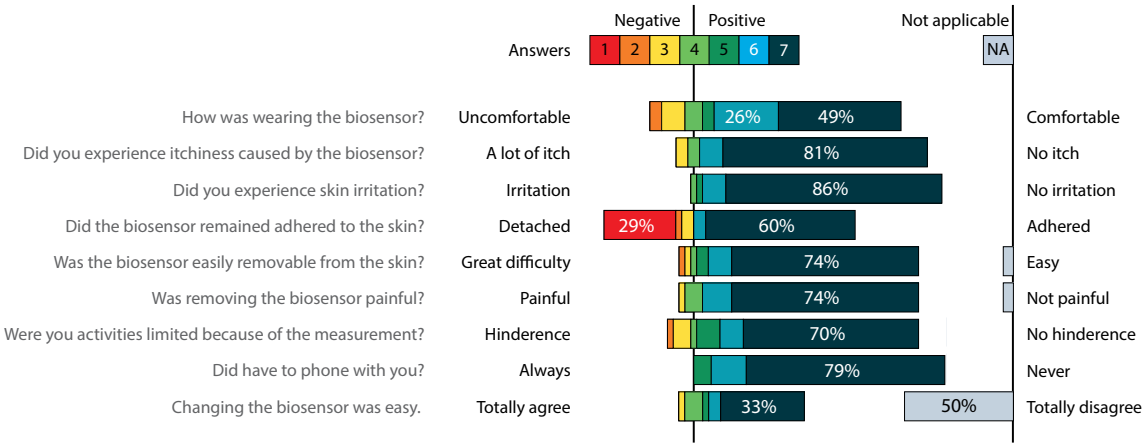


Figure 6.1 *Shows results from custom questionnaire averaged for T0, T1 and T2*

audible warnings on the signal strength. Although patients kept the phone close to the sensor, they received a lot of warnings on the phone. This was experienced as very disturbing and in one case even let to discontinuation of study participation (Chapter 4). Patients were given the option to turn of the audible warnings. Disadvantage hereof, was that patients could not receive the warnings and forget the phone. Preferably, the audible warnings should be broadcasted by the sensor instead of the phone. Which gives also the possibility to delay the warning, so warnings are only broadcasted when the signal is lost for several minutes.

6.5. Conclusion

In conclusion, this chapter shows the user experience of the wearable biosensor and system, in an elderly TAVI population. The wearability of the sensor is good, but probably compromises the longevity of the adhesiveness. The use of the phone was below expectation and audible warnings from the phone were experienced as very bothersome. A simplification of the system, would probably solve many of the experienced issues.

Chapter 7: Discussion

7.1. Implications

In current medicine, transcatheter aortic valve implantation (TAVI) is a widely accepted intervention in patients with severe symptomatic aortic valve stenosis with intermediate to high surgical risk. However, used risk scores are not sensitive for TAVI outcomes. Frailty is closely related to surgical outcomes, but no standardized assessment is available. Recently, the use of wearable sensors is explored in objective frailty assessment, but none use an integrated approach of physical activity and cardiac physiology. The Philips wearable biosensor (Philips Medical Systems, Andover, Massachusetts, USA) measures vital signs and posture for up to 4 days, which could allow for integrated screening tool. Currently no publication is available on the biosensor.

This master thesis was part of the TELE-TAVI study, a prospective trial investigating the possibilities of remote patient monitoring in TAVI patients (Chapter 3). However, little is known on the reliability and end-user experience of the wearable biosensor, which should be addressed first. The aim of this master thesis was to find an objective measure with the Philips wearable biosensor for screening of TAVI patients. Hereafter, an objective measure for physical activity was investigated. First preliminary results in Chapter 4 show that the study population has a good functional status compared to overall TAVI population and other TAVI study populations.

Chapter 5 discusses the reliability of the wearable biosensors outputs and data collection. Vital signs were compared to the high-end patient monitor and preliminary results show that the heartrate (HR) is reliable during sinus rhythm. However, in patients with atrial fibrillation (AF), the HR differed more from the reference. The RespR seems to be unreliable compared to the reference monitor, but could be used for hourly trend monitoring. The biosensors posture was deemed impractical, as the accuracy deteriorated within a day. Most surprisingly was that only somewhat more than halve of the 96 hours of data were stored. The reliability of the data collection and posture detection had consequences for other parts of this thesis.

The user experience of TAVI-patients, was addressed in Chapter 6. The use of the phone and application received mixed results, some patients were satisfied with the systems, others less. Even though, patients included in the study were probably more accustomed and open to technology, which overestimated the results. The wearability of the biosensor was good, as most experienced no discomfort of the sensor and patients found the burden of wearing a sensor low. However, in a third of the patients the sensor fell off before the measurement ended.

Finally, an objective physical activity measure was researched in Chapter 7. Physical activity can be estimated with the raw acceleration recorded by the wearable biosensor. With this, daily activity profiles could be made. However, more research should focus on finding a robust algorithm for physical activity.

In conclusion, implementation of the wearable biosensor is feasible in the TAVI workflow. However, one of the major setbacks was the reliability of the wearable biosensor., as much data were lost without a known cause. Also the posture classification was unworkable, which let to exploration of estimating physical

activity. Daily physical activity profiles could be made, which shows the potential of the biosensor usability. Next to that, patient tolerated wearing the biosensor well and encourages research in sensor technology in elderly.

7.1.1. Recommendations

During this master thesis, data collection reliability had the most impact on analysis of the biosensors data. Because of the many hours of data loss, only limited analysis were possible. Most notable, is that only 1 out of the 8 patients, who completed all measurements, had more than 80% of the data available at pre-TAVI screening, directly after TAVI and at six weeks follow-up. Consequently, data collection reliability must be improved, prior to new and larger study with the wearable biosensor.

Also user experience of the phone and application should be further improved. Most difficult for the TAVI patients was setting-up the sensor and phone connection and working with the phone. For this reason, it could be suggested to integrate the data collection module into the wearable sensor as it could also solve the data collection reliability. However, this will increase the costs of the sensor. Next to that, some potential additional functionalities of system will be lost, for example, manual data entry, such as measured blood pressure, would not be possible. However, with the wearable biosensors current functionalities, the data collection module could be integrated in the sensor.

Currently, the patient interface, which includes the phone and application is a disadvantage of the system. Improvement of the system should include end-users, in this case TAVI-patients [59]. New software for the application is available and addressed the issues with the frequent audio warnings when the connection between the phone and sensor was lost. A delay of 5 minutes between loss of connection and the warning was added, so short connection interruptions would not trigger a warning. However, the added value of the audio warning, is reduced, as patients could be moved too far away from the phone in this time period. Another addition of the new software, was that the interface of the app was secured with an 8-letter password. This will probably only decrease the usability of the phones application.

Before starting a new study with the wearable biosensor in TAVI-patients, the abovementioned problems should be addressed. Additionally, length of measurements could be improved, by developing an improved adhesive layer.

These recommendations do not imply that further research is not possible before these flaws are addressed. The data gathered during the TELE-TAVI study is rich and many algorithms could be developed for further use of the wearable sensors.

First, an algorithm that can detect physical activity is needed. Chapter 7 showed a promising start, however this is only an example of accelerometry analysis. Analysis of physical activity is a large research field and further profound investigation of possible algorithms is needed. Also, HR as a measure for screening should be considered. Yet, the standard heart rate variability (HRV) is less suitable in this patient population, as almost 29% of the TAVI population has atrial fibrillation, in which this analysis is impossible.

The end goal is to have an integrated analysis of vital functions and physical activity, as it would likely give an in-depth view into the patient's physical and cardiac condition and possible improvement after TAVI. However, a challenge will be handling the different parameters' resolution. Activity can be estimated every 10 seconds, but RespR is probably only reliable in slow hourly trends. Somehow, a smart algorithm should account for these differences.

Thus, before a new study is initiated, the wearable sensors data collection reliability, user interface and adhesive layer have to be improved. However, development of algorithms integrating physical activity and vital signs is possible with collected data. First focus should be making an algorithm for physical activity analysis.

7.2. Future perspectives

Although, the Philips wearable biosensor is not yet usable in all TAVI-patients, it is expected to be useful in the near future. In the meantime, both TAVI and wearable sensing will further develop.

7.2.1. TAVI

Three possible cases are defined where a wearable sensor could aid TAVI workflow; screening, post-procedure monitoring and follow-up. As TAVI is a relatively new intervention, management of TAVI workflow is changing constantly.

First, TAVI was only indicated in high risk patients with severe symptomatic aortic valve stenosis. The indication for TAVI is expanding, as now patients with intermediate mortality risks are also accepted. In addition, studies are currently exploring TAVI in low risk patients [60]. It is even suggested to study the early intervention of asymptomatic patients and prevents patient deterioration and irreversible myocardial damage [61], [62]. However, TAVI does come with peri- and post-procedural complication, which needs to considered. Wearable sensors could help identify the right timing and patient for TAVI, by monitoring activity and HR for long periods.

The use of wearable sensor is already acknowledged for monitoring patients post-TAVI [32]. Recently, a study started exploring the feasibility of ECG home-monitoring [33]. Next to monitoring, a wearable sensor could also benefit cardiac rehabilitation at home, by monitoring HR and physical activity, and engage exercise with serious interactive gaming [63].

Follow-up after TAVI could be expanded with wearable sensors, it can objectify patients improvement and give more insight in what happens between doctor's visits. Objectively measuring symptom improvement could be used as outcomes randomized control trials and could reduce number of subjects as could earlier detect patient improvement.

7.2.2. Wearable sensors

This thesis mainly focuses on the use of a wearable sensor in TAVI-patients, but more fields could benefit from wearable sensing. Generally speaking, wearable sensing has potential to improve diagnostics and monitoring of a variety of diseases. Next to that, long term monitoring could give insight in a person's health condition. With this, diseases could be found before symptoms are noticed or even prevented.

To make this happen, dedicated algorithms must be made. Currently, wearable sensors can measure a variety of outputs, but most are nonspecific without context. For example, HR can easily be measured, but without context an increase in HR could be caused by exercise or patient deterioration. Algorithm development could for example be established with machine learning, but these algorithms need vast amounts of data.

Functionality and wearability of wearable sensors is still being improved. Accuracy of sensor outputs are improving and more data can be recorded and stored. Battery life could be extended with body energy harvesting. Sensors are getting more flexible and miniaturized, which will improve wearability and extend wear-time. All together this will lead to more data collection of vital signs.

Chapter 8: Objective physical activity levels with the wearable biosensors in patients undergoing transcatheter aortic valve implantation: first results

8.1. Introduction

Aortic valve stenosis (AoS) is the most prevalent heart valve condition and is associated with aging. Nowadays, transcatheter aortic valve implantation is standard care for patients with intermediate to high risk at mortality. However, often used risk models poorly predict TAVI outcome and a specific TAVI model is needed [47], [48].

Adding frailty evaluation has shown to improve the already pre-existing scores [49]. Frailty is a syndrome, and can be observed as weight loss, muscle weakness, poor endurance and energy, slowness and low physical activity levels [15]. Physical performance tests are often utilized for assessing frailty [16], [17]. Physical performance can for example be determined with the six minute walk test (6MWT), short physical performance battery (SPPB) or gait speed and is related to the outcome of TAVI [50]–[52]. However, all give only a snapshot of the patient physical functioning in an estranged out-of-home environment.

Daily activity measured with sensor technology could extend physical performance analysis. Multiple studies are known to assess physical frailty with sensor technology [19]. Combining an objective frailty measure with heart rate, could allow for an extensive evaluation of cardiac condition, improving TAVI screening. The wearable biosensor (Philips Medical System, Andover, Massachusetts, USA), can measure vital signs and tri-axial acceleration and would allow for such evaluation. However, an activity algorithm is not embedded in the system and the posture detection is unreliable (Chapter 5).

The aim of this chapter is to find an objective physical activity measure with the wearable biosensor for TAVI patients.

8.2. Method

Development of an objective physical activity measure is part of the TELE-TAVI study, a prospective, investigator initiated study, exploring telemedicine in TAVI-patients. The design of the study is extensively described in Chapter 3. For now, a short description of study will be given.

In the TELE-TAVI study, six healthy volunteers and 24 TAVI-patients participated. Patients received a wearable sensor pre-TAVI (T0), directly after the TAVI (T1) and at 6 weeks follow-up (T2). The Philips biosensor (Philips Medical System, Andover, Massachusetts, USA), is a light-weight sensor measuring vital signs and tri-axial acceleration for up to 4 days. At T0 and T2, patients also underwent multiple physical function tests, with a six minute walk test (6MWT), short physical performance battery (SPPB) and grip strength. Healthy subjects, received the biosensor once, and performed the same physical analysis. Next to that, the healthy study population did a walking exercise, where they walked for 2 minutes at 100, 75 and 50 steps per minute with a metronome. The distance traveled during each 2 minute cycle was noted. Walking was alternated with one minute of sitting. After the protocol, the healthy study population maintained a diary in which they noted activities.

8.2.1. Data analysis

The biosensors raw tri-axial acceleration data were decrypted with the Research Kit (Philips Medical System, Andover, Massachusetts, USA) and retrieved in CSV format. All data were stored and processed using Matlab (The MathWorks, Natick, Massachusetts, USA). Missing data were interpolated with empty values (not-a-number).

8.2.2. IMA

Activity was estimated with the integral of the modulus of the accelerometer output (IMA), as described by Bouten et al. [53], [54]. IMA is dimensionless and defined as:

$$IMA = \int_{t=t_0}^{t_0+T} |a_x(t)|dt + \int_{t=t_0}^{t_0+T} |a_y(t)|dt + \int_{t=t_0}^{t_0+T} |a_z(t)|dt$$

In which t is the time, T is the time period in which the IMA is calculated, a is the acceleration in direction x, y and z.

Acceleration is first filtered with a bandpass filter from 0.11 to 20 Hz to remove off-set caused by gravity and vibrational components not caused by human motion [54]. Filtering the biosensors acceleration was complicated by many small and larger gaps were present in the data. Therefore, small gaps (< 10 samples) were linearly interpolated. Hereafter, acceleration was filtered in between the stretches with longer missing data. Finally, the IMA was computed with a window (T) of 10 seconds. When 10% of the data in the window was missing, the IMA was replaced with an empty value.

The IMA was averaged during 6MWT of the TAVI-patients and healthy subjects. Also the averaged IMA was computed during the metronome walking exercises of 100, 75 and 50 steps/min in the healthy subjects. Linear regression was computed between the walking speed and IMA of during the above mentioned walking exercises and 6MWT.

8.2.3. Activity levels

From the computed IMA, activity levels were determined by dividing the IMA into four categories; no, low, medium and high activity. The categories were determined by defining three thresholds (low, medium and high), separating the four categories. With this, activity profiles, which are percentages of detected activity levels, could be made for the whole measurement.

8.2.4. Daily activity levels

Full measurement activity profiles are largely influenced by the amount of sleep during the measurement, which does not reflect the activity pattern during the day. Therefore, daily activity profiles were made. Daily activity profiles are computed only for complete days, which are days that were recorded from waking up to going to bed.

First, awake hours must be separated from the whole measurement. For this, the calculated IMA was filtered with an averaging filter of two hours. With this, slow patterns are visible in the activity without losing

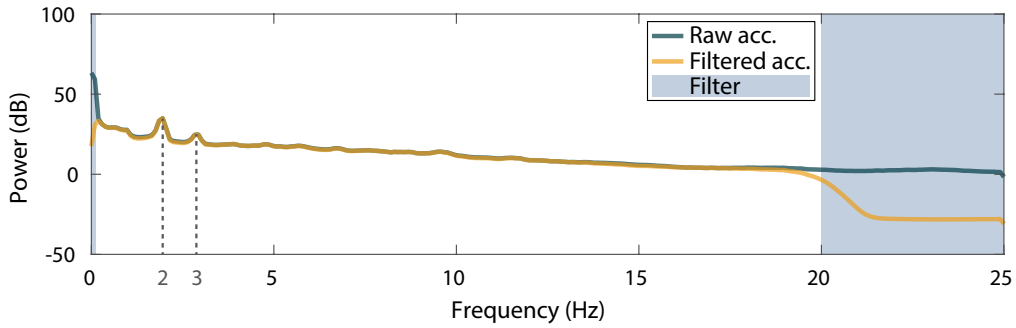


Figure 8.1 *Gives the estimated power spectrum of the unfiltered (dark blue) and filtered (yellow) acceleration data (x-direction). Acceleration is filtered with a bandpass filter of 0.11 and 20 Hz (grey areas).*

Table 8.1 *IMA and activity characteristics over full measurements.*

			Healthy		TAVI		Overall	
IMA	Mean		50.5	± 17.6	32.2	± 8.3	35.7	± 12.5
	Range	Min	3.9	± 0.8	3.9	± 0.5	3.9	± 0.6
		Max	703.9	± 299.2	348.3	± 55.3	415.0	± 191.8
Activity	No	(%)	54.5	± 9.0	65.3	± 9.6	63.3	± 10.3
	Low	(%)	28.2	± 4.1	24.6	± 6.8	25.2	± 6.5
	Medium	(%)	15.0	± 5.2	10.0	± 3.8	10.9	± 4.5
	High	(%)	2.4	± 2.2	0.2	± 0.3	0.6	± 1.2

IMA indicates integrated modulus of acceleration; TAVI, transcatheter aortic valve implantation.

Table 8.2 *IMA and activity characteristics during the day.*

			Healthy		TAVI		Overall	
	Mean IMA daily		52.4	± 10.1	33.8	± 8.7	37.9	± 11.8
Activity	No	(%)	31.8	± 4.3	43.3	± 7.8	40.8	± 8.6
	Low	(%)	35.6	± 7.2	26.8	± 5.6	28.7	± 6.9
	Medium	(%)	16.1	± 5.1	11.1	± 4.3	12.2	± 4.8
	High	(%)	2.1	± 1.0	0.2	± 0.4	0.6	± 0.9

IMA indicates integrated modulus of acceleration; TAVI, transcatheter aortic valve implantation.

to much resolution. Sleeping periods were easily determined with a threshold (Figure 8.2). However, naps or little activity during the day sometimes interfered and needed to be discarded. Thus, first an estimate of the number of nights was made. After this, the smallest awake or sleep parts were ignored till the number of nights was equal to the estimated number of nights. Finally, only days that were separated by nights were used to make a daily activity profile. With this, only daily activity profiles were only computed for completely measured days.

8.3. Results

The walking protocol and 6MWT was completed by all 6 healthy subjects. From the 24 patients, 8 completed the protocol and received a sensor at T2. One TAVI patient was not able to perform the 6MWT at T0 and T2, as the patient was wheelchair bound and, 1 was excluded from analysis, because patient stood for 30 seconds and 3 were not analyzed as biosensor data were lost. In total, 32 6MWT could be compared with the IMA (Figure 5.1).

8.3.1. IMA

The estimated power spectrum of the raw and filtered acceleration is given Figure 8.1. In the areas where is not filtered, the signal strength is unchanged. In the filtered frequencies, the acceleration is sufficiently damped. In the power spectrum, peaks can be found at 2 and 3 Hz.

Table 8.1 shows the average and range of the IMA on a full measurement, for healthy subjects and TAVI patients. The averaged IMA was higher for healthy subjects with 50.5 (± 17.6), compared to TAVI patients with 32.2 (±8.3). Also the IMA ranges were larger in healthy subjects (3.9 – 703.9) than in TAVI patients (3.9 – 348.3). Individual study subjects' results can be found in Appendix A.3.1. Figure 8.3, gives the linear regression between walking speed and calculated IMA. A significant correlation was found, between IMA and walking speed ($rs^2 = 0.80$ and $p<0.001$).

8.3.2. Activity levels

The thresholds to determine no, low, medium and high activity, were chosen on the basis of Figure 8.3.

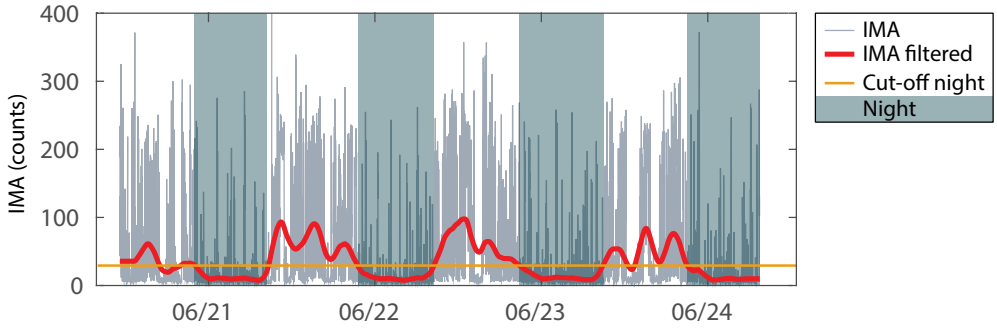


Figure 8.2 *Shows the data used for sleep detection. IMA (grey line) is filtered with a 2 hour averaging filter (red line). Hereafter sleeping periods (dark areas) are detected when the filtered IMA is below the (yellow) threshold.*

Walking was considered medium activity in TAVI patients. Most TAVI patients had an averaged IMA between 100 and 250 during walking of the 6MWT, which made the thresholds for medium activity. Averaged IMA values were not computed for lower activities. Therefore, the threshold between no and low activity was based on the diaries of healthy subjects. A threshold of 20 was selected, which was able to differentiate lying and sitting activities from standing. An example of the activity classification can be found in Figure 8.4. It shows the filtered acceleration and IMA. Every IMA window is classified in no, low, medium or high activity levels, which result in activity pattern, shown in the lower panel.

Over a complete measurement, TAVI-patients were more often not active than healthy subjects (65.3% (± 9.6%) and 54.5% (± 9.0%), respectively). High activity levels were sporadically seen in TAVI-patients (0.2% ± 0.3%), and very little in healthy subjects (2.4% ± 2.1%).

8.3.3. Daily activity levels

In 4 and 15 datasets from healthy and TAVI-patients respectively, a daily activity profile could be made. In Figure 8.2 the algorithm for day and night classification is visible. Longer inactive periods under the thresholds are classified as nights. Short periods under the cut-off are not detected as nights. Table 8.2, gives the overall result of the daily activity profiles. Averaged IMA during the day is 50.5 (± 17.6) and 32.2 (± 8.3). The percentage of no activity during the day was less compared to the complete measurement.

In one patient daily activity profiles could be made for T0, T1 and T2, which are displayed in Figure 8.5. No high activity was measured in all measurement. Similar portions of activity are found for T0 and T2, with low and medium activity of 25-37% and 15-22%, respectively. Directly post-TAVI (T1), less activity is detected, and low and high activity portions are 3-5% and 15-19%, respectively.

8.4. Discussion

An objective measure for physical functioning, can improve patient screening before TAVI. Physical functioning is estimated with the integrated modulus of tri-axial acceleration and gave a good correlation with gait speed. With this measure, daily physical activity profiles could be made, which could give more insight in patients physical performance.

Previous extensive work showed that IMA was related to daily energy expenditure [53]. In

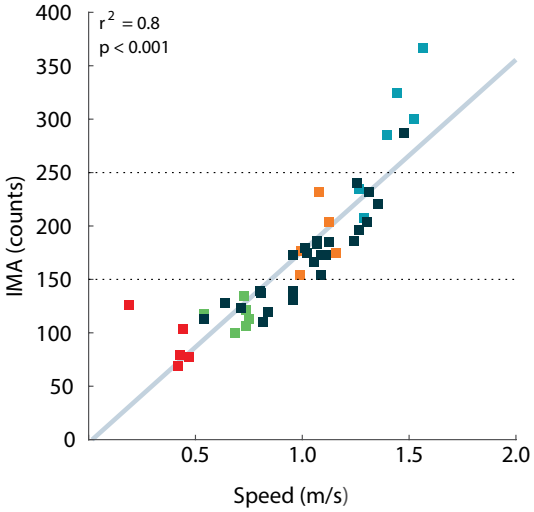


Figure 8.3 *Correlation between IMA and gait speed. Dark and light blue squares are the 6MWT results for the TAVI-patients and healthy subjects, respectively. Orange, green and red squares resulted from the metronome walking of 100, 75 and 50 steps/min, respectively. Correlation found between IMA and gait is r^2=0.8 (p<0.001).*

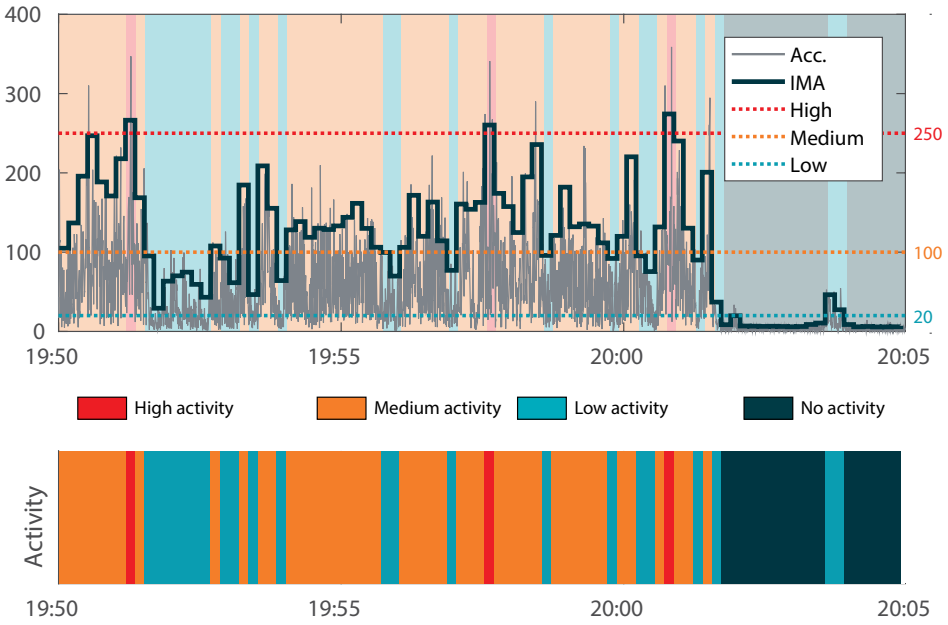


Figure 8.4 *Overview of the algorithm for detecting activity levels. The IMA is divided in 4 categories (high, medium, low and no activity) by thresholds. Hereafter, activity levels are computed every 10 seconds, given in the lower panel.*
Acc. indicates acceleromter data, IMA, integrated modulus of acceleration.

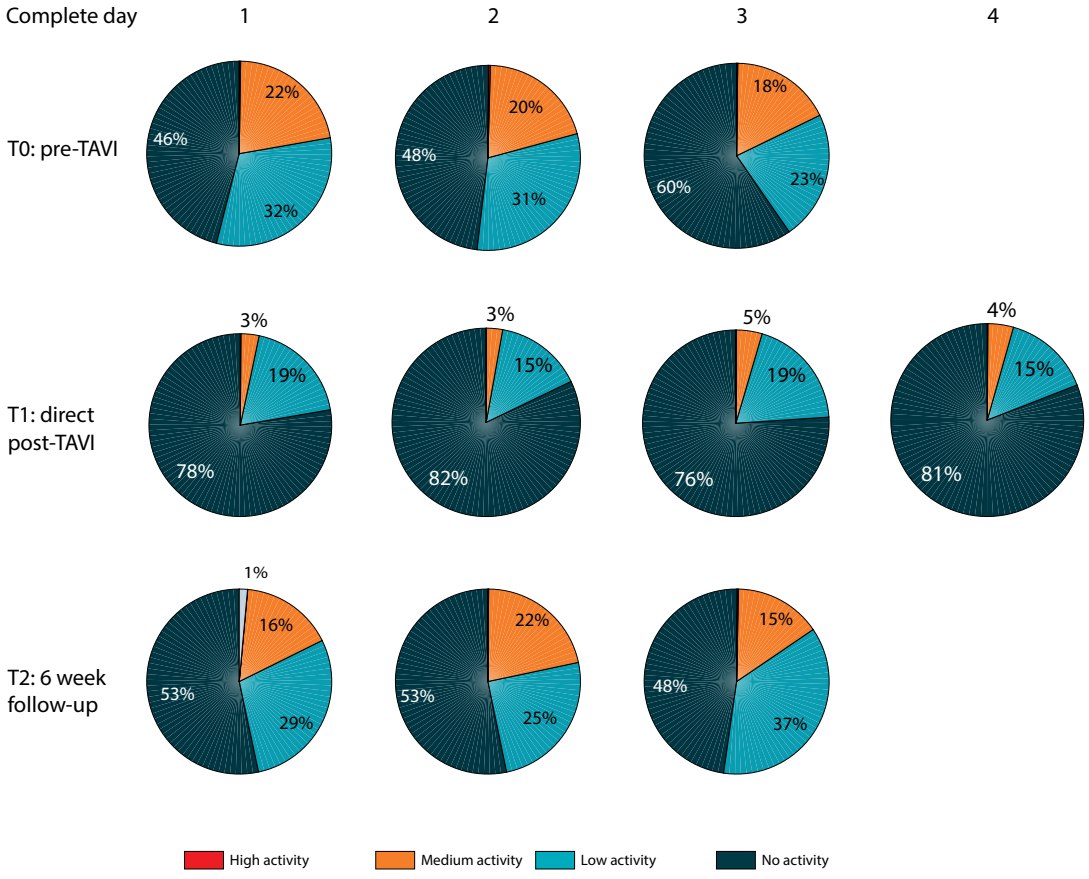


Figure 8.5 *Gives the activity levels per day, pre-TAVI, directly after TAVI and at 6 weeks follow-up for patient 201.The legend is given underneath. At T0 and T1 3 complete days are analyzed, at T2 4 days could be computed. There was no high activity detected at T0, T1 or T2.*

this paper a tri-axial accelerometer was attached to the lower back. The wearable biosensor is attached to the upper torso, so torso movement is also measured. Accordingly, IMA should again be validated to energy expenditure.

This study only shows some first ideas for using objective physical activity levels. But one of the major shortcomings here, is that the threshold selection was arbitrary. With the current thresholds, high activity was barely visible and minimal differences were visible between healthy subjects and TAVI patients. The thresholds should be optimized to show differences between patients with AoS. Other papers even suggest to analyze accelerometry without the use of cut-points, but rather using the raw data [55], [56]. It is believed this will improve physical activity characterization to estimate energy expenditure. Figure 8.1 shows already some promise, as there are two frequency peaks visible, in the walking frequency range [57]. The peak frequency could give insight into the gait and the power of the frequency could indicate how much a patient is walking. The physical activity classification research field has grown much the last two decades and an extensive study is needed to find a physical activity classification for the Philips wearable biosensor to provide essential information.

The work reported here is limited, but the use of activity levels shows great promise. Not only could it change TAVI screening, but also follow-up. Post-procedural, patients' activity could be monitored and coached to exercise more. Exercise training is known to have positive benefits on the exercise capacity and quality of life [58]. Also, pre- and post- TAVI activity could be compared as an objective outcome measure of TAVI. Moreover, regular objective assessment of activity levels could detect deterioration, as consequence of worsening AoS

The wearable biosensor also records vital signs, such as heart rate and respiratory rate. A further in-depth analysis of the patients cardiac function could made possible by combining these vital signs and activity analysis.

8.5. Conclusion

This chapter showed that objective activity levels could be estimated with the integrated modulus of the tri-axial acceleration. This measure shows promise to improve TAVI screening, as well as, monitoring and screening.

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Chapter A: Appendix

A.1. Overview of data collected during TELE-TAVI study

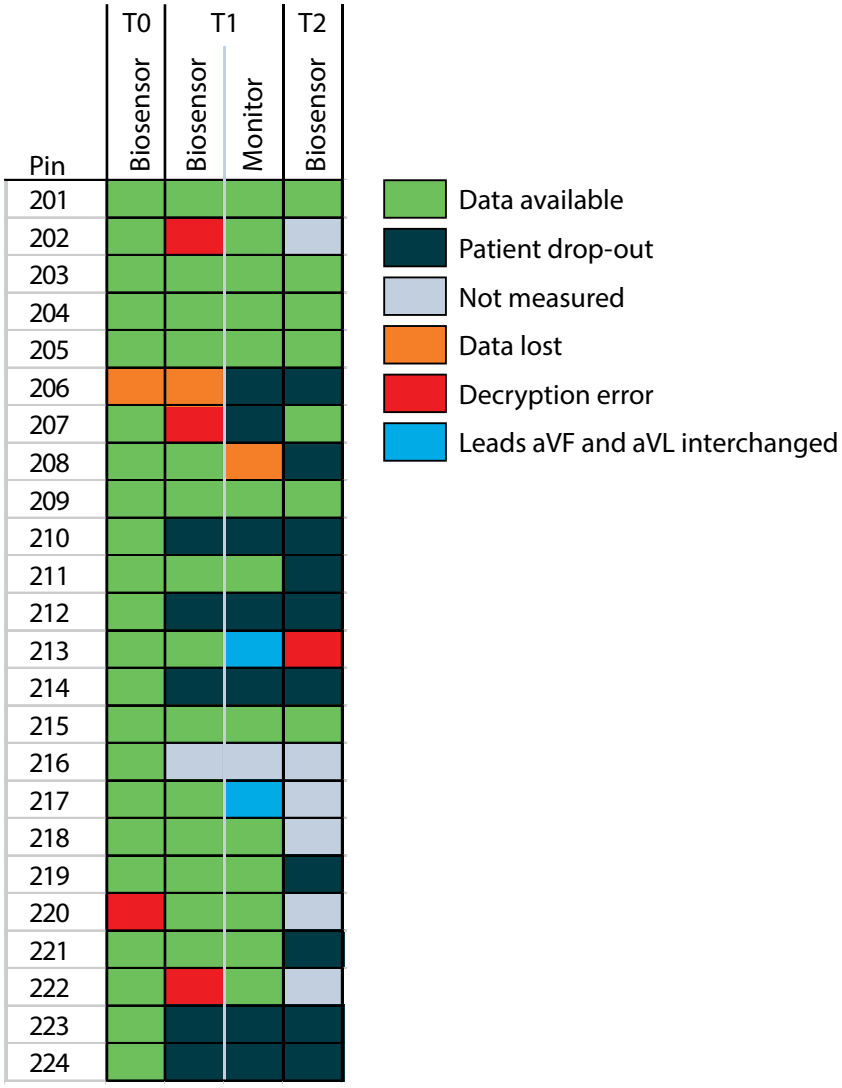

Figure A.1 *Overview TAVI-patient collected data and missing data. Data loss in 206 T0, occurred as files were deleted. Raw ECG data was missing in 206-T1 and in 208-T1 several leads were missing from the reference data.*

A.2. Supplementary data on the reliability of the Philips wearable biosensor

A.2.1. Distribution difference data

Table A.1 *Skewness and kurtosis of the difference between the biosensor and reference, unfiltered and filtered for HR and RespR. Skewness and kurtosis of normal distribution is 0 and 3, respectively*

			HR		HR filtered		**RespR**		**RespR filtered**	
		Pin	**s**	**k**	**s**	**k**	**s**	**k**	**s**	**k**
Healthy		101	4.4	35.9	4.4	37.8	0.6	3.7	-0.2	2.1
		102	0.8	11.1	1.1	14.9	-0.9	5.3	-0.4	3.6
		103	6.5	64.2	7.3	75.4	-0.4	3.4	0.9	3.6
		104	2.3	15.2	3.8	27.7	-0.1	2.6	1.0	4.9
		105	2.0	6.0	2.1	6.3	0.0	3.0	0.0	2.3
		106	2.2	17.9	2.4	20.8	-0.3	3.8	0.3	6.2
TAVI	Sinus	201	15.3	344.4	18.2	434.4	-0.2	3.5	-0.5	4.0
		204	3.6	38.6	3.8	37.2	-0.5	4.1	-0.6	4.4
		211	-2.9	30.8	-1.6	21.1	*	*	*	*
		213	1.8	20.9	2.8	23.0	0.2	4.8	0.2	5.5
		218	0.6	4.9	0.9	5.7	-1.5	6.7	-0.4	2.7
		219	0.9	8.0	1.3	9.4	-1.5	11.3	-0.4	2.7
		220	-8.9	138.8	-10.4	169.8	-1.1	8.7	-0.7	5.0
	AF	203	1.6	11.7	2.2	14.6	*	*	*	*
		205	-0.1	3.2	0.0	3.3	*	*	*	*
		209	-1.6	6.8	-2.1	9.1	*	*	*	*
		215	-2.1	9.5	-2.1	8.9	*	*	*	*
		217	0.5	3.1	0.6	3.3	-0.4	4.8	0.2	3.3
		221	0.6	5.5	0.7	6.2	-1.0	4.9	-0.9	5.1
Mean			1.4	40.9	1.9	48.9	-0.5	5.1	-0.1	4.0
SD			4.6	80.1	5.3	101.0	3.3	3.3	2.0	2.0

s indicates skewness; k, kurtosis; AF, atrial fibrillation; TAVI, transcatheter aortic valve implantation; HR, heart rate; RespR, respiratory rate, SD, standard deviation

** no data*

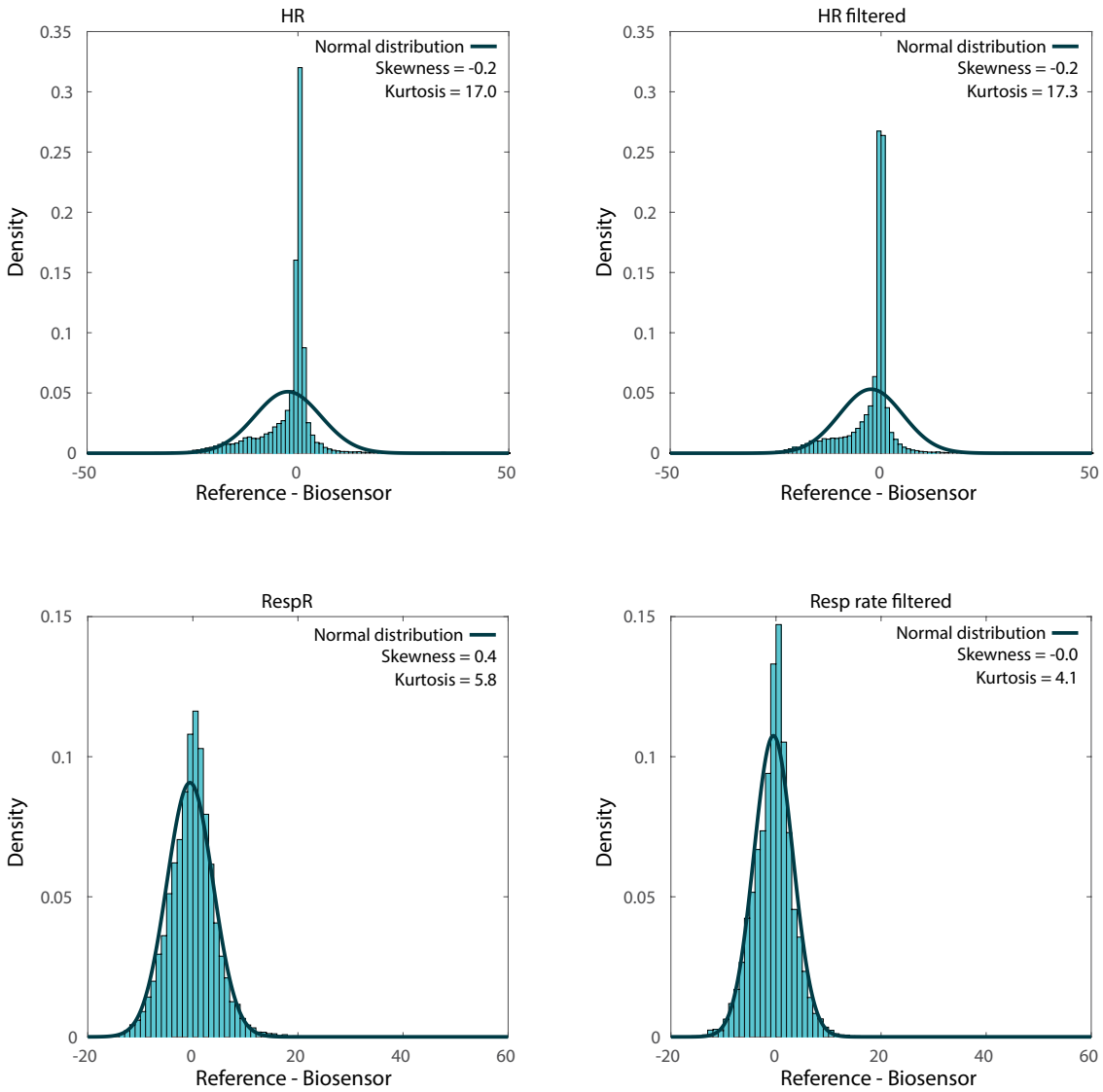

Figure A.2 *Distribution of the difference between the biosensor and reference, unfiltered and filtered for HR and RespR, for all subjects.*

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A.2.2. Precision and bias of the wearable biosensor

Table A.2 *Bias and precision of the wearable biosensors HR compared to the reference monitor for all subjects.*

		Pin	Mean reference	Mean biosensor	Bias	RPC	RPC	Lower LOA	Upper LOA
			Beats/min	*Beats/min*	*Beats/min*	*Beats/min*	*(%)*	*Beats/min*	*Beats/min*
Healthy		101	65.2	66.0	0.0	2.9	4.5	-2.9	2.9
		102	75.0	76.0	0.9	3.2	4.3	-2.2	4.1
		103	68.1	71.0	1.3	4.4	6.5	-3.1	5.6
		104	66.0	66.0	0.0	0.0	0.0	0.0	0.0
		105	70.0	75.0	1.0	11.3	17.0	-10.3	12.3
		106	72.0	72.0	0.0	1.5	2.0	-1.5	1.5
		Median	69.0	71.5	0.5	3.1	4.4	-2.6	3.5
		IQR	6.0	9.0	1.0	2.9	4.5	1.6	4.2
	Sinus	201	55.0	55.0	0.0	0.0	0.0	0.0	0.0
		204	52.0	52.0	0.0	1.5	2.7	-1.5	1.5
		211	69.0	69.0	0.0	2.0	2.9	-2.0	2.0
		213	57.0	57.0	0.0	1.0	1.7	-1.0	1.0
		218	79.0	79.0	0.0	2.9	3.7	-2.9	2.9
		219	64.0	65.0	0.0	1.5	2.6	-1.5	1.5
		220	75.0	75.0	0.0	0.5	0.7	-0.5	0.5
		Median	64.0	65.0	0.0	1.5	2.6	-1.5	1.5
		IQR	18.0	18.0	0.0	1.2	1.9	1.2	1.2
	AF	203	80.0	81.0	0.8	8.0	9.9	-7.1	8.8
		205	110.3	124.0	14.0	11.8	10.7	2.2	25.8
		209	96.0	101.0	3.8	16.1	16.6	-12.3	20.0
		215	86.4	88.0	0.1	12.6	14.4	-12.5	12.7
		217	99.0	102.0	3.0	7.7	7.9	-4.7	10.7
		221	90.7	95.0	3.7	14.7	16.0	-11.0	18.4
		Median	93.3	98.0	3.3	12.2	12.6	-8.8	15.5
		IQR	12.6	14.0	3.0	6.7	6.1	7.5	9.2
TAVI		Median	79.0	79.0	0.0	2.9	3.7	-2.9	2.9
		IQR	29.7	33.5	3.2	10.7	9.3	7.2	12.8
Median			75.2	77.3	1.5	5.4	6.5	-3.9	7.0
IQR			15.5	18.1	3.3	5.4	5.9	4.5	7.7

*IQR indicates inter quartile range; RPC, reproducibility coefficient (1.45*IQR, 1.96*SD); LOA, limit of agreement (1.45*IQR, 1.96*SD)*

Table A.3 *Bias and precision of the wearable biosensors HR filtered compared to the reference monitor for all subjects.*

		Pin	Mean reference	Mean biosensor	Bias	RPC	RPC	Lower LOA	Upper LOA
			Beats/min	*Beats/min*	*Beats/min*	*Beats/min*	*(%)*	*Beats/min*	*Beats/min*
Healthy		101	65.6	66.0	0.2	2.2	3.4	-2.0	2.4
		102	75.2	76.0	0.7	2.6	3.6	-1.9	3.4
		103	68.3	71.0	1.4	3.9	5.9	-2.5	5.3
		104	66.4	66.0	0.0	1.0	1.5	-1.0	1.0
		105	70.7	75.0	0.7	10.3	15.4	-9.6	11.1
		106	71.7	72.0	0.3	1.5	2.1	-1.2	1.8
		Median	69.5	71.5	0.5	2.4	3.5	-1.9	2.9
		IQR	5.3	9.0	0.5	2.4	3.8	1.3	3.6
	Sinus	201	55.1	55.0	0.0	0.8	1.4	-0.8	0.8
		204	52.2	52.0	0.0	1.3	2.4	-1.3	1.3
		211	69.0	69.0	0.0	1.3	1.8	-1.3	1.3
		213	56.7	57.0	0.1	0.8	1.5	-0.8	0.9
		218	79.4	79.0	0.0	1.8	2.3	-1.8	1.9
		219	64.4	65.0	0.2	1.0	1.7	-0.8	1.1
		220	75.3	75.0	0.0	0.9	1.2	-0.9	0.9
		Median	64.4	65.0	0.0	1.0	1.7	-0.9	1.0
		IQR	18.3	18.0	0.1	0.4	0.7	0.5	0.4
	AF	203	80.4	81.0	0.5	6.5	8.1	-6.0	7.0
		205	110.4	124.0	13.9	9.3	8.5	4.6	23.2
		209	96.3	101.0	4.1	12.5	12.9	-8.5	16.6
		215	86.4	88.0	0.6	11.5	13.2	-11.0	12.1
		217	98.9	102.0	3.0	5.8	5.9	-2.8	8.9
		221	90.7	95.0	3.4	13.6	14.8	-10.2	17.0
		Median	93.5	98.0	3.2	10.4	10.7	-7.2	13.6
		IQR	12.5	14.0	3.5	6.0	5.1	7.5	8.2
TAVI		Median	79.4	79.0	0.2	1.8	2.4	-1.6	2.0
		IQR	29.6	33.5	3.1	8.9	7.9	5.8	12.1
Median			75.4	77.3	1.5	4.7	5.7	-3.1	6.2
IQR			15.5	18.1	3.2	4.5	5.0	4.0	6.8

*IQR indicates inter quartile range; RPC, reproducibility coefficient (1.45*IQR, 1.96*SD); LOA, limit of agreement (1.45*IQR, 1.96*SD)*

Table A.4 *Bias and precision of the wearable biosensors RespR compared to the reference monitor for all subjects.*

		Pin	Mean reference	Mean biosensor	Bias	RPC	RPC	Lower LOA	Upper LOA
			Breaths/ min	*Breaths/ min*	*Breaths/ min*	*Breaths/ min*	*(%)*	*Breaths/ min*	*Breaths/ min*
Healthy		101	15.5	13.5	-1.9	7.8	54.9	-9.7	6.0
		102	15.9	13.4	-2.5	8.1	44.6	-10.6	5.6
		103	15.5	13.7	-1.7	6.9	40.7	-8.6	5.2
		104	17.0	16.3	-0.7	8.7	59.8	-9.4	8.0
		105	16.9	14.9	-2.1	10.7	64.4	-12.7	8.6
		106	16.2	16.2	-0.1	6.3	39.2	-6.4	6.2
		Median	16.2	14.7	-1.5	8.1	50.6	-9.6	6.6
		SD	0.7	1.3	0.9	1.5	10.6	2.1	1.4
	Sinus	201	19.3	18.2	-1.0	6.1	32.7	-7.1	5.0
		204	16.4	15.9	-0.6	5.7	35.0	-6.2	5.1
		211	16.4	17.1	0.8	7.4	78.1	-6.6	8.1
		218	14.7	15.6	1.0	7.4	49.2	-6.5	8.4
		219	14.3	14.5	0.0	9.9	81.8	-9.8	9.9
		220	15.9	15.7	-0.1	8.2	50.2	-8.4	8.1
		Median	16.2	16.2	0.0	7.4	54.5	-7.4	7.4
		SD	1.8	1.3	0.8	1.5	21.0	1.4	2.0
	AF	217	17.6	21.2	3.6	9.0	75.5	-5.4	12.5
		221	18.0	20.9	2.9	9.2	55.6	-6.3	12.2
		Median	17.8	21.1	3.2	9.1	65.6	-5.9	12.3
		SD	0.3	0.2	0.5	0.2	14.1	0.6	0.3
TAVI		Median	16.6	17.4	0.8	7.9	57.3	-7.0	8.7
		SD	1.7	2.5	1.6	1.5	19.2	1.4	2.8
Median			16.4	16.2	-0.2	7.9	54.4	-8.1	7.8
SD			1.3	2.5	1.8	1.5	15.9	2.1	2.5

*ISD indicates standard deviation; RPC, reproducibility coefficient (1.45*IQR, 1.96*SD); LOA, limit of agreement (1.45*IQR, 1.96*SD)*

Table A.5 *Bias and precision of the wearable biosensors RespR filtered compared to the reference monitor for all subjects.*

		Pin	Mean reference	Mean biosensor	Bias	RPC	RPC	Lower LOA	Upper LOA
			Breaths/ min	*Breaths/ min*	*Breaths/ min*	*Breaths/ min*	*(%)*	*Breaths/ min*	*Breaths/ min*
Healthy		101	15.8	13.5	-1.9	4.8	34.5	-6.8	2.9
		102	15.9	13.4	-2.5	5.8	35.2	-8.3	3.2
		103	15.3	13.7	-1.6	4.5	29.6	-6.1	3.0
		104	17.1	16.3	-0.8	7.6	60.9	-8.4	6.8
		105	17.6	14.9	-2.1	10.2	54.9	-12.3	8.1
		106	16.1	16.2	0.0	3.9	25.5	-4.0	3.9
		Median	16.3	14.7	-1.5	6.2	40.1	-7.7	4.6
		SD	0.9	1.3	0.9	2.4	14.3	2.8	2.2
	Sinus	201	19.3	18.2	-1.0	5.0	25.9	-6.0	4.0
		204	16.4	15.9	-0.5	4.2	25.0	-4.7	3.6
		211	16.6	17.1	0.5	6.2	55.3	-5.7	6.7
		218	14.7	15.6	0.9	6.2	45.5	-5.3	7.2
		219	14.2	14.5	0.0	7.5	56.1	-7.5	7.5
		220	15.9	15.7	-0.1	6.9	42.4	-7.1	6.8
		Median	16.2	16.2	0.0	6.0	41.7	-6.0	6.0
		SD	1.8	1.3	0.7	1.2	13.7	1.1	1.7
	AF	217	17.8	21.2	3.4	7.3	54.4	-3.9	10.7
		221	18.0	20.9	2.9	7.9	47.1	-5.0	10.8
		Median	17.9	21.1	3.1	7.6	50.7	-4.5	10.7
		SD	0.2	0.2	0.4	0.4	5.2	0.8	0.0
TAVI		Median	16.6	17.4	0.8	6.4	43.9	-5.7	7.2
		SD	1.7	2.5	1.6	1.3	12.5	1.2	2.6
Median			16.5	16.2	-0.2	6.3	42.3	-6.5	6.1
SD			1.4	2.5	1.7	1.7	12.9	2.2	2.7

*SD indicates standard deviation; RPC, reproducibility coefficient (1.45*IQR, 1.96*SD); LOA, limit of agreement (1.45*IQR, 1.96*SD)*

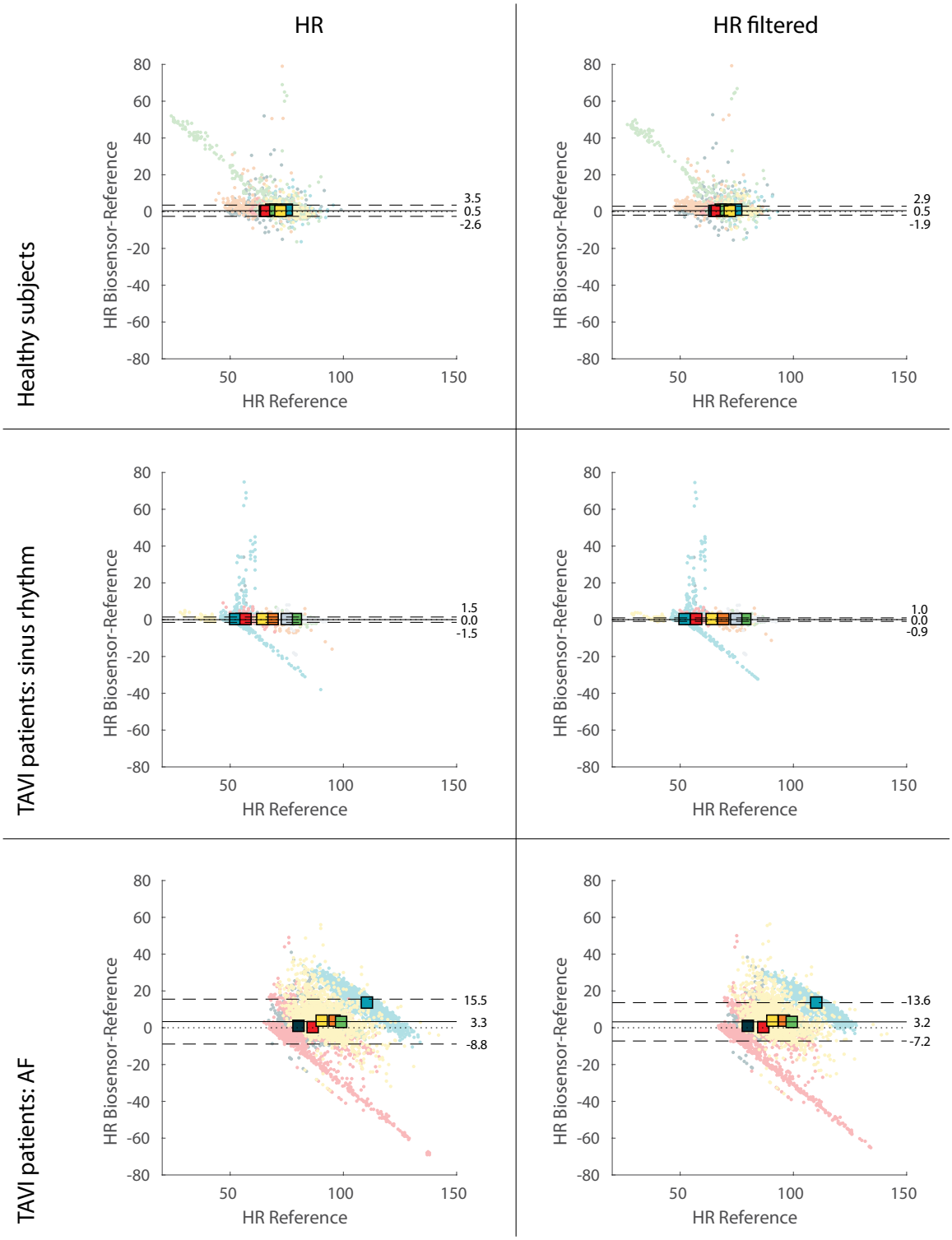


Figure A.3 *Bland-Altman figures comparing HR from the biosensor to the reference monitor (unfiltered on the left, filtered on the right), for healthy subjects (top panels), TAVI patients with sinus rhythm (middle panels) and AF (bottom panels).*

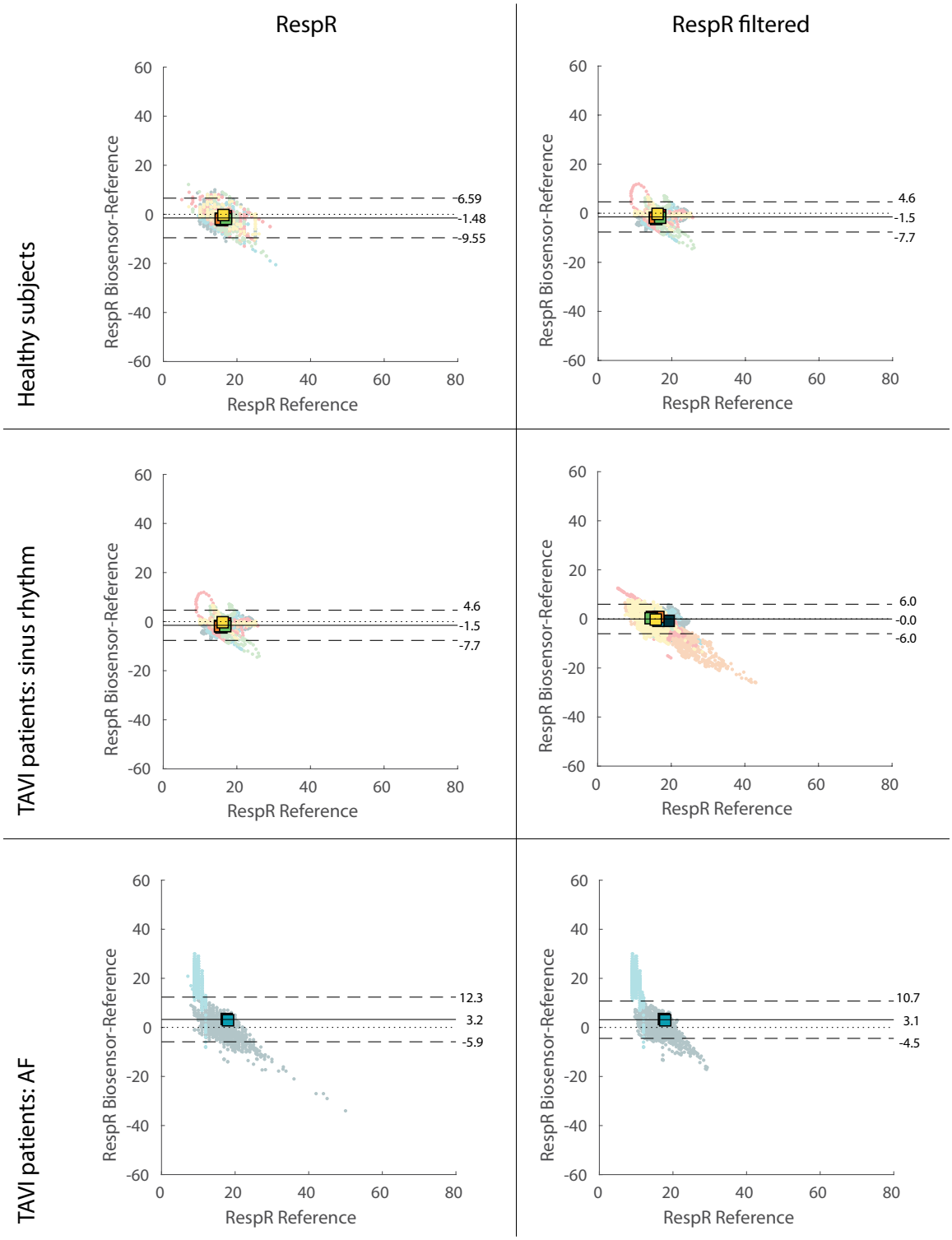


Figure A.4 *Bland-Altman figures comparing RespR from the biosensor to the reference monitor (unfiltered on the left, filtered on the right), for healthy subjects (top panels), TAVI patients with sinus rhythm (middle panels) and AF (bottom panels).*

A.2.3. Walking detection of the wearable biosensor

Table A.10 *Detection of walking by the wearable biosensor during the walking exercises of the healthy subjects.*

	100 steps/min		75 steps/min		50 steps/min	
	Percentage walking	Speed	Percentage walking	Speed	Percentage walking	Speed
Pin	(%)	(m/s)	(%)	(m/s)	(%)	(m/s)
101	100,0	1.25	95,5	0.83	1,8	0.48
102	96,2	1.19	98,1	0.82	0,0	0.49
103	100,0	1.11	97,2	0.81	2,8	0.22
104	100,0	1.10	78,3	0.77	0,0	0.47
105	100,0	1.29	71,2	0.82	0,0	0.52
106	100,0	1.20	8,6	0.60	0,0	*
Mean	99,4	1.19	74,8	0.77	0,8	0.43
SD	1,5	0.08	34,3	0.09	1,2	0.12

SD indicates standard deviation; min, minute, m/s, meter per second

** no data available*

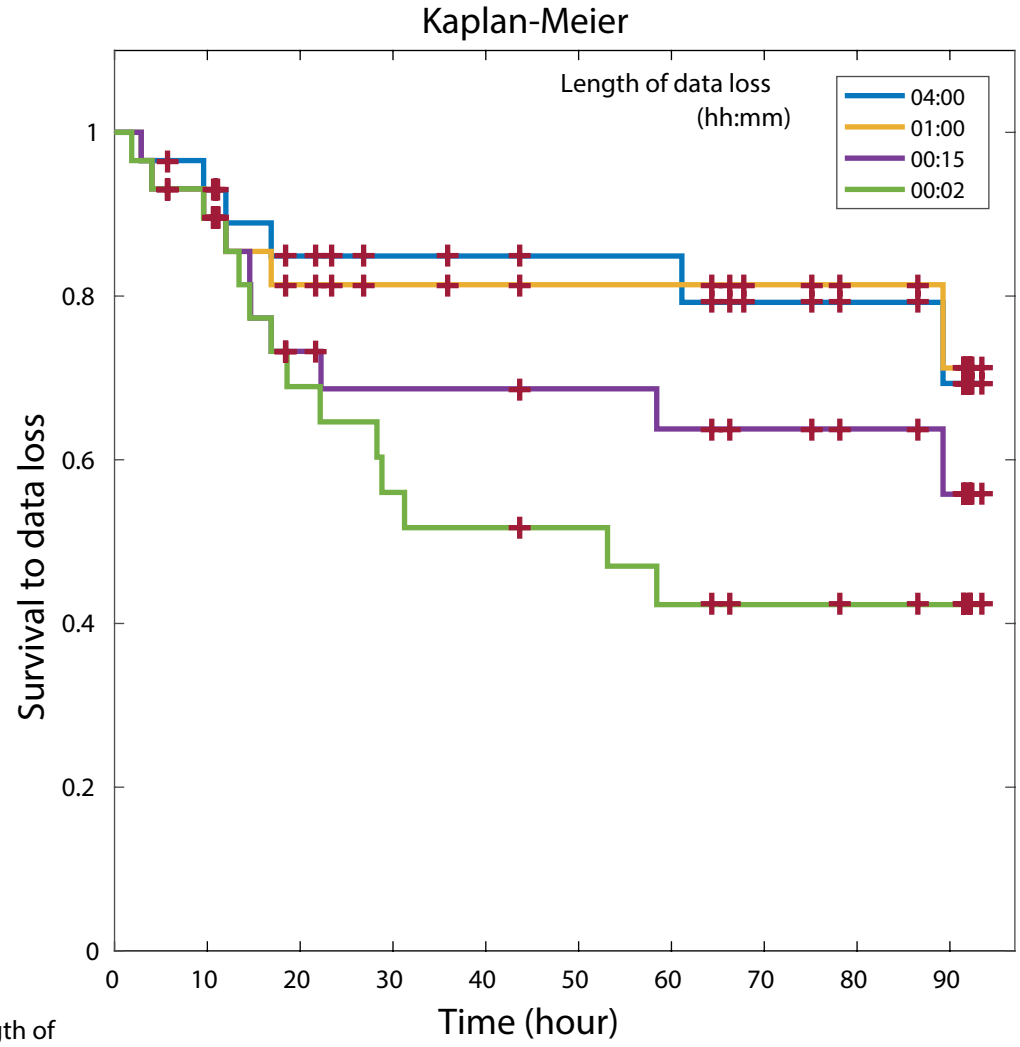
Table A.6 *Detection of walking by the wearable biosensor during the walking exercises of the healthy subjects.*

	Pin		Walking detection (%)	Speed (m/s)
Healthy	101		100.0	1.60
	102		99.4	1.55
	103		100.0	1.41
	104		99.1	1.70
	105		100.0	1.44
	106		100.0	1.74
	Mean		99.8	1.57
	SD		0.4	0.13
TAVI	201	T0	91.6	1.41
	201	T2	100.0	1.50
	202	T0	98.3	1.21
	203	T0	91.7	0.90
	203	T2	92.9	0.79
	204	T0	91.7	0.91
	204	T2	100.0	1.21
	207	T0	100.0	1.45
	207	T2	100.0	1.46
	208	T0	93.2	1.06
	209	T0	73.5	0.60
	209	T2	97.7	1.19
	210	T0	99.7	1.06
	211	T0	100.0	1.06
	212	T0	100.0	1.39
	213	T0	100.0	1.17
	215	T0	99.1	1.14
	215	T2	100.0	1.25
	216	T0	85.0	0.71
	217	T0	100.0	1.13
	218	T0	100.0	1.19
	219	T0	97.4	0.94
	221	T0	100.0	1.38
	222	T0	98.6	0.89
	223	T0	99.4	1.24
	224	T2	99.4	1.64
	Mean		96.5	1.15
	SD		6.1	0.26
Mean			97.1	1.23
SD			5.6	0.29

SD indicates standard deviation; m/s, meter per second

** no data available*

A.2.4. Measurement length



Length of data loss (hh:mm)	Number recording:									
04:00	29	26	20	17	16	15	15	11	9	7
01:00	29	25	19	16	15	14	14	11	9	7
00:15	29	25	17	15	15	14	13	11	9	7
00:02	29	25	16	13	12	11	9	7	6	5

Figure A.5 *Gives the Kaplan-Meier figure for the survival to first data loss, with gaps of 2 minutes, 15 minutes, 1 hour and 4 hours. Every plus sign represents the end of a measurement. Under the figure, the number at risk are shown, every 10 hours.*

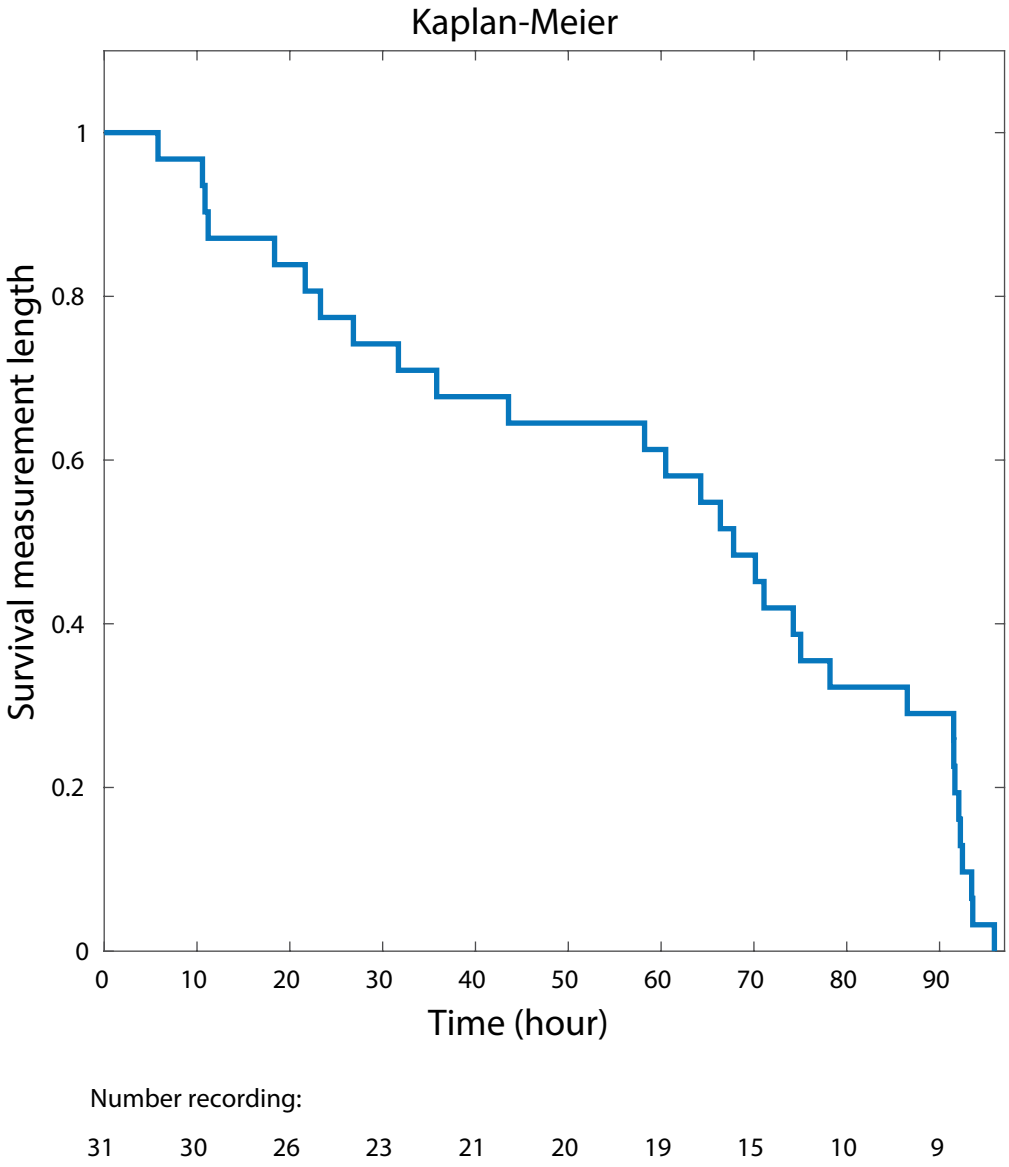


Figure A.6 *Gives survival of the measurement of the wearable biosensor in the TELE-TAVI study. Under the figure, the number at risk are shown, every 10 hours.*

Table A.7 *Measurement length, data loss and usable data for all subjects. Detection of walking by the wearable biosensor during the walking exercises of the healthy subjects.*

	Pin		Length measurement	Data loss	Data not lost	Usable data	Usable data
			hh:mm:ss	hh:mm:ss	(%)	hh:mm:ss	(%)
Healthy	101		95:55:39	00:47:29	99.2	95:08:10	99.1
	102		05:52:23	00:01:57	99.4	05:50:26	6.1
	103		46:10:51	00:04:59	99.8	46:05:52	48.0
	104		95:56:12	00:00:12	100.0	95:55:59	99.9
	105		40:35:40	00:01:09	100.0	40:34:30	42.3
	106		91:28:13	39:34:20	56.7	51:53:52	54.1
	Mean		62:39:50	06:45:01	92.5	55:54:48	58.2
	SD		37:29:21	16:04:56	17.5	34:37:36	36.1
TAVI	201	T0	92:14:32	00:01:36	100.0	92:12:56	96.1
	201	T2	91:39:04	00:11:44	99.8	91:27:19	95.3
	202	T0	75:02:01	00:11:38	99.7	74:50:23	78.0
	203	T0	95:54:26	50:07:03	47.9	45:47:22	47.7
	203	T2	93:27:29	00:00:13	100.0	93:27:16	97.3
	204	T0	66:23:06	00:02:21	99.9	66:20:44	69.1
	204	T2	58:13:13	20:27:23	64.5	37:45:49	39.3
	205	T0	78:11:44	00:02:50	99.9	78:08:54	81.4
	205	T2	43:33:33	00:00:04	100.0	43:33:28	45.4
	207	T0	70:09:22	48:10:39	31.1	21:58:43	22.9
	207	T0	71:05:05	11:56:04	83.0	59:09:00	61.6
	208	T0	11:12:10	00:04:25	99.3	11:07:45	11.6
	209	T0	35:49:16	01:26:56	96.0	34:22:19	35.8
	209	T2	05:47:52	00:00:04	100.0	05:47:48	6.0
	210	T0	64:16:00	00:01:07	100.0	64:14:53	66.9
	211	T0	92:27:50	00:26:52	99.5	92:00:58	95.9
	212	T0	26:50:52	01:59:21	92.6	24:51:31	25.9
	213	T0	21:39:36	00:07:09	99.4	21:32:26	22.4
	214	T0	10:35:13	00:01:14	99.8	10:33:59	11.0
	215	T0	74:14:33	59:14:40	20.3	14:59:53	15.6
	215	T2	93:34:31	04:30:38	95.3	89:03:53	92.8
	216	T0	67:48:32	00:37:47	99.1	67:10:45	70.0
	217	T0	18:21:17	00:00:03	100.0	18:21:13	19.1
	218	T0	92:04:21	00:01:36	100.0	92:02:44	95.9
	219	T0	91:31:47	00:01:33	100.0	91:30:13	95.3
	221	T0	10:51:45	00:00:00	100.0	10:51:45	11.3
	222	T0	91:31:13	00:00:15	100.0	91:30:57	95.3
	223	T0	23:18:07	01:06:52	95.1	22:11:14	23.1
	224	T0	86:31:24	00:00:07	100.0	86:31:17	90.1
	Mean		60:29:39	06:55:36	90.4	53:34:03	55.8
	SD		31:41:52	16:24:38	21.4	32:22:33	33.7
Mean			60:51:58	06:53:47	90.8	53:58:11	56.2
SD			32:10:07	16:07:08	20.6	32:15:16	33.6

hh:mm:ss indicates hours:minutes:seconds

Table A.8 *First point of data loss for every subject in the TELE-TAVI study.*

	Pin		Point of first data loss			
			2 min	**15 min**	**1 hour**	**4 hours**
Healthy	101		17:06:11	17:06:11		
	102					
	103					
	104					
	105					
	106		10:17:14	10:17:14	10:17:14	10:17:14
TAVI	201	T0				
	201	T2	31:14:41			
	202	T0	28:16:10			
	203	T0	09:35:51	09:35:51	09:35:51	09:35:51
	203	T2				
	204	T0				
	204	T2	16:52:49	16:52:49	16:52:49	16:52:49
	205	T0				
	205	T2				
	207	T0	01:51:06	02:52:50	02:52:50	02:52:50
	207	T0	04:01:19	04:01:19	04:01:19	61:07:28
	208	T0				
	209	T0	14:34:01	14:34:01		
	209	T2				
	210	T0				
	211	T0	28:48:31			
	212	T0	13:24:47	14:39:51		
	213	T0	18:35:13			
	214	T0				
	215	T0	11:59:37	11:59:37	11:59:37	11:59:37
	215	T2	53:06:42	89:15:37	89:15:37	89:15:37
	216	T0	58:24:58	58:24:58		
	217	T0				
	218	T0				
	219	T0				
	221	T0				
	222	T0				
	223	T0	22:09:26	22:14:44		
	224	T0				

hh:mm:ss indicates hours:minutes:seconds

A.3. Supplementary data of the wearability questionnaires

A.3.1. Wearability questionnaires

As given to patients (in Dutch)

Evaluatie systeem en sensor

Op de volgende bladzijde gaat u een vragenlijst invullen over het gebruik van het systeem; de draagbare biosensor, met bijbehorende telefoon en app. Deze vragenlijst moet ingevuld worden door diegene die het meest het systeem heeft gebruikt. Deze vragenlijst bestaat uit 16 stellingen waarbij U kunt aangeven of deze stelling overeenkomt. U kunt kiezen uit zeven opties; van helemaal eens (1) tot helemaal niet mee eens (7) of niet van toepassing (N.v.t.). Denk vooral niet te lang na over de antwoorden.

Hierna volgen nog eens 9 vragen over het comfort tijdens het dragen en het vervangen van de sensor.

Deze vragenlijsten zijn ingevuld door (aankruisen wat van toepassing is):

- ☐ Patiënt/proefpersoon
- ☐ Mantelzorger
- ☐ Anders, namelijk:

Evaluatie systeem

		Helemaal eens						Helemaal niet mee eens	
		1	**2**	**3**	**4**	**5**	**6**	**7**	N.v.t.
1	Over het algemeen, ben ik tevreden met het gebruiksgemak.	O	O	O	O	O	O	O	O
2	Het was eenvoudig om het systeem te gebruiken.	O	O	O	O	O	O	O	O
3	Ik kon de taken en scenario's snel afmaken in de app.	O	O	O	O	O	O	O	O
4	Ik voelde me op mijn gemak tijdens het gebruik van het systeem.	O	O	O	O	O	O	O	O
5	Het was gemakkelijk om te leren hoe ik het systeem moest gebruiken.	O	O	O	O	O	O	O	O
6	Ik denk dat ik met dit systeem snel in de praktijk kan werken.	O	O	O	O	O	O	O	O
7	Ik kreeg foutmeldingen waaruit bleek hoe ik een probleem kon oplossen.	O	O	O	O	O	O	O	O
8	Als ik een foutje maakte, kon ik dit snel en gemakkelijk recht zetten.	O	O	O	O	O	O	O	O
9	De informatie (zoals de berichten op het scherm en de handleiding) was duidelijk.	O	O	O	O	O	O	O	O
10	Het was gemakkelijk om de juiste informatie te vinden.	O	O	O	O	O	O	O	O
11	De informatie die ik op het scherm kreeg hielp bij het gebruiken van de app en sensor.	O	O	O	O	O	O	O	O
12	De indeling van de informatie op het scherm was duidelijk.	O	O	O	O	O	O	O	O
13	De interface zag er aangenaam uit (Met de interface wordt bedoeld alle onderwerpen die je kunt zien die nodig zijn om het platform te gebruiken. Bijvoorbeeld: het scherm, de plaatjes en de taal.)	O	O	O	O	O	O	O	O
14	Ik vond het fijn om de interface te gebruiken (invullen van gegevens op de diverse schermen).	O	O	O	O	O	O	O	O
15	Dit systeem heeft alle functies en mogelijkheden die ik ervan verwacht.	O	O	O	O	O	O	O	O
16	Over het algemeen, ben ik tevreden met het systeem.	O	O	O	O	O	O	O	O

Evaluatie sensor

1. Hoe was het dragen van de biosensor?

Comfortabel						Oncomfortabel	N.v.t.
O	O	O	O	O	O	O	O

2. Hebt u last gehad van jeuk door de biosensor?

Geen jeuk						Veel jeuk	N.v.t.
O	O	O	O	O	O	O	O

3. Hebt u last gehad van huid irritatie?

Geen irritatie						Veel irritatie	N.v.t.
O	O	O	O	O	O	O	O

4. Bleef de biosensor goed op de huid vastplakken?

Bleef volledig plakken						Is losgekomen	N.v.t.
O	O	O	O	O	O	O	O

5. Kwam de biosensor gemakkelijk los van de huid?

Gemakkelijk						Veel moeite	N.v.t.
O	O	O	O	O	O	O	O

6. Was het verwijderen van de sensor pijnlijk?

Niet pijnlijk						Erg pijnlijk	N.v.t.
O	O	O	O	O	O	O	O

7. Was u beperkt in uw activiteiten door de meting?

Niet beperkt						Erg beperkt	N.v.t.
O	O	O	O	O	O	O	O

8. Had u de telefoon altijd bij u?

Altijd						Nooit	N.v.t.
O	O	O	O	O	O	O	O

9. Het verwisselen van de sensor was gemakkelijk.

Helemaal eens						Helemaal oneens	N.v.t.
O	O	O	O	O	O	O	O

Opmerkingen, aanvullingen en praktische beperkingen:

A.3.2. Results from PSSUQ for every study participant

Table A.11 *PSSUQ results for every study participant*

Pin		Overall	SysUse	InfoQual	IntQual	Mean	SD
201	T0	85.6	88.9	80.6	88.9	86.1	4.8
201	T1	96.4	94.4	97.2	100.0	97.2	2.8
201	T2	90.5	94.4	88.9	83.3	88.9	5.6
202	T0	55.6	75.0	0.0	33.3	36.1	37.6
202	T1	55.6	75.0	0.0	33.3	36.1	37.6
203	T0	84.7	86.7	83.3	83.3	84.4	1.9
203	T1	83.3	83.3	83.3	83.3	83.3	0.0
203	T2	92.9	93.3	91.7	94.4	93.1	1.4
204	T0	57.1	53.3	83.3	50.0	62.2	18.4
204	T1	84.4	80.6	88.9	83.3	84.3	4.2
204	T2	46.7	44.4	33.3	66.7	48.1	17.0
205	T1	88.9	91.7	83.3		87.5	5.9
205	T2	66.7	66.7			66.7	0.0
206	T1						
207	T0	15.6	25.0	13.9	4.2	14.4	10.4
207	T1	44.8	33.3	52.8	50.0	45.4	10.5
207	T2	26.0	25.0	33.3	16.7	25.0	8.3
208	T0	12.5	16.7	0.0	25.0	13.9	12.7
209	T0	38.1	33.3	38.9	44.4	38.9	5.6
209	T1	50.0	60.0	40.0	50.0	50.0	10.0
209	T2	37.8	44.4	30.6	38.9	38.0	7.0
211	T0	40.6	38.9	47.2	33.3	39.8	7.0
212	T0	73.8	75.0	75.0	66.7	72.2	4.8
213	T0	87.2	86.7	87.5	87.5	87.2	0.5
213	T1	94.8	100.0	91.7	91.7	94.4	4.8
213	T2	100.0	100.0	100.0	100.0	100.0	0.0
214	T0						
215	T0	40.9	46.7	38.9	33.3	39.6	6.7
215	T1						
215	T2	91.1	100.0	77.8	100.0	92.6	12.8
216	T0	100.0	100.0	100.0	100.0	100.0	0.0
217	T0	37.8	66.7	16.7	22.2	35.2	27.4
217	T1	2.8	2.8			2.8	0.0
218	T0	97.8	100.0	94.4	100.0	98.1	3.2
218	T1	4.8	10.0	0.0	4.2	4.7	5.0
219	T0	77.1	91.7	83.3	45.8	73.6	24.4
219	T1	16.7	16.7	16.7	16.7	16.7	0.0
220	T0	26.4	16.7	20.0	50.0	28.9	18.4
220	T1	45.5	20.0	66.7		43.3	33.0
221	T0	88.5	94.4	88.9	79.2	87.5	7.7
221	T1	34.4	27.8	41.7	33.3	34.3	7.0
222	T0	100.0	100.0	100.0	100.0	100.0	0.0
222	T1	100.0	100.0	100.0	100.0	100.0	0.0
223	T0	81.0	72.2	100.0	50.0	74.1	25.1
224	T0	100.0	100.0	100.0	100.0	100.0	0.0
Mean		63.2	65.0	61.7	61.7	62.8	9.3
SD		30.7	31.9	34.7	31.5	32.7	10.4

Overall system use (SysUse), information quality (InfoQual) and interface quality (IntQuality), SD indicates standard deviation

A.3.3. Results custom made questionnaire for every measurement moment

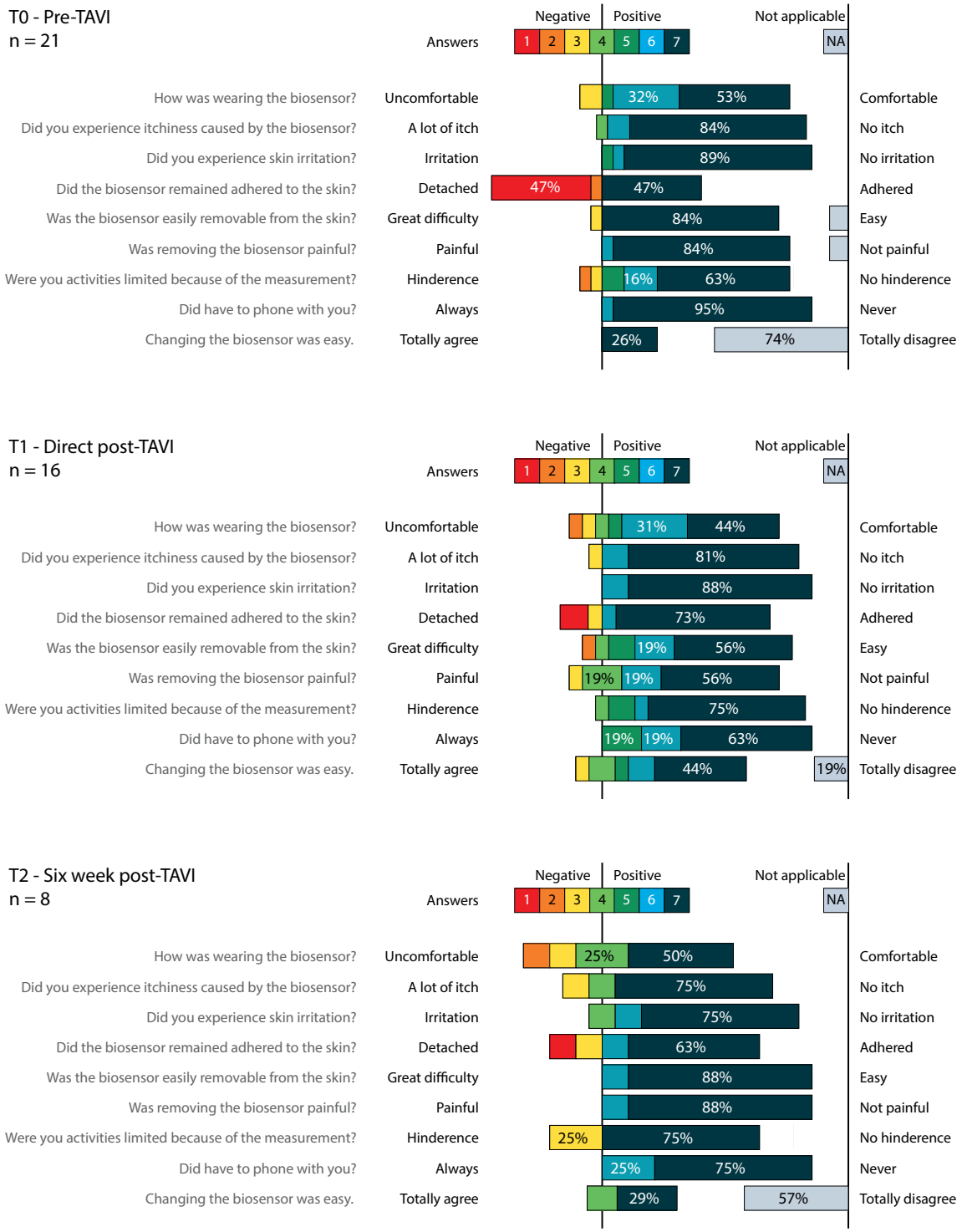


Figure A.7 *Results of custom made questionnaire for T0, T1 and T2.*

A.4. Supplementary data of the activity results

A.4.1. Results of activity analysis

Table A.9 *IMA and activity characteristics of a full measurement, for all study participants.*

			IMA					Activity levels			
	Pin		Mean	SD	Range		Empty	No	Low	Medium	High
							(%)	(%)	(%)	(%)	(%)
Healthy	101		44.4	72.2	3.6	767.4	1.1	55.2	31.2	12.2	1.4
	102		85.3	119.2	5.5	1214.5	0.8	38.4	30.8	24.5	6.3
	103		35.2	54.6	3.4	394.1	0.6	64.4	24.0	10.9	0.7
	104		45.1	68.4	3.6	588.0	0.1	57.7	28.1	11.0	3.2
	105		47.3	61.3	3.6	806.0	0.2	51.3	32.5	15.0	1.2
	106		45.7	63.9	3.6	453.1	43.8	59.7	22.4	16.5	1.4
	Mean		50.5	73.3	3.9	703.9	7.8	54.5	28.2	15.0	2.4
	SD		17.6		0.8	299.2	17.7	9.0	4.1	5.2	2.1
TAVI	201	T0	31.1	48.8	4.0	359.3	0.1	71.6	17.2	11.0	0.1
	201	T2	34.4	48.3	3.6	347.6	0.3	66.9	20.5	12.5	0.1
	202	T0	34.5	43.2	3.7	310.9	0.4	61.8	27.8	10.4	0.1
	203	T0	28.9	41.3	4.0	313.0	52.2	68.6	22.5	8.7	0.1
	203	T2	20.0	30.4	3.9	333.4	0.1	79.0	16.4	4.5	0.0
	204	T0	20.7	29.9	3.1	305.3	0.3	75.9	20.4	3.6	0.1
	204	T2	22.8	34.6	3.5	279.7	39.5	75.9	18.0	6.1	0.0
	207	T0	35.3	46.3	4.5	312.1	69.0	60.7	28.3	10.9	0.1
	207	T2	39.8	50.4	3.3	332.8	17.1	57.6	28.2	14.1	0.1
	208	T0	38.6	44.7	4.4	297.6	0.8	54.1	31.8	14.0	0.1
	209	T0	26.1	31.0	3.7	269.8	4.4	63.9	30.9	5.3	0.0
	209	T2	44.9	50.6	5.4	384.4	0.3	48.0	37.0	15.0	0.0
	210	T0	42.2	57.3	3.5	497.0	0.1	57.2	29.0	13.1	0.8
	211	T0	31.2	41.8	3.4	495.6	0.7	64.4	26.7	8.7	0.2
	212	T0	41.2	60.0	3.8	364.3	7.5	66.1	17.6	15.5	0.8
	213	T0	26.5	43.1	3.7	402.3	0.7	72.5	19.1	8.3	0.1
	215	T0	41.6	51.3	3.9	344.0	79.7	55.1	29.2	15.6	0.1
	215	T2	32.2	45.8	3.6	370.5	4.8	70.5	17.7	11.6	0.2
	216	T0	19.7	29.9	3.8	310.4	1.0	80.8	14.2	5.0	0.0
	217	T0	22.0	34.2	4.7	295.2	0.1	78.8	15.7	5.5	0.0
	218	T0	30.5	43.2	4.0	355.0	0.1	65.7	24.8	9.3	0.1
	219	T0	20.5	30.0	4.0	334.4	0.1	76.8	18.6	4.6	0.0
	221	T0	46.7	52.3	4.8	323.8	0.0	46.4	38.2	15.2	0.1
	222	T0	29.8	40.7	3.6	377.1	0.1	65.9	25.7	8.3	0.1
	223	T0	35.9	43.6	3.6	347.1	5.1	58.3	30.4	11.2	0.1
	224	T0	40.9	53.9	3.8	392.8	0.0	55.2	32.6	11.0	1.2
	Mean		32.2	43.3	3.9	348.3	10.9	65.3	24.6	10.0	0.2
	SD		8.3		0.5	55.3	22.5	9.6	6.8	3.8	0.3
Mean			35.7	48.9	3.9	415.0	10.3	63.3	25.2	10.9	0.6
SD			12.5		0.6	191.8	21.5	10.3	6.5	4.5	1.2

TAVI indicates transcatheter aortic valve implantation; IMA, integrated modulus of acceleration; SD, standard deviation; T, measurement at T0, T1, or T2.

A.4.2. Results of daily activity

Table A.12 *IMA and activity characteristics of full days, for all study participants.*

	Pin		Days	IMA		Activity levels			
				Mean	SD	No	Low	Medium	High
						(%)	(%)	(%)	(%)
Healthy	101		3	48.0	1.9	34.9	32.7	12.8	2.0
	103		2	49.2	0.7	27.1	33.7	17.5	1.0
	104		3	45.1	0.1	35.9	29.8	11.4	3.3
	105		1	67.2	0.1	29.5	46.1	22.6	1.9
	Mean		2.3	52.4	0.7	31.8	35.6	16.1	2.1
	SD		1.0	10.1		4.3	7.2	5.1	1.0
TAVI	201	0	3	41.2	0.1	42.2	23.6	16.4	0.2
	201	2	3	38.0	0.6	42.0	25.3	14.7	0.1
	202	0	2	36.1	0.6	34.9	28.7	12.7	0.1
	203	2	3	20.4	0.0	58.6	18.9	5.0	0.0
	204	0	2	24.4	0.3	42.0	29.1	4.4	0.0
	207	2	1	49.0	0.0	47.2	33.8	18.8	0.2
	210	0	2	43.9	0.1	31.5	29.6	14.6	0.9
	211	0	3	30.8	0.5	44.1	27.0	9.3	0.1
	215	0	3	31.8	0.4	50.8	17.8	12.4	0.1
	216	0	2	22.0	0.0	51.0	19.6	6.0	0.0
	218	0	3	34.0	0.2	40.0	30.2	11.4	0.0
	219	2	3	26.6	0.1	49.5	24.6	8.1	0.1
	222	0	3	31.2	0.1	42.8	29.6	9.4	0.1
	224	0	3	44.0	0.0	30.2	37.4	12.6	1.4
	Mean		2.6	33.8	0.2	43.3	26.8	11.1	0.2
	SD		0.6	8.7		7.8	5.6	4.3	0.4
Mean			2.5	37.9	0.3	40.8	28.7	12.2	0.6
SD			0.7	11.8		8.6	6.9	4.8	0.9

TAVI indicates transcatheter aortic valve implantation; IMA, integrated modulus of acceleration; SD, standard deviation; T, measurement at T0, T1, or T2..