# Medication Incompliance and Vital Signs in Heart Failure Patients

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*Abstract*— **The success of medication treatment is a crucial part of chronic cardiac patients' therapy. Health professionals are requested to dynamically optimize this procedure (medication initiation, titration, change of medication plans) for each patient. Assessment of the person's response to treatment, and assessment of adherence to treatment are essential in supporting these medical decisions. In this work, methods that apply biosignal analysis on vital signs data are presented, aiming to detect differences due to medication incompliance. These data, although gathered in controlled conditions, encompass physiological fluctuations introduced by different factors of daily life, such as medication timing and activity. Heart Failure data are normalized to personal levels, and classification models trained with a pair of features (SBP and HR in semirecumbent position) succeed in achieving accuracy over 97% in a crossvalidation setup, in detecting 48 hrs incompliance. Additionally, the differences in incompliance patterns between heart failure and hypertensive subjects are discussed. These results constitute a promising step towards application of vital signs measurement and analysis in homecare for incompliance detection.**

*Keywords*— **telemonitoring data, patient medication compliance, personal health systems.**

## I. INTRODUCTION

Chronic cardiac patients' therapy is heavily dependent on successful medication treatment. In this respect, the health professionals are requested to make crucial decisions for medication initiation, titration, and change of medication plans for each patient, in order to have a desirable impact on the patient's vital signs and wellbeing. They do this based on medical evidence and on the as accurate as possible assessment of patient's condition and response to treatment.

More than a decade of telemedicine systems, not only introduced and cultivated the idea of continuum of care but also extended the medical evidence, especially regarding patients' actual health status and needs, as well as the diversity and dynamics that have to be met. Emerging technology on personal health systems (PHS) for chronic cardiac patients now promises improved and personally tailored health services, based on three axes[1] : a) ambient and/or body (wearable, portable or implantable) devices, which acquire, monitor and communicate physiological parameters and other health related context of an individual, b) Intelligent processing of the acquired information to derive meaningful interpretations about individual's health status, and c) decisions and actions (e.g. on care plan adaptations, interventions, etc.,) based on new insights, assisting in better health (diagnosis, treatment, rehabilitation or prevention).

At present, PHS makes it possible to have extended amounts of data collected. However, their transformation to valuable knowledge in terms of what the data mean, is still limited. The consequence is confining PHS only to the role of monitoring with little actuation and treatment, while the demands for intervention increase the pressure for healthcare professionals. Along with clinical parameters, the PHS data, e.g. vital signals, need to be employed and interpreted within their contextual perspective, and taking into account personalized properties and dynamics.

In order to make the PHS promise come true, and make the best medical use of this new abundance of available information, a series of challenges need to be met. The PHS data, being gathered in large amounts under uncontrolled conditions, need to be validated. The data and interpretations obtained via clinical and controlled studies need to be compared with data in uncontrolled conditions (from context aware PHS) to identify patterns of parameters, and decision making possibilities.

In the scope of PHS data analysis, two basic pillars that may support medical decision, especially in complex or multimorbid chronic patients, are:

- Assessment of the person's response to treatment, including complications, which links directly to the needs for care plan updates by the health professional.
- Assessment of compliance (or adherence) to treatment, which reflects the patient's responsibility in following the therapy as agreed and prescribed by the professional.

Treatment effectiveness and compliance as well as lifestyle patterns, would need the processing of longitudinal data for detection and reasoning. In this respect, within Heartcycle project [2], and based on knowledge built from the analysis of pretrial Life Challenges data [3], there are preliminary hints on the effects of medication incompliance to vital signs, which are also intertwined with the subject's activity during measurement, and diet, and differ between Heart Failure (HF) and hypertension (HTN) patients. The present work, based on the analysis of HeartCycle trial data

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was meant to strengthen evidence regarding the effects of medication compliance and the possibility to detect it via vital sign measurements, focusing on HF patients.

## II. METHODS

The questions investigated in this work aim to : a) Detect incompliance via vital signs in HF, b) Investigate how vital signs during activity are affected by medication, in HF, and c) Investigate differences in incompliance patterns between HF and HTN.

### A. Data Description

This analysis is based on a series of vital sign measurements that took place within the EU Project HeartCycle. The protocol and data collection were implemented in Castle Hill Hospital, UK, with 20 HF patients and 10 HTN patients. Patient characteristics are summarized in Table 1. For the HF patients, Systolic and Diastolic Blood Pressure (SBP, DBP) and Heart Rate (HR) are measured via conventional sensors on three different days, baseline, day with medication taken (medtaken), day with medication omitted for 48 hrs (medomit). For HTN patients, measurements on baseline and medication omit days were available. Measurements were taken during different patient activities and physiological maneuvers. An overview is depicted in Fig. 1. These measurements were done two times within a day.

Table 1: Patient Demographics. AF: Atrial Fibrillation, DM: Diabetes Mellitus, COPD: Chronic Obstructive Pulmonary Disease, HL: hyperlipidaemia, BB: Betablocker, ACEi: angiotensin-converting-enzyme inhibitor, Ald: Aldosterone.

| Group | HF | HTN |
|---|---|---|
| Size | 20 | |
| Age | 69.95±10.72 | 67.90±7.86 |
| Gender | 16M, 4F | 7M, 3F |
| Comorbidities | 18/20 (HTN, COPD, AF, DM) | 8/10 (HL, AF) |
| on loop Diuretics >=40mg Frusemide | 100% | 10% |
| NYHA class | 4 in NYHA 1, 16 in NYHA 2 | NA |
| Medication | ACEi 14/20, BB 20/20, Ald 5/20, combinations 19/20 | ACEi 7/10, BB 4/10,Ald 2/10, combinations 9/10 |

*Preparation of Features.* In HF, incompliance analysis was based on the pairwise intrasubject comparison of vitals between medomit and medtaken days. Comparison between the HF and HTN groups was performed via calculating the 'medomit - baseline' differences, and comparing these differences between the two groups, for the features available in both datasets (supine, standing, sitting). The two measurements available within the same day (2 cycles) were averaged, as they represent to some extent similar conditions (not taking into account time of the day, etc). In the HF group, 9/360 values were missing (2.5%) and were treated via nearest neighbor imputation (knnimpute function in matlab). In HTN, 11% of the values were missing and respectively imputed.

*Normalization of Values:* As baseline values vary among patients, there is a need for normalization to personal levels. In the HF case, the semirecumbent position in medtaken condition was considered as reference value for the compliance detection. As a method for normalization, the division by reference value was adopted. For the HF-HTN comparison, the differences between medomit and baseline day were considered, as dF=Fomit-Fbaseline.

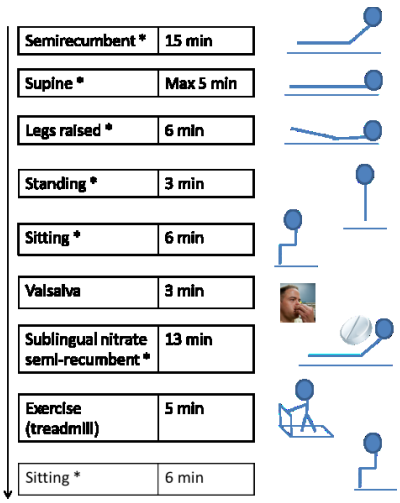


Fig. 1: An overview of the protocol. '*' denotes the postures/maneuvers with available vital sign measurement.

### B. Statistical Analysis and Classification

In HF incompliance detection, the normalized medtaken and medomit days where compared pairwisely in HF, with Wilcoxon signed rank test (signrank), as some of the features did not have normal distribution. An SVM classifier (with SMO optimization and RBF kernel function) was employed (Matlab implementation) for the incompliance detection. The classifier was trained and tested via 10-fold crossvalidation. After filtering out the statistically insignificant features, univariate and bivariate models were considered and compared regarding their sensitivity and specificity. Statistical

analysis of differences between HF-HTN groups was performed via t- test for normal distributions.

## III. RESULTS

### A. Statistical Analysis of Incompliance in HF

As can be seen in Table 2, significant differences are present in most blood pressure measurements, and in some of the heart rate measurements. This is in accordance with the previous findings [3]. The Bonferonni corrected threshold for statistical significance is set as 0.05/21=0.0023. The most consistent changes (small p-values) are found in SBP. In medomit all values are increased, as expected, but semirecumbent position presents the biggest difference.

Table 2: Statistical Significance of medtaken-and medomit comparison in HF, and respective median/quartiles. Normalized Values are employed.. '*' denotes the cases passing the stricter threshold p< 0.0023.

| Feature | Median and 25-75 Quartiles | | p |
|---|---|---|---|
| | medtaken | medomit | |
| SBP Semirecumbent | 1.00 [1.00 1.00] | 1.12 [1.10 1.18] | 0.00009* |
| SBP Supine | 0.97 [0.92 1.00] | 1.04 [1.02 1.09] | 0.00059* |
| SBP LegRaised | 0.97 [0.92 1.02] | 1.07 [1.01 1.13] | 0.00039* |
| SBP Standing | 0.98 [0.92 1.03] | 1.10 [1.06 1.20] | 0.00039* |
| 'SBP Sitting' | 1.00 [0.98 1.06] | 1.13 [1.08 1.19] | 0.00025* |
| SBP Semirec nitrate | 0.94 [0.89 0.98] | 1.03 [0.99 1.09] | 0.00014* |
| SBP Sitting6min | 1.09 [0.98 1.14] | 1.18 [1.15 1.26] | 0.01124 |
| DBP Semirecumbent | 1.00 [1.00 1.00] | 1.12 [1.05 1.19] | 0.00102* |
| DBP Supine | 0.92 [0.89 0.97] | 1.06 [0.96 1.13] | 0.00170* |
| DBP LegRaised | 0.95 [0.91 0.98] | 1.04 [0.99 1.09] | 0.00112* |
| DBP Standing | 1.02 [0.96 1.08] | 1.05 [1.03 1.21] | 0.01113 |
| DBP Sitting | 1.01 [0.95 1.16] | 1.16 [1.08 1.22] | 0.01237 |
| DBP Semirec nitrate | 0.99 [0.94 1.04] | 1.08 [1.01 1.13] | 0.00331 |
| DBP Sitting6min | 1.00 [0.95 1.09] | 1.13 [1.00 1.22] | 0.00740* |
| HR Semirecumbent | 1.00 [1.00 1.00] | 1.07 [1.02 1.14] | 0.00285* |
| HR Supine | 0.96 [0.95 1.01] | 1.03 [0.96 1.17] | 0.01762 |
| HR LegRaised | 0.97 [0.93 1.01] | 1.08 [0.97 1.14] | 0.00151* |
| HR Standing | 1.08 [1.04 1.14] | 1.18 [1.12 1.26] | 0.00319 |

As regards activity, in both medication conditions one can see that vitals sign values vary with activity, and patterns are similar in medtaken and medomit (with an offset due to medication omission), as can be seen in the average values depicted in Fig 2. In SBP, minimum value is found in Semirec nitrate, and maximum in Sitting6min,in DBP, minimum in supine and maximum in sit, and in HR, minimum in supine and maximum in standing and sit6min.

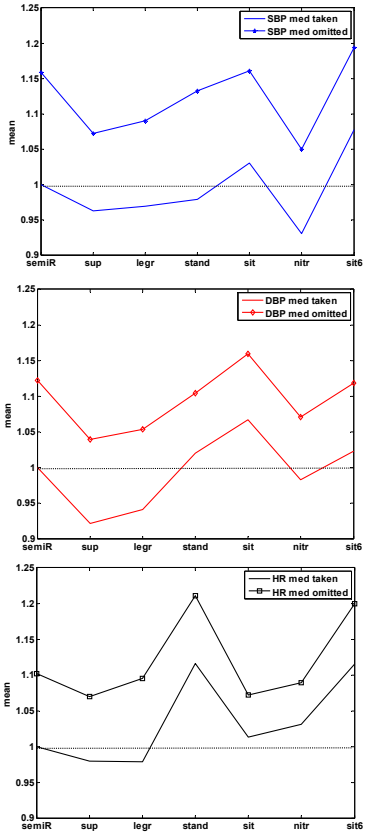


Fig. 2: medtaken and medomit mean values.

### B. Classification of Compliance

As can be seen in Table 3, the SVM classifier with two features is able to successfully classify a 48 hrs incompliance in HF patients. The best outcome is obtained with SBP and HR in semirecumbent position.

Table 3: Incompliance Classification Results (%). Positive class stands for medtaken and negative class stands for medomit. Semirec= Semirecumbent, LR=LegsRaised.

| feature | Sensitivity | Specificity | Accuracy |
|---|---|---|---|
| SBP Semirec | 100 | 80 | 90 |
| SBP Semirec+HR LR | 95 | 90 | 92.50 |
| DBP Semirec+HR LR | 95 | 90 | 92.50 |
| SBP +HR Semirect | 100 | 95 | 97.50 |

### C. HF-HTN Comparison of Incompliance Patterns

The significant differences between HF and HTN as regards incompliance are depicted in Table 4. Additionally, a visual inspection of the vitals in supine, standing and sitting position is available in Fig 3.

Table 4: HF-HTN Comparison in terms of mean/standard deviation and ttest p-value. No values were below the Bonferroni-corrected p-value threshold 0.05/9=0.0056

| | HF | HTN | p |
|---|---|---|---|
| SBP Supine [mmHg} | 2.46 ±13.55 | -10.39 ±12.36 | 0.01785 |
| DBP Supine [mmHg] | 1.48±10.14 | -6.48± 8.02 | 0.03952 |

It is worth mentioning that these differences are positive in HF (increase of vitals from baseline to medication omission) and negative in HTN. This difference could be due to the diuretic dynamics. The difference Combo medication, and evident existence of comorbidities in HF, is also another issue. However, as the baseline day also included the subject's familiarization and potentially some stress, the interpretation of these results is not straightforward. Yet, one can safely say that incompliance models need to be customized per disease. Additionally, while heterogeneity among the patients was partially addressed via normalization, among the possible limitations of this study can be considered some lifestyle options, like consumption of caffeine and the influence of circadian cycle.

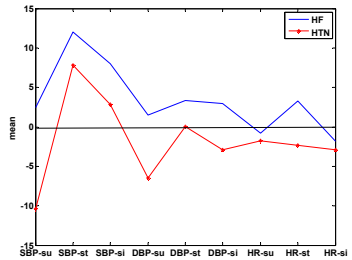


Fig. 3: The values depicted are differences between medomit and reference day. (su:supine, st: standing, si: sitting)

## IV. Conclusions

This paper presents an analysis of the vital signs differences between medication intake and 48 hrs medication omission. Statistically significant differences are found between the two states, with the latter presenting higher values. An SVM based classifiers succeeds in classifying incompliance with a high accuracy (97.50%), employing SBP and HR in semirecumbent position. Although this is a controlled experiment (in a clinical setting), it is easily realisable in a home setup. In fact, the validation of these findings in a home environment is a necessary next step.

Extending these methods to an uncontrolled PHS case would be extremely exciting, setting the base for the discovery of new knowledge [4] and for understanding patient's health condition in real life, and guiding patients in achieving health goals. Still, such an effort would present a series of new challenges, including: a) how can the various daily life conditions (activities, diet, etc) be mapped to unambiguous and quantitatively processable factors, and how can these factors be combined to a personalized model that may help interpret data, and guide patient/health professional. Vital signs data gathering, managing and analyzing for compliance detection in PHSs can be seen as a new frontier towards leveraging of personal health services.

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## Conflict of Interest

The authors declare that they have no conflict of interest.

## References

1. Codagnone C, Reconstructing the Whole: Present and Future of Personal Health Systems, Report, (2009) at: http://ec.europa.eu/information_society/activities/health/docs/projects/phs2020/phs2020-book-rev16082009.pdf
2. Maglaveras N, Reiter H. (2011) Towards closed-loop personal health systems in cardiology: the HeartCycle approach. IEEE EMBS Proc. 33rd Annual International IEEE EMBS Conference, Boston Ma, USA,pp 892-895
3. Chouvarda IG, Antony R, Torabi A., Caffarel J, van Gils M, Cleland J, Maglaveras N (2013), Temporal Variation in telemonitoring data: on the Effect of Medication and Lifestyle Compliance. International Journal of Bioelectromagnetism 15(1):30 - 35
4. Weitzman ER, Adida B, Kelemen S, Mandl KD (2011) Sharing Data for Public Health Research by Members of an International Online Diabetes Social Network. PLoS ONE 6(4): e19256. doi:10.1371/journal.pone.0019256

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