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EXECUTIVE SUMMARY OF THE THESIS

Holter analysis of electro-mechanical activity and circadian rhythm through ECG and inertial sensors: a novel approach

TESI MAGISTRALE IN BIOMEDICAL ENGINEERING – INGEGNERIA BIOMEDICA

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1. Introduction

Cardiovascular (CV) diseases are the principal source of an increasing number of deaths across the globe. The cost associated with monitoring and diagnosing all CV diseases is going to increase in the next 10 years and at the same time there will be a projected shortage of doctors. To cope with this increasing number of people affected by CV diseases, and with the decreasing number of doctors, new modalities of treating and monitoring the patients at home rather than at the hospital are needed [1]. Furthermore, new technological development and device miniaturization (MEMS) open the possibility for mobile or wearable devices to be used for physiological data collection. Among the emerging non-invasive continuous monitoring techniques, seismocardiography (SCG) is one of the most promising. Using small, portable, user-friendly and unobtrusive devices, it allows the monitoring of precordial micro-vibrations produced at every heartbeat generated by cardiac contractions, valves opening and closing and blood ejection into the vascular tree [2]. A typical SCG-beat waveform (dorso-ventral component) is characterized by peaks and valleys that have been correlated to specific physiological events in the cardiac cycle: mitral valve closure (MC), isovolumetric contraction (IVC), aortic valve opening (AO), rapid ejection of blood (RE), aortic valve closure (AC), mitral valve opening (MO) and rapid filling (RF). It has also been proven that there is a correspondence between electrical activity peaks in the electrocardiogram (ECG) and mechanical activity fiducial points in SCG (*Figure 1.1*) [3,4].

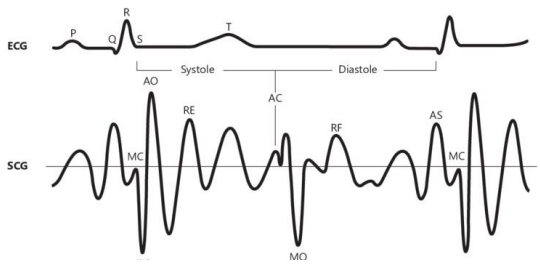

Figure 1.1: Comparison between ECG and SCG

During the last years many studies focused on evaluating the potential of using SCG signals for monitoring cardiac activity, developing algorithms to extract fiducial points using the synchronously acquired ECG signal as a reference [5]. All methods, however, were applied and evaluated on

short recordings acquired in laboratory conditions. After the identification of fiducial points, parameters of potential clinical interest can be computed and their circadianity (physiological oscillation over a 24-hours period) can be evaluated as most physiological parameters and pathological events of the CV system demonstrated a robust circadian rhythm [6].
The availability of novel technologies incorporating both ECG and SCG sensors and allowing for extended time acquisitions (even over 24 hours) opens the possibility of non-invasively studying both electrical and mechanical cardiac activity through innovative approaches, also evaluating the circadianity of derived parameters. The aim of this study was to determine feasibility of such approach and to propose a novel method for beat-by-beat detection of cardiac mechanical events and relevant circadian rhythms, to determine normality ranges for future comparisons.

2. Methods

A total of 22 healthy volunteers were recruited for the synchronized acquisitions of ECG and SCG signals for 24 hours, during which the subject carried out the normal activities of his/her every-day life. The physical activity sensor EcgMove4 from Movisens Gmbh was positioned between the 5th and 6th ribs and was used to acquire a single channel ECG signal (f_s = 1024 Hz) and dorso-ventral SCG (f_s = 64 Hz) , which has been proven to contain more information relevant to heartbeat occurrence.

2.1 ECG and SCG pre-processing

ECG and SCG signals were pre-processed to remove noise and breathing related motion artifacts with 4° order, zero-phase, band-pass Butterworth filters (0.5-30 Hz for the ECG signal and 5-25 Hz for the SCG signal).
Afterwards, AO and R peaks were identified as reference points to measure heart activity. ECG and SCG signals were divided into 30 sec segments. The Pan Tompkin algorithm was applied to each ECG window to extract the R peaks; while an ECG-free algorithm based on a template matching technique was applied to detect AO peaks. For each acquisition, a template of 10 seconds was selected, and cross-correlation was computed between each 30-second segment and the template: the position of maximum values of the cross-correlation were used to identify a search window for each heartbeat to locate systolic complexes (SC).

2.2 Extraction of SCG fiducial points

An innovative ECG-dependent approach that combines signal's morphology, cardiac properties and physiological information was developed to identify analyzable heartbeats over the 24-hour signals and to extract fiducial points on the SCG signals.
The identified R peaks of the ECG were used to extract a window ranging between R_i – 200 ms and R_{i+1} - 200 ms both from the ECG and SCG signals. The two windows were compared, and algorithm developed for fiducial points identification was applied on the SCG signals if the following three conditions were met:

- Two consecutive R_iR_{i+1} intervals were not outliers;
- At least one systolic complex was identified in that SCG segment;
- Typical SCG beat waveform was identifiable (at least three positive peaks after the R peak).

2.2.a Aortic valve opening - AO

For each segment, the three maximum peaks on the SCG occurring after the R peak on the ECG were identified, possibly corresponding to AO, RE and AC. The first occurring maxima was labelled as AO.

2.2.b Mitral valve closure – MC

For each segment, the MC point was identified as the maximum before AO. The position of MC with respect to R was a crucial condition to decide whether to consider or not such fiducial point: if MC was identified outside a maximum allowed distance from the R peak, then the SCG window was not further analyzed.

2.2.c Isovolumetric contraction – IVC

For each segment, the IVC point was identified as the minimum peak between MC and AO.

2.2.d Rapid ejection of blood – RE

The RE fiducial point was identified as the peak following AO. In addition, the negative peak between AO and RE was also extracted and used for further analysis.

2.2.e Aortic valve closure – AC

AC was identified after the end of the T-wave of the ECG. Given the position of the T peak, the T-end wave end location was identified based on the computation of successive trapezium's areas [7] with three fixed vertexes (the point with the highest absolute derivative in a 40 ms searching window starting from the T-wave peak and a point located approximately on the T-P isoelectric segment) and one mobile vertex (T-wave end). The T-end point was defined as the point where the area of the trapezium was maximum.

Given the T-wave end point position, AC was identified as the first peak in time after it. The position of AC with respect to Q (i.e. QS2) was a crucial condition to decide whether to consider or not the detected fiducial points for that beat. The QS2 maximum physiological distance was computed and if AC was identified after it, then the SCG was not further analyzed.

2.2.f Minimum before AC

Given the position of the fiducial point corresponding to the closure of the aortic valve, the minimum before AC was extracted as the negative peak prior to AC.

2.3 Beat-to-beat Labelling – Tags

To evaluate the feasibility of the proposed SCG analysis, a tag value was associated to each window based on the detected fiducial points. In total 10 different tag values were defined:

Tag	Description	Further analyzed
0	Perfect ECG and SCG window. All fiducial points are identified	*Yes*
1	At least one of two consecutive R_iR_{i+1} intervals are outlier	*No*
2	No correspondence between R peak and SCs in the specific window (0 SC found)	*No*
3	Typical SCG beat waveform not identifiable	*No*
4	Typical ECG beat waveform not identifiable	*No*
5	Wrong identification of T peak: T in the diastolic phase or QT_c longer than the physiological value	*Only Early Systole*
6	Cardiac cycle too short	*No*
7	RE coincides with AC, RE not reliable	*Yes (no RE)*
8	MC was identified after R peak: data from both early and late systole are not reliable	*No*
9	AC was identified after the maximum distance allowed from Q (QS2 max): data from late systolic phase are not reliable	*Only Early Systole*

Table 2.1: Tags values identified during the analysis

The beat-to-beat labeling and the number of heartbeats corresponding to each tag were functional to the subsequent feasibility analysis, whose objective was to understand what percentage of the 24h signals could be used to extract SCG parameters to compute normality ranges and circadian analysis, and what percentage instead needed to be discarded. In addition, the analysis was carried out separately for daytime and nighttime to understand if there was a particular period within the 24 hours of recording, in which a greater percentage of the signal could be better analyzed.

2.4 Computation of SCG parameters

For each time window, the detected fiducial points were used to calculate the morphological (amplitude and slope) and temporal parameters:

Parameters [millig]	Description
ΔA(IVC-AO)	Difference in amplitude between IVC and AO
ΔA(IVC-MC)	Difference in amplitude between IVC and MC
ΔA(AO-RE)	Difference in amplitude between AO and RE
ΔA(RE-minAORE)	Difference in amplitude between RE and the minAO-RE
ΔA(AO-AC)	Difference in amplitude between AO and AC
ΔA(AO-minAORE)	Difference in amplitude between AO and minAO-RE
ΔA(AC-minAC)	Difference in amplitude between AC and minAC

Table 2.2: Amplitude parameters

Parameters [millig/ms]	Description
SLOPE(IVC-AO)	Slope between IVC and AO
SLOPE(minAC-AC)	Slope between minAC and AC
SLOPE(minAO RE-RE)	Slope between minAORE and RE

Table 2.4: Slope parameters

Parameters [ms]	Description
ΔT(IVC-AO)	Time delay between IVC and AO
ΔT(IVC-MC)	Time delay between IVC and MC
ΔT(AO-RE)	Time delay between AO and RE
ΔT(AO-AC)	Time delay between AO and AC
ΔT(AO-minAORE)	Time delay between AO and minAO-RE
ΔT(AC-minAC)	Time delay between AC and min bef AC
LVET	Time delay between AO and AC
QS2	Time delay between Q and AC
QT	Time delay between Q and T-end
QT_c	Time delay between Q and T-end (Bazett's correcion)
PEP	Time delay between Q and AO
ΔT(R-AO)	Time delay between R and AO
ΔT(R-AC)	Time delay between R and AC
ΔT(R-MC)	Time delay between R and MC
R_iR_{i+1}	Time delay between R_i and R_{i+1}
AO_iAO_{i+1}	Time delay between AO_i and AO_{i+1}

Table 2. 3: Temporal Parameters

2.5 Circadian rhythm analysis

Cardiac circadian analysis aimed to evaluate whether there was a circadian behavior or not.
A visual analysis used previously calculated parameters to create approximate representations of the distribution of data between sleeping and awakening period and normalized and non-normalized data through histograms, to understand if the analyzed parameter was likely to have a circadian rhythm. Moreover, for each parameter, day-night differences were verified through Wilcoxon Signed Rank test ($p < 0.05$).

Then, the Cosinor analysis – the traditional method to analyze circadian rhythm – was applied to previously identified parameters and four circadian parameters were computed:

- Mesor: midline of the oscillation;
- Amplitude: distance between the peak of the Cosinor curve and the mesor;
- Acrophase: time corresponding to the positive peak of the curve;
- P-value: significant if > 0.05.

Cosinor was computed both as a separate and cumulative analysis. Points were translated to ensure that all recordings started at the same time (8 AM for separate analysis and time at which the subject went to bed for cumulative analysis) and Cosinor was computed considering a moving average window lasting 5 minutes without overlapping.
The coupling between the cardiac electro-mechanical activity was evaluated through a statistical test (Wilcoxon Signed Rank, $p<0.05$) of the acrophases of R_iR_{i+1} and AO_iAO_{i+1}.

3. Results

3.1 Feasibility Analysis

For each subject, the number of R peaks identified from the ECG and the number of SCs identified from the SCG were compared during 24 hours, and separately day and night. As regards 24 hours, the median value was equal to 71.75% (62.09%; 80.91%). Regarding the comparison of SCs and R peaks identified during daytime and night-time, the percentage of SCs (with respect to R peaks) identified during night-time was always higher than the percentage identified during day-time. Indeed, the median percentage value reached during night-time was 95.72% (92.04%; 98.3%), while the median percentage value computed during day-time was 64.18% (53.03% ; 74.16%).
Another crucial part of the feasibility analysis was to establish for which subjects the T wave was visible in most beats (R_iR_{i+1} intervals). A visual analysis was carried out and T-waves were visible, and it was possible to identify T peaks in 15 volunteers only, while they were not visible and identifiable in 7 subjects. In subjects in which the T wave was not identified, fiducial points and parameters in the late systolic phase were not sought in the subsequent analysis.

The second step of feasibility analysis was beat-to-beat labeling. This operation allowed to establish what percentage of the acquired signals could be used for subsequent circadian analysis (tag 0,5,7 and 9) and what percentage would need to be discarded (other tags).

Tags	Day	Night
T wave	51.82 (43.26 ; 56.98)	82.51 (69.08 ; 92.14)
No T wave	33.23 (26.24 ; 41.92)	79.48 (56.79 ; 81.41)

Table 3.1: Distribution results (median, 25th and 75th percentiles) for tags 0,5,7,9

3.2 Visual analysis

Based on such visual analysis, the following parameters (13 out of 26 parameters) were selected:

Parameter		
ΔA(IVC-AO)	**ΔA(AO-minAORE)**	QTc
ΔA(IVC-MC)	**ΔA(AC-minAC)**	PEP
ΔA(AO-RE)	**SLOPE(IVC-AO)**	**R_iR_{i+1}**
ΔA(RE-minAORE)	**LVET**	**AO_iAO_{i+1}**
ΔA(AO-AC)	**QT**	

Table 3.2: Selected parameters

For each parameter, the cumulative histograms among all subjects were computed with the respective median, 2,5th, 25th, 75th and 97.5th percentiles, in order to identify a normality range, separately for day and night.

3.3 Cosinor Analysis

For the Cosinor analysis we considered the slope parameters, not normalized amplitude and temporal parameters. In the separate Cosinor analysis, two similar patterns can be identified among the analyzed data. Temporal parameters R_iR_{i+1}, AO_iAO_{i+1}, QT and LVET intervals presented the acrophase early in the morning, in particular for R_iR_{i+1}, AO_iAO_{i+1}, LVET was around 4 AM. The other parameters presented the acrophase between 3 PM and 4 PM. As regard the cumulative Cosinor analysis, 9 out of 13 parameters presented the acrophase around 14 hours after the moment in which the subject went to bed (more or less at 3 PM). On the contrary, the acrophase was around 5 hours after the beginning of the sleep period for temporal parameters as R_iR_{i+1}, AO_iAO_{i+1}, QT intervals and LVET (around 6 AM).

Regarding the separate Cosinor analysis, every parameter reached a significance level > 80% of the subjects, while 100% significance levels were obtained for each studied parameter in the cumulative analysis.

4. Discussion

Through feasibility analysis the possibility to analyze the 24h SCG recordings to extract cardiac mechanical activity parameters was evaluated. Results of the comparison between the total number of identified R peaks in the ECG signal and the total number of SCs identified in the SCG signal shows that such approach is feasible, despite the low sampling frequency of the SCG signal (64 Hz). This study proves that, for the device utilized and the sampling rate, relevant information could be derived in a long-term acquisition. The % of identified peaks was found higher during night-time rather than day-time; as possible explanation, it can be assumed that during night-time the subject rests still in a horizontal position and consequently the SCG signal is less subject to movement's artifacts.

Beat-to-beat labeling aimed at classifying heartbeats, assigning a label to each of them, to identify analyzable ones and to categorize the reasons why this was not possible. Labels were defined empirically, based on the various morphologies and scenarios observed in multiple patients during the analyses, and constitute a novelty of the proposed approach. Also, this step will constitute the basis of future work for the development of machine learning algorithms for automated classification of beats on the SCG signal, as the provided labels can be used in a supervised learning approach.

Even if the % of analyzable heartbeats among those identified on the SCG was still high, a significant number was excluded. Interestingly, in all subjects the % of beats labelled as analyzable during night-time was higher than the one during day-time.

To extract fiducial points from analyzable heartbeats over the 24h signals, an innovative algorithm that combines signal's information, cardiac properties, and physiological information was developed. New biomarkers were identified

and could be used to study electro-mechanical cardiac activity and make intra- and inter-subject comparisons. In previous studies, cardiac kinetic energy was proposed to characterize the CV status and using specific algorithms, kinetic energy and its temporal integral were computed from SCG waveforms as scalar parameters [8]. However, given the intrinsic dependency from kinetic energy, it hasn't been possible to use energy derived parameters as biomarkers. In fact, kinetic energy is related to the position and posture of the subject, to the position of the device and thus is not possible to acquire repeated acquisitions under the same conditions, and thus to make comparison between the obtained data.

All temporal parameters were characterized by a significant difference between day and night and the presence of a circadian rhythm was validated through the Cosinor analysis (cumulative analysis). All acrophases occurred between 05:00 and 07:00, a circadian behavior in accordance with the R_iR_{i+1}. Interesting considerations about the coupling between the electrical and mechanical activities could be derived from the comparison between AO_iAO_{i+1} and R_iR_{i+1} intervals. Given the results of the Cosinor analysis and of the day-night comparison, we can deduce that the mechanical temporal variability of AO_iAO_{i+1} reflects the electrical temporal variability of R_iR_{i+1} , while the maximum value of the AO_iAO_{i+1} (acrophase) occurred after the one of R_iR_{i+1}, we can thus speculate that the cardiac electrical activity reaches its higher value before the cardiac mechanical activity. Morphological parameters were characterized by a significant difference between day and night and the presence of a circadian rhythm was validated through the Cosinor analysis (cumulative analysis). All acrophases, following the circadian pattern of stroke volume and myocardial contractility as described in literature occurred between the 15:00 and 16:00.

5. Conclusions

This research was the first attempt to evaluate the circadianity of cardiac electro-mechanical activity parameters though Holter (24h) acquisitions during the participant's normal daily life and activity. An innovative approach that combines signal's morphology, cardiac properties and physiological information was developed to identify analyzable heartbeats over 24h signals and to extract cardiac mechanical parameters. Normality ranges were then defined from 22 healthy participating volunteers.

New parameters identified in this study could be used as important biomarkers for comparisons of the electro-mechanical cardiac activity when monitoring pathological patients and as a prevention tool in healthy subjects in longitudinal studies outside of the clinical setting through new wearable, user-friendly and non-invasive devices.

Furthermore, this study lays the foundation providing normal reference values for future research on the coupling of electro-mechanical cardiac activity in different scenarios currently under evaluation, such as during underwater immersions and during prolonged isolation.

6. Bibliography

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