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Monitoring in cardiovascular disease patients by nonlinear biomedical signal processing

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Abstract— **Due to recent advances in technology extensive cardiovascular monitoring is widely introduced today. An essential component of cardiovascular monitoring is the analysis of several biosignals as electrocardiogram, blood pressure and other vital signs. This manuscript provides an overview about several application fields of cardiovascular monitoring with the main focus on nonlinear dynamics analysis.**

I. Introduction

MONITORING describes a process in which a time varying system will be controlled and includes prospective supervision, proactive and targeted observation, testing of an ongoing process, analysis and action. In the process, monitoring examines if a desired system status has been or will be achieved, otherwise it suggests changes to the system to obtain this status [1]. Due to recent advances in technology extensive cardiovascular monitoring is widely available today. In a multitude of studies, besides linear heart rate variability (HRV) analysis methods which consider the time- and frequency domain, especially methods from nonlinear dynamics were suggested to be useful for the identification and differentiation of several cardiovascular disorders and it was assumed that they may prove to be clinically useful differentiating the progression of a disease [2]. Furthermore it could be demonstrated that nonlinear indices may perform in some circumstances even better than traditional linear indices in risk stratification of cardiac patients [3]. In the field of monitoring real-time or discontinuous analyzing of changes in both linear and nonlinear indices were used to examine patients' status. Due to the high potential of nonlinear analysis methods for diagnostics and risk stratification, their integration into cardiovascular monitoring systems will be expected resulting most likely in an enhancement of prediction and classification accuracies and false alarm reductions. This manuscript provides an overview without claiming any completeness (e.g. imaging, in-vitro analyses, and analytics are completely ignored) about several application fields of cardiovascular monitoring with the main focus on nonlinear dynamics analysis.

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II. General Aspects of monitoring

A. General application fields of monitoring

(1) Monitoring of the general state of health
by observing the main medical and physiological parameters especially in elderly people plays an important role in e.g. the prophylaxis of diseases, detection of sudden health state changes and accidental injuries.

(2) Monitoring in acute medicine
(intensive and critical care units) of persons around-the-clock who are critically ill, medically unstable and/or have a potentially life-threatening disorder is a cost intensive standard procedure.

(3) Vital function Monitoring
for controlling and assessment of the post-operative recovery of patients after surgery with a heart-lung machine and of the progression and prognosis of several heart diseases. Especially in different clinical studies patients with chronic heart failure (CHF), coronary heart diseases (CAD), malignant arrhythmic events and patients after myocardial infarction (AMI) were investigated to prove the suitability for predicting patients' outcome for a later integration in monitoring systems. Implantable cardioverter-defibrillators (ICD) monitor the heart's electrical activity and rhythms (at or outside the hospital). In case of detected life-threatening events, ICDs prevent a sudden cardiac arrest by delivering adequate electrical shocks.

(4) Monitoring of signal and system quality
Signal quality and data fusion of monitored ICU data is associated with adequate false alarm (FA) suppression. FAs can lead to a disruption of care, impacting both the patient and the clinical staff. The resultant excessive noise pollution, desensitization to warnings and slowing of response times can lead to missed alarms, decreased quality of care, sleep problems, stress for both patients and staff, depressed immune systems and longer patient stays. Some promising algorithms to suppress these FAs were reviewed in [4].

B. Common applied nonlinear methods for cardiovascular monitoring

Several studies investigated the suitability of nonlinear methods especially from nonlinear dynamics for identification and differentiation of several cardiovascular diseases and disorders and for differentiating the progression of a disease. The most common applied nonlinear dynamics methods are: approximated entropy (ApEn), compression entropy (CE), correlation dimension (CD), detrended fluctuation analysis (DFA), multiscale entropy (MSE), Poincare plot analysis (PPA), power-law analysis (PLA), sample entropy (SampEn), symbolic dynamics (SD) and joint symbolic dynamics (JSD).

C. Common monitored biosignals

Patient's vital signs that are most common analyzed in cardiovascular monitoring are the electrocardiogram (ECG), HRV and blood pressure (BP). Further biosignals as respiration, pulse oximeter data, cardiac output and others are of growing interest and importance

III. APPLICATIONS OF CARDIOVASCULAR MONITORING

A. Prediction of cardiovascular disease outcome

Different studies investigated the suitability of linear and nonlinear indices of HRV to predict the outcome of cardiovascular diseases which seem promisingly for future applications in monitoring devices. In the following some of the significant studies in this field are mentioned.

Makikallio et al. [5] examined selected dynamic HRV analysis indices in 159 patients with depressed left ventricular (LV, ejection fraction EF<35%) function after AMI with a 4-year follow-up (survivors: n=87, patients who died: n=72). They found a reduction in fractal correlation properties (alpha1 from DFA) in AMI patients with increased risk of death which indicates more random short-term heart rate dynamics in these patients. These results were affirmed by Huikuri et al. [6] who found out a reduced alpha1 (relative risk 3.0) as most powerful predictor of all-cause mortality in a population (enrolled in DIAMOND study) of 446 survivors of AMI. In a prospective multicenter study with 697 AMI patients, Tapanainen et al. [7] demonstrated that in a multivariate analysis alpha1 was the most significant independent HRV index that predicted subsequent mortality.

Stein et al. [8] determined HRV from Holter-ECG recordings of 740 AMI patients and found also associations between altered nonlinear HRV indices (alpha1, slope from PLA), and SD12 (PPA) and mortality after AMI. The study's results suggest that decreased long-term HRV and increased randomness of heart rate are independent risk factors for mortality in AMI patients.

A multivariate approach performed by Voss et al. [2, 9], using all domains and especially SD, revealed the best prediction for all-cause mortality as well as for sudden arrhythmic death. In this study, 572 survivors of acute myocardial infarction were enrolled. Within the follow-up period, 43 patients died. A combination of four HRV parameters from all domains (time and frequency domain, NLD) in this multivariate approach improved the diagnostic precision more than twofold.

B. Monitoring of intensive care unit patients

The main objective is to analyze patient's disease dynamics during ICU stay based on real-time or discontinuous physiological data monitoring. In the following section some encouraging examples are presented.

In a study of Stein et al. [10] 106 patients admitted to the ICU after abdominal aortic surgery (AAS) were investigated to determine whether measurement of HRV during the first postoperative day would predict prolonged recovery after surgery. Therefore, 24-h Holter recordings were analyzed applying time and frequency domain indices and the nonlinear index β-slope (PLA) of HRV. They found a decreased value of the β-slope index which predicted membership in the group with a longer stay. The results suggest that HRV monitoring in the ICU may identify patients at risk for requiring extensive postoperative care.

Wu et al. [11] investigated 86 patients after AAS who were randomized into a control and an ischemic preconditioning (IP) group. They analyzed 24-h Holter recordings with linear and nonlinear HRV indices. The exponent alpha1 (DFA) was reduced in pre- and postoperative condition and predict the higher incidence of postoperative atrial fibrillation and worse postoperative outcome.

Laitio et al. [12] investigated 40 patients before and after coronary artery bypass surgery (CABG) in the immediate postoperative phase of CABG. Therefore, 24-h Holter recordings up to 72-h postoperatively were analyzed applying time and frequency domain indices and nonlinear indices. The reduced scaling exponent alpha1 of the first postoperative 24-h was the best HRV index in differentiating between the patients that had normal or prolonged ICU stay.

In 2006 Papaioannou et al. [13] investigated longitudinally over time the heart rate dynamics (daily basis, 600 seconds) and their relation with mortality and organ dysfunction alterations in 53 patients admitted to a multidisciplinary ICU applying linear and nonlinear HRV indices (DFA, ApEn). They found a loss of variability and increase in periodicity (decreased ApEn) in heart rate of critically ill patients which are linked with high mortality.

Norris et al. [14] hypothesized that MSE predicts death using short-term heart rate recordings of shorter duration and lower density. They investigated during the initial 24-h of ICU stay, 3154 patients. MSE could stratify patients by mortality and was an independent predictor of death. They concluded that MSE within hours of admission predicts death occurring days later and that MSE is robust to variation in bedside data duration and density occurring in a working ICU.

Caminal et al. [15] investigated interactions between heart and breathing rate (HR & BR) applying JSD analysis from 94 patients with successful weaning and 39 patients that failed to maintain spontaneous breathing. In comparison to linear indices, the discriminant analysis of nonlinear JSD indices revealed significant better results when differentiating between both weaning trial patients groups (max. accuracy: 65.4% vs. 78.2%). The authors assume that JSD analysis could be suitable for reducing the number of patients that had to be reintubated because of respiratory distress.

Pfeifer et al. [16] investigated whether there are differences in autonomic cardiovascular regulation in 18 resuscitated patients undergoing therapeutic hypothermia (TH) in relation to the clinical outcome. Resuscitated patients show a significantly reduced HRV Linear indices and SD) before, during and after TH. Compared to survivors, the non-survivors show a further and significantly decrease of HRV immediately after hypothermia.

C. *Prediction of life-threatening events*

The following studies investigated how changes of HRV can predict the onset of life-threatening arrhythmias and could classify different types of arrhythmias in patients with an ICD. Skinner et al. [17] investigated Holter recordings from 11 high-risk patients who manifested ventricular fibrillation (VF) and in high-risk controls having only nonsustained ventricular tachycardia (14 patients) or premature ventricular complexes (13 patients) to prove whether indices of heartbeat dynamics are more suitable to predict the risk of mortality due to arrhythmias than stochastic indices. They found that CD has shown to be able to detect alterations in HRV before the onset of arrhythmic events shortly prior the onset of ventricular tachycardia (VT).

Lombardi et al. [18] investigated 60 patients with implanted ICD applying linear and nonlinear indices (β–slope PLA) of short-term HRV at rest and immediately before VT. They found altered HRV pattern in comparison to controls before VT confirmed by reduced β–slope values. Wessel et al. [19] analyzed 1000 beat-to-beat intervals of 17 CHF ICD patients before the onset of a life-threatening arrhythmia and at a control time without a VT or VF event using time and frequency domain and nonlinear indices of HRV. They could show that two indices from SD as well as the finite-time growth rates discriminate significantly between VT and no VT. In a study of Baumert et al. [20] the last 1000 normal beat-to-beat intervals before 50 VT episodes stored by the ICD were analyzed for short-term forecasting of VT in order to improve VT monitoring and to enable a patient warning of forth-coming shocks. They found that the CE revealed significant alterations in VT compared with control time series suggesting a decreased complexity before the onset of VT. A current study of Sayadi et al. [21] proposed a novel nonlinear joint dynamical model and a Bayesian filter for the verification of five categories of life-threatening arrhythmias by simultaneous tracking the signal fidelity and the polar representation of pulsatile cardiovascular (CV) estimations. In particular, the addition of more CV signals improved the positive predictivity of the proposed method to 99.27% for the total arrhythmic types. The method was also used for false arrhythmia suppression issued by ICU monitors, with an overall false suppression rate reduced from 42.3% to 9.9%. The authors concluded that their proposed method can contribute to clinical life-threatening arrhythmia monitoring.

Shin et al. [22] investigated the spontaneous onset of paroxysmal atrial fibrillation (PAF) using nonlinear indices. They analyzed 105 Holter recordings in which PAF was recorded, 44 PAF episodes in 33 patients, preceded by sinus rhythm for more than 1h. The results showed that the scaling exponent alpha1 (DFA), ApEn and SampEn decreased before the onset of PAF and seem to be a hallmark of altered heart rate dynamics preceding the spontaneous onset of PAF. Recently in a study of Sovilj et al. [23] 50 patients undergoing CABG surgery (14 patients developed atrial fibrillation –AF- during or after the recordings, 36 patients did not develop AF) were investigated to identify patients at high risk of post-operative AF. ECGs were continuously recorded for 48-h following CABG. Appling a nonlinear multivariate prediction model the prediction accuracy was found to increase over time. At 48-h following CABG, the measured best smoothed sensitivity was 84.8%, the specificity 85.4%, the positive and negative predictive values were 72.7% and 92.8%, respectively.

In a prospective study (n=57) [24] the suitability of ApEn of BP was investigated to predict the risk of hypertensive crisis from 24-h ambulatory BP monitoring (ABPM). A multivariable regression analysis was performed in which ApEn, combined with other measures of 24-h ABPM, was proven as a potentially powerful predictor of hypertensive crisis.

D. *Progression control*

A dataset of 7-day Holter recordings of 22 CHF patients was investigated by Goya-Esteban et al. [25] to characterize the infradian, circadian, and ultradian components and a bootstrap test yielded automatically the rhythmometric model for each patient applying linear and nonlinear HRV indices. Circadian components were the most significant from all HRV indices, but the infradian ones were also strongly present in linear and nonlinear (alpha1 DFA, SampEn) indices. They concluded that long-term monitoring of HRV conveys new potentially relevant rhythmometric information, which can be analyzed by using the proposed automatic procedure in monitoring HRV.

Retzlaff et al. [26] investigated the differences in the post-operative recovery of autonomic regulation after mitral valve (MV, n=17) and aortic valve (AV, n=26) surgery with a heart-lung machine. Therefore, BP and ECG signals were recorded the day before, 24-h after and one week after surgery and afterwards analyzed with standard linear and nonlinear HRV indices (SD) as well as with the dual sequence method to assess the baroreflex sensitivity (BRS). A decreased ability to recover in MV patients exists, probably attributed to traumatic lesions of the autonomic nervous system by opening the atria. Monitoring of long-term changes would be of interest in order to estimate the ongoing progression in recovery

IV. DISCUSSION

Indices derived from nonlinear dynamics complementing traditional time- and frequency domain indices and give new insights and additional information about altered HRV changes in cardiovascular disease [2]. An improvement in monitoring of cardiovascular diseases and e.g. the prediction of life-threatening arrhythmias is expected, and partly proven, by univariate and coupling analyses between different physiological biosignals.

It can be assumed that in the near future nonlinear analyses will increasingly be integrated into medical systems for ambulatory- or home care (e.g., ambient assisted living) applications to monitor cardiovascular diseases, function control of medical equipments even of implanted devices and the general physiological state of patients which will expand the capabilities of clinicians to describe patient's disease dynamics in an easier and cost efficient way and improve diagnosis and management of cardiac patients.

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