



Schlussbericht für Tabakpräventionsprojekte und -programme

(bitte nicht handschriftlich ausfüllen)

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1 Zusammenfassung des Schlussberichts

*Stellen Sie kurz den Projektverlauf, wichtigste Erkenntnisse, Schlussfolgerungen und Empfehlungen dar.
Max. 1 Seite*

The initial phase of our project mainly consisted in data preparation and quality control (preprocessing of raw ECG data to generate artifact-free inter-beat interval time series), on the one hand, and, on the other hand, in the efficient implementation of computer algorithms to calculate quantitative measures of heart rate variability.

Quantitative measures of heart rate variability were obtained from the analysis of the generated inter-beat interval time series using the implemented non-linear time series analysis techniques, such as detrended fluctuation analysis (DFA), the largest Lyapunov exponent, etc. For comparison purposes, we also analyzed the inter-beat interval time series using more traditional measures of heart rate variability such as frequency-domain measures and global statistics like the standard deviation.

Once we calculated a collection of quantitative heart rate variability parameters for each suitable participant of the SAPALDIA cohort, we addressed the task of proving a significant association between tobacco smoke exposure and changes in heart rate variability. To this end, we used multivariable regression models regressing each of the aforementioned parameters on the levels of exposure to tobacco smoke. The models were adjusted for all known confounders (age, BMI, gender, environmental tobacco smoke exposure, alcohol consumption, physical activity, diabetes, cardiovascular disease, and average annual NO₂ exposure).

We hypothesized in the initial grant proposal the existence of **a load effect: A critical amount of tobacco smoke exposure capable of causing an irreversible change in the regulation of the cardiovascular system, reflected as a permanent change in heart rate variability**. To investigate this, we turned our attention **to the smoking cessation status** and the amount smoked for each participant of the SAPALDIA cohort. Thus, each participant was categorized as current light smoker, current heavy smoker, former light smoker or former heavy smoker. The statistical analysis of our multivariable regression models provides evidence supporting the following conclusions:

1. Smoking triggers adverse changes in the regulation of the cardiovascular system, even at low levels of exposure. Indeed, all the standard measures of heart rate variability were decreased in light and heavy current smokers compared to never smokers.
2. After cessation, light smokers seem capable of recovering the levels of heart rate variability characteristic of never smokers.
3. In heavy smokers, some of the nonlinear time series analysis parameters studied in this project nearly retain the levels characteristic of a smoker, even after many years of cessation. Other parameters indicate a full recovery. Thus, for heavy smokers our results are not conclusive, hinting that a full recovery after cessation might not be achievable.

However, we were not able to detect a significant association between passive smoking and changes in the cardiovascular regulation system. This topic will require further investigation.

Nevertheless, our findings support our initial claim that non-linear time series analysis techniques may be able to unveil subtle, but important changes in the regulation of the cardiovascular system not detectable by traditional analysis methods. Therefore, we highly recommend to other researchers the use of these techniques for the quantitative assessment of heart rate variability and autonomic heart rate control. We have developed computer software within the R environment (<http://www.R-project.org/>) that can be used for this purpose. Other researchers have made their software available in several platforms that vary in their degree of user friendliness (see, for instance, García, Constantino et al. A Software Toolkit for Nonlinear Heart Rate Variability Analysis. In Computing in Cardiology Conference (CinC), 2013 (pp. 393-396). IEEE. <http://rhrv.r-forge.r-project.org/>).

In conclusion, our results suggest that smoking triggers adverse changes in the regulation of the cardiovascular system, even at low levels of exposure. This finding provides a strong argument for health policy makers who advocate for a more intense prevention campaign aimed at discouraging teenagers and young adults from smoking. However, smoking cessation in light smokers can have a very strong effect towards a normalization of heart rate variability, potentially reducing the risk of developing cardiovascular disease later in life. This underpins the value of public healthcare programs supporting the benefits of smoking cessation. For heavy smokers, smoking cessation might only allow for partial recovery, indicating that long term exposure to high levels of tobacco smoke might have an irreversible effect on the regulatory mechanisms of the cardiovascular system.

2 Kurzer Projektbeschreibung

(Der Projektbeschreibung ermöglicht es, den Bericht auch ohne Projektkenntnisse zu verstehen)

An association between the levels of environmental tobacco smoke and air pollutants and the long-term risk of cardiovascular mortality in exposed humans has been previously demonstrated. However, such long-term manifestations of the pathogenic influence of environmental tobacco smoke and air pollutants are believed to be at the end of a chain of modifications in the cardiovascular and respiratory system, and could, therefore, be the result of additional confounding factors.

The cardiovascular system is a complex network of mutually interacting subsystems. Consequently, it is difficult to assess the overall impact of environmental tobacco smoke and air pollutants on it. A systems biology approach may overcome these limitations. We argue that a more comprehensive indicator of a potential influence of environmental tobacco smoke and air pollutants on the cardiovascular system is the study of autonomic heart rate control.

The SAPALDIA cohort study in Switzerland has approached the problem from this perspective by studying heart rate variability, a measure of cardiac autonomic control. In their study, specifically targeted at examining the effects of long-term air pollution exposure on cardiovascular and respiratory health, it was shown that heart rate variability was reduced in those subjects chronically exposed to NO₂ and environmental tobacco smoke. While these results were obtained using well-established global metrics of mean heart rate variability and different frequency power measures, the long time series of cardiac function obtained in the SAPALDIA cohort are suitable for a more sophisticated analysis, which takes into account changing properties of the heart rate fluctuations throughout the observed period. We hypothesize that the repeated exposure to environmental tobacco smoke and air pollutants can trigger a fundamental change in the state of the cardiovascular system comparable to a phase transition or to a "resettlement" of the system in a dynamically different attractor. This new state might show a reduced adaptability to external challenges, which may explain the higher long-term risk for cardiovascular diseases described in the literature. We expect this transition to be detectable as alterations of the complexity of heart rate variability. Moreover, we conjecture a load effect for this phase transition to take place.

We propose a systems biology approach to studying heart rate variability in the epidemiological context of tobacco smoke exposure. Specifically, we will analyze previously recorded time series of inter-beat intervals obtained from subjects who participated in the SAPALDIA cohort using computational techniques borrowed from the theory of nonlinear dynamics, statistical physics, and information theory. Previously, all these techniques have been successfully applied to the analysis of (patho-)physiological cardiac time series. Nevertheless, by the time our original grant proposal was written, they had never been utilized in reference to tobacco smoke exposure.

3 Geplante Ziele

Stellen Sie das strategische Ziel (gemäss der Nationalen Strategie zur Tabakprävention) des Projekts dar, zu dessen Erreichung Sie mit dem Projekt beitragen wollten.

Stellen Sie die projektspezifischen Ziele gemäss Ihrem Finanzierungsgesuch dar.

Our strategic aim is to provide quantitative evidence for a load effect of repeated exposure to tobacco smoke on the regulatory mechanisms of the cardiovascular system. That is, we want to show, that an irreversible change takes place in the cardiovascular regulatory mechanisms upon repeated exposure to tobacco smoke during an even limited amount of years.

4 Erreichte Ziele

Führen Sie einen Soll-Ist -Vergleich der projektspezifischen Ziele durch.

(Falls die Ziele nicht oder nur teilweise erreicht wurden, dann erläutern Sie die Gründe dazu unter Pt. 7)

Our research activities have revealed a significant association between smoking habits and the value of parameters that describe the dynamic properties of inter-beat interval time series. The latter are a proxy for the intrinsic properties of the cardiovascular regulatory mechanisms.

Moreover, our findings suggest that after smoking cessation, **light smokers seem capable of recovering the levels of heart rate variability characteristic of never smokers**. However, in heavy smokers, some of the nonlinear time series analysis parameters studied in this project nearly retain the levels characteristic of a smoker, even after many years of cessation. Other parameters indicate a full recovery. Thus, **for heavy smokers our results are not conclusive, hinting that a full recovery after cessation might not be achievable**.

However, we were not able to detect a significant association between passive smoking and changes in the cardiovascular regulation system.

In conclusion, our results provide partial evidence for a load effect of repeated exposure to tobacco smoke on the regulatory mechanisms of the cardiovascular system.

5 Leistungsergebnisse (Output)

Bitte nennen Sie die erbrachten Leistungen (z.B. Manual, Broschüre, Schulungsunterlagen u.ä.)

Wurden alle geplanten Leistungen erbracht?

(Falls die Leistungen nur teilweise erbracht wurden, dann erläutern Sie die Gründe dazu unter Pt. 7)

We have presented our research approach and results at the following national and international conferences and symposia:

1. "Non-linear time series analysis methods to assess heart-rate variability and its association to air pollution and tobacco smoke exposure" oral presentation at the UKBB Forschertag, August 23th 2012, Basel.
2. "Non-linear time series analysis methods to assess heart-rate variability and its association to air pollution and tobacco smoke exposure" poster presented at the 2012 European Conference on Computational Biology in Basel, September 9th-12th 2012.
3. "Predictability of Heart Rate and its Relation to Long-Term Smoking". Poster presentation at the 2013 Jahrestagung der Schweizerischen Gesellschaften für Pneumologie, April 19th 2013.
4. "Variability in Physiological Systems – Methods and Applications". Presentation at the Scientific Winter Retreat of the PhD Club, Department of Biomedicine, University of Basel, March 21st-23rd 2013.
5. "Heart Rate Variability and its Relation to Long-Term Smoking". Poster presentation at the 2013 European Respirator Society Annual Meeting, September 7th-11th 2013, Barcelona, Spain.
6. "Smoking cessation and heart rate dynamics: Is it possible to fully recover?" Poster presentation at the 2014 European Respirator Society Annual Meeting, September 6th-10th 2014, Munich, Germany.
7. "Smoking cessation and heart rate dynamics: Is it possible to fully recover?" Poster presentation at the 2014 UKBB Forschertag, September 18th 2014, Basel.
8. Peer reviewed journal publication in preparation: "Smoking cessation and heart rate dynamics: Is it possible to fully recover?" To be submitted to the European Heart Journal.

6 Erreichte Wirkungen (Impact)

(Diese Angaben stellen eine qualitative und subjektive Sichtweise der Projektleitenden dar..)

Wurde eine externe Wirkungsevaluation durchgeführt? Ja (bitte Bericht beilegen) / Nein

Wenn nein:

Welche Wirkungen haben Sie mit Ihrem Projekt erreicht? Worauf stützen sich Ihre Aussagen?

To our best knowledge, this is the first report about the long term effects of cessation on tobacco smoke exposure induced changes in heart rate regulation. Since the latter are related to risk of cardiovascular disease, cessation is therefore one of the most important prevention strategies for cardiovascular disease. Our study gives raise to the hope that in light smokers, cessation will result in a normalisation of heart rate variability. The importance of this finding has been discussed at the 2014 international conference of the European Respiratory Society and was well perceived. Particularly the large number and quality of the data have been positively rated. We are currently writing up the manuscript, which is close to submission during the next 3 months. After publication, our findings may be used for health policy statements.

7 Projektrückblick und Erfahrungen

Bitte beantworten Sie alle Fragen:

1) Wie erklären Sie sich die tatsächliche Zielerreichung und die Leistungsergebnisse?

- 2) Welche Massnahmen zur Zielerreichung haben sich bewährt, welche nicht? Welches waren förderliche und hinderliche Faktoren (Erfolgs- resp. Misserfolgskriterien)?
- 3) Wie schätzen Sie den Aufwand und die Kosten im Vergleich zum Nutzen ein?
- 4) Welche allgemeinen Erfahrungen haben Sie mit dem Projekt gemacht?
- 5) Weitere Aspekte?

1) In our opinion, this grant money enabled us to perform a unique analysis of data obtained within the SAPALDIA cohort. Our approach using nonlinear time series analysis techniques allowed us to unveil effects previously not visible due to the usage of more conventional quantitative methods. Moreover, our results provide partial evidence for a load effect of repeated exposure to tobacco smoke on the regulatory mechanisms of the cardiovascular system.

2) We proceeded as originally planned with a focus on a careful and well-planned analysis. However, private circumstances of the researcher initially involved introduced some delays. In addition, the move to Basel caused additional idling time.

From a methodological point of view, the nonlinear time series analysis approach was very helpful. Some artifacts in the data set and occasional availability issues of the data caused interim problems that we, nevertheless, were able to overcome.

3) Considering the dissemination of our results at international conferences and the publication that will result from this funding, as well as the general interest in the public, and the potential impact on health policy making, we feel that the study has been very cost-effective.

4) As with any other research project involving or requiring the collaboration with other large research consortia, such as the SAPALDIA team, the human interactions are very critical for the success of the project. While this is often underestimated, our experience has shown how important it is to make sure beforehand that all collaborators are on the same page regarding the overall goals, their interests, and their availability for a successful conduction and conclusion of the project.

8 Nachhaltigkeit und Valorisierung (Nutzung)

Wie beurteilen Sie die Nachhaltigkeit Ihres Projekts? z.B.

- bleibt die Wirkung des Projekts auch nach Projektende bestehen?
- zieht das Projekt weitere Wirkungen nach sich (Nachahmung, Schneeballeffekt)?
- gehen die durch das Projekt entstandenen Prozesse weiter und wirken sie über die Zielgruppe hinaus?

Haben Sie die Möglichkeiten der Multiplikation des Projekts geprüft? Welche Möglichkeiten haben Sie ausgemacht?

Wie werden Sie das erarbeitete Know-how sowie die gemachten Erfahrungen für andere Projekte und Anliegen nutzbar machen?

With this money from the Tobacco Prevention Fund, we were able to develop the computational infrastructure to carry out the computations required for nonlinear analysis of time series. This computing platform, implemented in the widely used R environment (<http://www.R-project.org/>), will be used for future projects involving the analysis of time series of physiological signals. Many of these projects will take place within our group and therefore will be located in the epidemiological context of respiratory and cardiovascular health. We anticipate that our success will encourage other scientist to use this kind of quantitative methodology.

Our results suggest that smoking triggers adverse changes in the regulation of the cardiovascular system, even at low levels of exposure. This finding provides a strong argument for health policy makers who advocate for a more intense prevention campaign aimed at discouraging teenagers and young adults from smoking. Moreover, our findings regarding light smokers underpin the value of public healthcare programs promoting smoking cessation.

9 Chancengleichheit

Haben Sie spezifische Massnahmen zur Förderung der Chancengleichheit unternommen (Gender, soziale Schicht und ethnische Zugehörigkeit)? Ja / Nein?

Wenn ja, welche Erfahrungen haben Sie damit gemacht?

Wenn nein, hätten dank solcher Massnahmen Ihrer Meinung nach bessere Ergebnisse erzielt werden können?

The data set used in our study is part of the SAPALDIA cohort in which participants were randomly chosen. Thus, the proportions of female and male participants simply reflect Swiss demographics.

The recommendations for public health policy makers that may potentially be derived from our findings apply equally to females and males.

10 Auf den Punkt gebracht

Welches sind die Stärken und die Schwächen des Projekts?

The strengths of our study are that we are able to put to work powerful quantitative techniques to address the associations between heart rate variability and tobacco smoke exposure. Moreover, we were able to provide partial evidence for a load effect of repeated exposure to tobacco smoke on the regulatory mechanisms of the cardiovascular system. Our investigations regarding light smokers highlight the benefits of smoking cessation.

The weakness of our study has been the relative long time that it has taken us to achieve our goals. Furthermore, in our initial analysis we were not able to detect a significant association between passive smoking and changes in the cardiovascular regulation system. This topic will require further investigation.

11 Empfehlungen

Welche Empfehlungen geben Sie anderen Akteuren ab, die ein ähnliches Projekt planen?

One very important aspect to successful and efficient research is scientific collaboration. However, the concrete execution of the research plan and the required involvement of the different parties should be carefully discussed and defined prior to the project start.

12 Zusammenfassung für den Laien

Im Rahmen unseres Forschungsprojektes „Influence of tobacco exposure on heart rate variability“ waren wir in der Lage, unter Verwendung von quantitativen Verfahren eine signifikante Assoziation zwischen Tabakrauchexposition und Herzfrequenzvariabilität nachzuweisen bei den Partizipanten der SAPALDIA Kohorte. Die Herzfrequenzvariabilität kann als Mass verstanden werden für die Eigenschaften der kardiovaskulären Regulation.

Unsere quantitativen Untersuchungen haben partielle Evidenz dafür geschaffen, dass ein kumulativer Effekt der Tabakrauchexposition existiert, bei dem durch wiederholte Exposition zum Tabakrauch eine irreversible Veränderung der Eigenschaften der kardiovaskulären Regulation hervorgerufen wird. Teil der von uns betrachteten nicht linearen Parameter suggerieren, dass, selbst viele Jahre nach dem Aufhören, in ehemaligen starken Rauchern diese Veränderung der eigenen kardiovaskulären Regulation durch quantitative Methoden nachweisbar ist. Andererseits fanden wir auch heraus, dass leichte Raucher durch den Verzicht aufs Rauchen die tabakkonsumbedingte, krankhafte Veränderung der eigenen kardiovaskulären Regulation wieder rückgängig machen können. Dies unterstützt die Wichtigkeit der Aussage, dass Raucher unbedingt so früh wie möglich mit dem Rauchen aufhören sollten.

Im Bezug auf passives Rauchen ist es uns nicht gelungen, eine signifikante Assoziation mit Veränderungen der Eigenschaften der kardiovaskulären Regulation und der Herzfrequenzvariabilität nachzuweisen.